30 Glycopeptides (Vancomycin and Teicoplanin) and Lipoglycopeptides (Telavancin, Oritavancin, and Dalbavancin)

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SHORT VIEW SUMMARY

VANCOMYCIN

- Vancomycin inhibits late stages of cell wall synthesis in dividing gram-positive microorganisms by interacting with the D-Ala-D-Ala termini of peptidoglycan precursors.
- *Staphylococcus aureus* is a major target for vancomycin; strains with decreased susceptibility to vancomycin include vancomycin-intermediate *S. aureus* (VISA), which display minimal inhibitory concentrations (MICs) between 4 and 8 µg/mL, and vancomycin-resistant *S. aureus* (VRSA) isolates harboring the enterococcal *vanA* gene cluster with even higher MICs. The precursors of VISA, heteroresistant VISA (hVISA) strains, exhibit MICs within the susceptible range (≤2 µg/mL).
- Vancomycin-resistant enterococci (VRE), usually *Enterococcus faecium*, are found worldwide, with the VanA and VanB phenotypes accounting for the majority of these isolates.
- In adults with normal renal function, the average dose is 15 to 20 mg/kg every 8 to 12 hours. For many infections, 15 mg/kg every 12 hours is adequate (obtaining trough levels ≤15 µg/mL). Even though trough levels of 15 to 20 µg/mL have been suggested for serious infections caused by methicillin-resistant *S. aureus* (MRSA), the optimal vancomycin concentration for efficacy and avoidance of toxicity is still a matter of debate; a loading dose of 25 to 30 mg/kg achieves therapeutic levels sooner. The use of area under the concentration-time curve estimation for optimal vancomycin dosing may be a better parameter to follow than trough levels. Dosing should be modified in patients with renal failure, and adjustment based on blood levels is still recommended.
- Red neck or red man syndrome can be seen during vancomycin administration and is related to a rapid infusion and/or a large dose. The risk for vancomycin-induced nephrotoxicity increases with trough levels ≥15 µg/mL, concomitant use of nephrotoxic agents, and duration of therapy. Ototoxicity, vertigo, and tinnitus, as well as neutropenia and thrombocytopenia, are rarely reported.
- Vancomycin is still the drug of choice for treatment of severe skin infections and osteomyelitis and probably also for treatment of bacteremia and endocarditis caused by MRSA; many clinicians still use it as the first-line agent for MRSA pneumonia and as an alternative agent for enterococcal endocarditis and for endocarditis caused by other gram-positive bacteria. Vancomycin is used for suspected or proven penicillin-resistant pneumococcal meningitis (in combination with cefotaxime or ceftriaxone) and for cerebrospinal fluid shunt–related infections caused by methicillin-resistant staphylococci.
- Oral vancomycin is used for severe *Clostridioides difficile* (formerly *Clostridium difficile*) colitis.

TEICOPLANIN

- Teicoplanin is available in many countries in Europe, Asia, and South America but not in the United States. The spectrum of antimicrobial activity overlaps with that of vancomycin.
- It is administered once daily by intravenous (IV) bolus or by the intramuscular route. After an IV loading dose of 6 mg/kg every 12 hours for three doses, the maintenance dose follows with 400 mg (6 mg/kg) every 24 hours. For more serious infections the loading dose should be 800 mg (up to 12 mg/kg) every 12 hours three times and then every 24 hours.
- Teicoplanin appears less nephrotoxic than vancomycin, and the most common side effects are rash and drug-related fever. The red neck syndrome is uncommon.
- In countries where both antibiotics are available, teicoplanin is infrequently used in place of vancomycin, although it could be considered for enterococcal infections or to continue the outpatient treatment of certain MRSA infections.

TELAVANCIN

- Telavancin is the first commercially available agent among lipoglycopeptides, a group of semisynthetic derivatives of glycopeptides that is approved in the United States for acute bacterial skin and skin structure infections (ABSSSI) due to gram-positive pathogens and nosocomial pneumonia caused by susceptible *S. aureus* when other alternatives are not suitable.
- Telavancin inhibits peptidoglycan synthesis as do glycopeptides and produces concentration-dependent alterations of the cell membrane.
- The in vitro spectrum of activity includes *S. aureus,* coagulase-negative staphylococci, and vancomycin-susceptible *Enterococcus faecalis* and *Enterococcus faecium* strains. Higher concentrations are needed to suppress growth of VanA-type VRE in vitro. Telavancin seems to have good activity in vitro and in vivo against VISA strains.
- The approved dose is 10 mg/kg/day, which should be reduced to 7.5 mg/kg/day and to 10 mg/kg every 48 hours in those with a creatinine clearance of 30 to 50 mL/min and 10 to 30 mL/min, respectively.
- In the ABSSSI and the hospital-acquired pneumonia trials, the rate of creatinine increase was higher in patients receiving telavancin than those treated with vancomycin. Besides this reversible renal impairment, other potential side effects are infusion-related reactions, and minor increases in the QTc.

DALBAVANCIN

- Dalbavancin is approved for use in adults with ABSSSI caused by various susceptible gram-positive organisms in United States and Europe.
- Dalbavancin shows in vitro activity against all gram-positive pathogens except those intrinsically resistant to glycopeptides and those exhibiting high-level resistance to

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SHORT VIEW SUMMARY—cont'd

vancomycin, mainly mediated by the *vanA* gene cluster.

- The terminal half-life is 8 to 9 days, with a high volume of distribution and protein binding of 93%.
- The current approved dosing is a single administration of 1500 mg or 1000 mg, followed by 500 mg 1 week later for adults with ABSSSI.
- Patients on hemodialysis can receive the regular dose, and those not on hemodialysis with a creatinine clearance <30 mL/min should receive 1125 mg as a single dose or 750 mg on day 1 and 375 mg on day 8 in the two-dose regimen. No need for dose adjustment is required in patients with hepatic insufficiency.
- Adverse reactions include nausea, diarrhea, pruritus, mild elevations of alanine aminotransferase (ALT), and infusion-related reactions.
- A two-dose regimen of dalbavancin is currently under study in an open-label trial of pediatric patients with ABSSSI.

ORITAVANCIN

- Oritavancin is the third lipoglycopeptide available and is approved for use in adults with ABSSSI caused by susceptible gram-positive organisms in United States and Europe.
- Oritavancin is a derivative of the lipoglycopeptide chloroeremomycin, similar to vancomycin, and acts by inhibiting transglycosylation, transpeptidation, and disrupting the cell membrane.
- Oritavancin is active in vitro against staphylococci, streptococci, and enterococci, including VRE.
- The approved dose is one infusion of 1200 mg over 3 hours; the drug is widely distributed, has high protein binding (85%–90%), and a prolonged terminal half-life (≈240 hours), allowing the one-time dosing strategy.
- Headache, nausea, vomiting, diarrhea, infusions reactions such as flushing and pruritus, and mild ALT elevation were among the observed side effects.
- Oritavancin has a potential for drug-drug interaction through the inhibition of several cytochrome P450 enzymes. In addition, because oritavancin causes false elevation of activated partial thromboplastin time for up to 5 days, the use of IV unfractionated heparin sodium is contraindicated in this period.
- Patients with moderate liver or renal impairment do not require dose adjustment.

GLYCOPEPTIDES

Vancomycin

Vancomycin, the first glycopeptide antibiotic developed for clinical use, was isolated from *Amycolatopsis orientalis* (known previously as *Streptomyces orientalis* and later as *Nocardia orientalis*), found in a soil sample from Borneo in the mid-1950s. In 1958 vancomycin was introduced into clinical practice as an agent active against penicillin-resistant *Staphylococcus aureus*. However, a few years later the use of vancomycin was relegated to patients allergic to β-lactam antibiotics because of the availability of new penicillinase-resistant β-lactams, methicillin and cephalothin, and the high rate of toxicity observed with the initial vancomycin formulation. Indeed, early lots of vancomycin (compound 05865) were called "Mississippi mud" owing to the color provided by their large quantity of impurities, but later manufacturing procedures markedly improved purification. Since the 1980s a steady rise in vancomycin use has occurred in the United States, from 2000 kg/yr in 1984 to 11,200 kg/yr in 1996,[1] a trend that also occurred in most European countries[2] and has likely contributed to the rise of strains exhibiting decreased glycopeptide susceptibility. Of note, an important proportion (between 40% and 70%) of the inpatient and outpatient use of vancomycin has been considered to be inappropriate.[3,4]

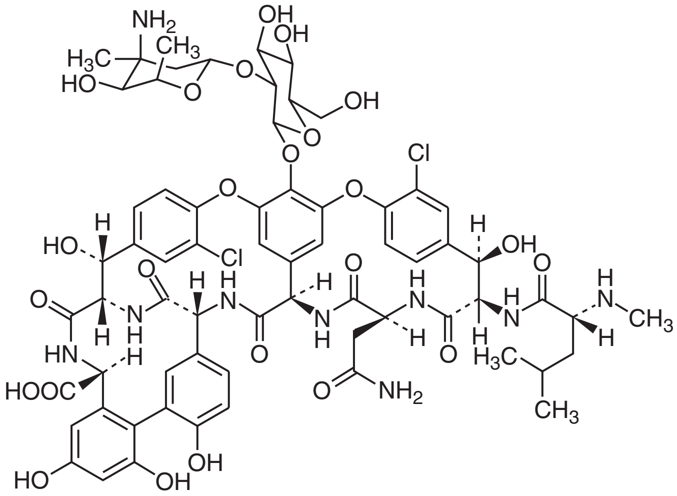

FIG. 30.1 Chemical structure of vancomycin.

Structure and Mechanism of Action

Vancomycin is a complex tricyclic glycopeptide that consists of a seven-membered peptide chain forming the tricyclic structure (Fig. 30.1) and an attached disaccharide composed of the amino sugar vancosamine and glucose. The molecular weight is 1485.73 dalton (Da), much higher than that of other antimicrobial agents except teicoplanin, daptomycin, and lipoglycopeptides.

The primary effect of glycopeptides is inhibition of late stages of cell wall synthesis in dividing bacteria. The target of glycopeptides is the nascent peptidoglycan precursor units (lipid II) as they emerge from the bacterial cytoplasm. Vancomycin and other glycopeptides form complexes with the two carboxyl-terminal D-alanine residues of peptidoglycan precursors, and molecular modeling studies indicate that the acyl-D-alanyl-D-alanine moiety is held firmly by the antibiotic via five hydrogen bonds. Binding of the antibiotic at this step blocks the incorporation of disaccharide pentapeptide subunits into the nascent peptidoglycan by transglycosylation and also likely inhibits transpeptidation.

Antimicrobial Activity

Vancomycin has broad activity against gram-positive microorganisms. Staphylococci are normally susceptible to vancomycin, with minimal inhibitory concentrations (MICs) ≤2 μg/mL and minimal bactericidal concentrations (MBCs) within twofold of the MIC; heteroresistance of *S. aureus* to vancomycin (the hVISA phenotype) is discussed later. Vancomycin remains active against most *Enterococcus faecalis* and a variable percent of *Enterococcus faecium* isolates but is not bactericidal even against susceptible isolates, with MBCs more than 32 times the MICs; however, as with other cell wall agents, the addition of an aminoglycoside (if the strain is not highly aminoglycoside resistant) increases the bactericidal activity. All strains of *Streptococcus pneumoniae* and *Streptococcus pyogenes* are susceptible to vancomycin, as are virtually all *Streptococcus agalactiae* and group C and group G streptococci, although rare isolates of streptococci (e.g., *Streptococcus gallolyticus*) have acquired *vanB* genes. Vancomycin also shows good in vitro activity against *Granulicatella* spp. and *Abiotrophia defectiva* (formerly classified as nutritionally variant streptococci).

Listeria monocytogenes is susceptible to vancomycin, but strains with high MBCs have been reported. Vancomycin also displays good in vitro activity against *Bacillus anthracis* isolates, *Bacillus cereus,* and other *Bacillus* spp., with MICs of 2 μg/mL or less. Against *Corynebacterium* spp., including *Corynebacterium jeikeium,* vancomycin has good activity and is the drug of choice for serious infections caused by these organisms until susceptibilities are known. *Rhodococcus equi* is also susceptible to vancomycin. The typical susceptibility to vancomycin of *Lactobacillus acidophilus* helps differentiate this organism from other *Lactobacillus* spp., which are intrinsically vancomycin resistant. *Leuconostoc* spp., *Pediococcus* spp., and *Erysipelothrix rhusiopathiae* are also intrinsically resistant to glycopeptides.

Among the gram-positive anaerobes, *Peptostreptococcus* spp., *Actinomyces* spp., *Propionibacterium* spp., and *Finegoldia magna* are usually susceptible to vancomycin, as are most *Clostridium* spp., including *Clostridioides difficile* (formerly *Clostridium difficile*), except strains of *Clostridium ramosum* (MIC in 90% of isolates [MIC_{90}], 8 μg/mL) and *Clostridium innocuum* (MIC_{90}, 16 μg/mL). Vancomycin displays no in vitro activity against most gram-negative organisms, except for some nongonococcal *Neisseria* spp.

Mechanisms of Resistance

Development of resistance to vancomycin by mutations was predicted to be a rare occurrence in the clinical setting because the MIC of vancomycin against staphylococcal isolates increased only modestly after serial passages in the presence of the drug, compared with 100,000-fold when penicillin was used. Although higher MICs and MBCs of vancomycin are noted when using high inocula (10^7 colony-forming units [CFUs]/mL) of *Staphylococcus epidermidis* isolates,[5] it was not until the mid-1980s that the first clinical isolates of *S. epidermidis* with reduced susceptibility to glycopeptides were described. Several years later vancomycin-resistant enterococci (VRE; MIC ≥32 μg/mL) isolates were reported in Europe and subsequently the rest of the world. In 1997 the first clinical isolate of *S. aureus* with diminished susceptibility to vancomycin (strain Mu50) was described from Japan.[6] This strain displayed a vancomycin MIC of 8 μg/mL, which is in the range of intermediate susceptibility (4–8 μg/mL) per current Clinical and Laboratory Standards Institute (CLSI) breakpoints[7] and thus was referred to as vancomycin-intermediate *S. aureus* (VISA) or glycopeptide-intermediate *S. aureus* (GISA). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has deleted the intermediate classification for *S. aureus,* and strains with MICs >2 μg/mL are considered vancomycin resistant (www.eucast.org/clinical_breakpoints). The initial VISA strain report was followed by others from various countries. Precursors of these VISA isolates are isolates that harbor subpopulations of cells that are able to grow in the presence of higher concentrations of vancomycin (designated heteroresistant VISA, hVISA, or hGISA). More recently, highly vancomycin-resistant *S. aureus* (VRSA) strains with much higher MICs (ranging from 32 μg/mL–024 μg/mL[7]) that harbor the enterococcal *vanA* gene cluster have been described, mostly from the United States, including a community-associated strain of methicillin-resistant *S. aureus* (MRSA).

Enterococci

Among enterococci, nine types of glycopeptide resistance have been described (VanA, VanB, VanC, VanD, VanE, VanG, VanL, VanM, and VanN), which are named based on their specific ligase that catalyzes the binding of the last two amino acids or substitutes of peptidoglycan precursors (e.g., D-Ala-D-Lac or D-Ala-D-Ser ligases). Related gene clusters have been found in nonpathogenic organisms: *vanF,* in *Paenibacillus* (formerly *Bacillus*) *popilliae* strains (a biopesticide used in the United States to suppress Japanese beetle population) and *vanJ* and *vanK* in the non–glycopeptide-producing actinomycete *Streptomyces coelicolor.* The common end point for vancomycin resistance is the formation of peptidoglycan precursors with decreased affinity for glycopeptides, resulting in decreased inhibition of peptidoglycan synthesis. Peptidoglycan precursors ending in the depsipeptide D-alanyl-D-lactate are produced by VanA-, VanB-, and VanD- and VanM-type strains, whereas VanC, VanE, VanL, and VanN isolates produce precursors terminating in D-alanyl-D-serine, instead of the normally occurring D-alanyl-D-alanine. The *vanA* gene cluster is often found on Tn*1546* transposon or related genetic elements that are usually carried on plasmids and occasionally on the host chromosome; *vanA*-carrying Tn*1546* also has been found in clinical isolates of *S. aureus* (VRSA strains).

Glycopeptide resistance in enterococci is classified as either intrinsic (as a species characteristic) or acquired. The former is a characteristic of the motile species *Enterococcus gallinarum* and *Enterococcus casseliflavus/flavescens,* members of which all carry the naturally occurring *vanC-1,* and *vanC-2/vanC-3* genes, respectively, as part of their core genome. These enterococci show variable MICs of vancomycin, with many falling in the susceptible range, and clinical failures have been reported after vancomycin use. In general, the isolation of these species does not require strict infection control isolation procedures, unless they are highly resistant, suggesting the added presence of potentially transferable *vanA* or *vanB* genes.

Acquired glycopeptide resistance is found most often in *E. faecium,* followed by *E. faecalis* (≈80% of *E. faecium* and ≈5% of *E. faecalis* strains in the United States are vancomycin resistant), and is much less common in other enterococcal species. VanA and VanB account for the vast majority of glycopeptide resistance, with the former more frequently found. VanA isolates (and the recently described VanM) show high MICs of vancomycin and teicoplanin, whereas VanB strains often have lower vancomycin MICs and, typically, are susceptible to teicoplanin. VanD strains have moderate-level resistance to both glycopeptides, whereas VanC, VanE, VanG, VanL, and VanN isolates display low-level resistance to vancomycin and susceptibility to teicoplanin.

Expression of the *vanA* gene cluster is regulated by a membrane-associated sensor kinase (VanS) that likely senses changes in the cell envelope and activates the cytoplasmic response regulator (VanR), which triggers transcription of the resistance as well as the regulatory genes. Similarly, the *vanB* gene cluster has $VanS_B$ and $VanR_B$; the VanB sensor kinase ($VanS_B$) does not appear to recognize teicoplanin.

Recent work has revealed two very distinct clades of *E. faecium* that differ significantly in both their core and accessory genomes and appear to have diverged from each other long before the modern antimicrobial era.[8] The clade with most human clinical and outbreak strains also contains animal isolates and shows higher MICs of ampicillin. The community-associated clade consists primarily of non–hospital-associated human isolates with MICs of ampicillin ≤2 μg/mL. Remarkably, hospital-associated isolates carry not only a variety of antimicrobial-resistance genes but also more putative virulence genes, such as *esp*, *ebpA* and *hyl*, encoding an adhesin, a gene involved in the synthesis of pili and a glycosyl hydrolase, respectively, which likely contribute to a survival advantage in the hospital environment. Some particular clonal clusters (CC2 and CC9) of *E. faecalis* have also been reported to predominate in clinical specimens from hospitalized subjects.

The epidemiology and the beginning of VRE spread in Europe and the United States have notable differences. In Europe the glycopeptide avoparcin was frequently fed to animals as a growth enhancer, apparently selecting for vancomycin resistance in commensal strains found in the intestinal microbiota of animals. The contamination of food from animals, such as poultry products, presumably led to the VRE colonization seen in many healthy individuals from European countries. In the United States, on the other hand, glycopeptides were never approved for animal feed use, and VRE carriage was not detected (except the endogenously resistant species *E. gallinarum* and *E. casseliflavus*) outside the health care setting, at least early on. The widespread use of vancomycin in the hospital setting is likely one of the culprits, along with the widespread broad-spectrum cephalosporin use, for the rapid selection and proliferation of VRE within this environment. The proportion of *E. faecium* among enterococcal isolates from health care–associated infections is significant because this species has accounted for 25% of all enterococci, as reported by the National Healthcare Safety Network of the Centers for Disease Control and Prevention (CDC).[9] About 80% of *E. faecium* strains are vancomycin resistant, and 90% of them are also ampicillin resistant.

In the last 1 to 2 decades, the evolution of *E. faecium* in the European Union has followed the earlier trend in the United States. Namely, there has been spread of a major hospital-adapted *E. faecium* subcluster (largely CC17), which typically shows higher levels of resistance to ampicillin than non-CC17 strains, with subsequent acquisition of vancomycin resistance by these ampicillin-resistant strains. Among European Union countries, the overall mean percentage of vancomycin resistance among *E. faecium* isolates causing invasive infections showed a slight increase from 9% in 2013 to 11.8% in 2016 albeit with considerable variability, that is, four European countries had rates of vancomycin resistance between 5% and 10%, seven between 10% and 25%, and seven >25% but <50% (European Antimicrobial Resistance Surveillance System, www.ecdc.europa.eu 2017 report).

Another phenomenon described in *E. faecalis* and *E. faecium* is the existence of strains that can only sustain growth in the presence of vancomycin, so-called vancomycin-dependent enterococci (VDE), or when supplemented with the dipeptide D-alanyl-D-alanine. VDE strains have an inactive D-alanine-D-alanine ligase (and thus do not produce D-alanyl-D-alanine) but, with vancomycin exposure, are able to synthesize cell wall using the D-alanine-D-lactate ligase produced from their *vanA* or *vanB* gene cluster. When vancomycin is not present, these precursors are not produced and the organism cannot grow. Dependence on vancomycin has been reported after prolonged exposure and appears to be related to mutations in the gene *ddl,* leading to loss of the cell's endogenous D-alanine-D-alanine ligase and loss of peptidoglycan synthesis. VDE strains can revert to vancomycin-independent (and resistant) growth, either by reverting the mutation in the *ddl* gene or by constitutively expressing their *van* genes, which leads to D-alanine-D-lactase ligase activity and peptidoglycan synthesis is restored. VDE strains seem to be extremely rare and treatment involves stopping vancomycin and following closely because the isolates revert readily to a nondependent phenotype.

Staphylococcus aureus

Heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA)/VISA. As mentioned earlier, the different phenotypes of decreased susceptibility in *S. aureus* isolates include VISA/hVISA and VRSA. Because the disk diffusion method only detects strains with very high vancomycin MICs (i.e., VRSA) and fails to detect VISA isolates, MIC determinations by agar or broth dilution or by Etest (bioMérieux, Marcy l'Étoile, France) (a gradient diffusion method using antibiotic impregnated strips) are recommended for vancomycin susceptibility. In 2006, and to improve the correlation of the in vitro susceptibility assessment with clinical response, the CLSI decreased the vancomycin MIC breakpoints for *S. aureus* to be susceptible at ≤2 μg/mL, intermediate at 4–8 μg/mL, and resistant at ≥16 μg/mL. It should be noted that VISA isolates also display decreased susceptibility to teicoplanin (MIC ≥8 μg/mL)[10] and that *S. aureus* strains with decreased susceptibility to teicoplanin, while remaining susceptible to vancomycin, were reported before the emergence of VISA isolates. The combination of vancomycin plus β-lactams (e.g., nafcillin, cefazolin, and ceftaroline) showed synergistic activity against hVISA and VISA isolates with an in vitro infection model,[11,12] but conflicting data were found in different animal models using oxacillin[13] and ceftobiprole.[14] *S. aureus* isolates exhibiting vancomycin MICs within the susceptible range might still have another form of decreased susceptibility to vancomycin, a phenomenon called heteroresistance. hVISA are considered precursors of VISA isolates having the same but less pronounced changes associated with decreased susceptibility to vancomycin. It is recognized that hVISA strains are more often encountered in clinical practice than VISA isolates. The exact prevalence of these isolates has been difficult to establish largely because the only reliable manner to detect hVISA isolates is by population analysis (see later), a technique that is too cumbersome for clinical laboratories. Geographic variability in the hVISA prevalence is seen, which may be related to clonal spread in certain institutions.

A systematic literature review of 91 published studies found an overall increase of hVISA and VISA strains among thousands of MRSA tested—from 4.7% and 2% before 2006 to 7% and 7.9% between 2010 and 2014, respectively.[15] In this report the prevalence of hVISA/VISA strains was more common in Asia than in Europe/America and in blood culture samples than from other clinical specimen; MRSA isolates within the sequence types (ST) 239 and ST5 and those carrying staphylococcal cassette chromosome (SCC)*mec*II and III were the most prevalent among VISA strains. Increasing rates of hVISA are usually seen among isolates with higher vancomycin MIC; one study found a rate of 10.5% in those MRSA strains with an MIC of 2 μg/mL and only 0.1% in those with an MIC of 1 μg/mL determined by Etest.[16]

Mechanisms of decreased susceptibility to vancomycin. The exact mechanism and genetic basis underlying the decreased susceptibility to vancomycin of VISA isolates remains a subject of active investigation, but none of these strains carries the vancomycin-resistance genes found in enterococci. A common feature of VISA isolates appears to be the presence of a thickened cell wall; indeed, it has been postulated that the D-alanyl-D-alanine–ending precursors of thickened cell walls may trap vancomycin molecules in outer layers of the peptidoglycan, allowing newly emerged peptidoglycan precursors to be used for transglycosylation and transpeptidation reactions (close to the cytoplasmic membrane).[10] Other common phenotypic characteristics of the VISA strains include an increased cell wall turnover, decreased autolytic activity, an increased positive cell wall charge (presumably responsible also for decreased susceptibility to daptomycin), and reduced accessory gene regulator (Agr) functionality. The hVISA phenotype appears to be a precursor of VISAs and has been associated with mutations in a two-component regulatory system (TCS, designated glycopeptide-resistance–associated sensor/regulator [GraSR]) that controls several genes involved in cell wall homeostasis, including the susceptibility of *S. aureus* to lysozyme and cationic antimicrobial peptides. Further sequential mutations in other TCSs have been shown to be responsible for full expression of the VISA phenotype.

One of these TCSs is vancomycin-resistance–associated sensor/regulator (VraSR), consisting of the histidine-kinase VraS and the response regulator VraR that are involved in the regulation of transcription of genes encoding proteins and enzymes participating in cell wall turnover (designated cell wall regulon, ≈30 genes) and cell envelope stress response.[17] Another TCS associated with full expression of the VISA phenotype is WalKR (also designated YycFG; WalK is the histidine kinase, and WalR is the response regulator), which appears to contribute to decreased autolytic activity.[18,19] Mutations in these TCSs are associated with increased vancomycin MICs and cell wall thickness and with significant reduction in autolytic activity and biofilm formation.[19] Of note, alteration of some of these two-component regulatory systems is also associated with decreased susceptibility to daptomycin, suggesting a common pathway of resistance to cell envelope–acting antimicrobial agents.

The *agr* gene operon in *S. aureus* encodes a global regulatory system that coordinates several virulence pathways. The loss of *agr* functionality (*agr* genotype II) predominates among VISA strains and has been linked to a survival advantage in the presence of vancomycin and to vancomycin treatment failure.[20–22] Because downregulation of expression of the *dhl* gene (encoding delta-hemolysin) was seen in both hVISA and VISA isolates, the delta-hemolysin assay has been proposed as a biomarker for reduced vancomycin susceptibility.[23]

Laboratory detection of hVISA strains. Heteroresistance means that only some of cells in a culture, sometimes as low as 1 in 100,000 bacteria, are able to grow at a higher concentration of vancomycin (>2 μg/mL) on vancomycin-containing agar. When testing these isolates at a standard inoculum (5×10^4 per well with broth microdilution MIC), this subpopulation of cells will not be detected, and the vancomycin MIC will fall within the susceptibility range most of the time. Therefore conventional susceptibility tests would not identify heteroresistance until a much higher fraction of resistant cells is present; population analysis profile (PAP; determination of the number of surviving cells at increasing antibiotic concentrations) is required for detection. This test was later modified by calculating the area under the time-concentration curve (AUC) of the original PAP result and comparing it with the PAP of the reference hVISA strain Mu3; a PAP/AUC ratio <0.9, from 0.9 to 1.3, and >1.3 defines a strain as vancomycin-susceptible *S. aureus* (VSSA), hVISA, and VISA, respectively.[24] As mentioned earlier, this test is not suitable for clinical practice; thus several screening methods have been studied for routine laboratory conditions to detect these strains using a higher inoculum, prolonged incubation, or more nutritious agar. In routine laboratory conditions the "macro" Etest method (MET) may be used to identify hVISA with a fair degree of accuracy. The method uses a higher inoculum (equivalent to a 2 McFarland standard) that is streaked onto the surface of a brain-heart infusion agar to which vancomycin and teicoplanin Etest strips are applied; readings take place at 24 and 48 hours and are considered positive if vancomycin and teicoplanin MICs are ≥8 μg/mL or the teicoplanin MIC is ≥12 μg/mL.[25] Another method for hVISA screening uses a double-strip Etest combining vancomycin and teicoplanin with a nutritional supplement (Etest GRD [bioMérieux, Marcy l'Étoile, France]), a Mueller-Hinton 5% blood agar with standard inoculum, and a 24- and 48-hour reading; an MIC of vancomycin or teicoplanin ≥8 μg/mL by one of these methods for a strain that tested as susceptible for standard methods defines an hVISA strain.[26] Both the MET and Etest GRD methods may be used to identify hVISA strains with a fair degree of accuracy, although some differences in sensitivity and specificity with the population analysis exist.[25,27] The vancomycin and teicoplanin MIC determined by broth macrodilution method (10^5 CFU in 1 mL) or agar testing when read at 48 hours could detect a significantly higher number of strains classified as hVISA and VISA than the standard microdilution method; the higher number of bacteria used in the broth macrodilution method likely explains these findings.[28] Several other screening tests have been developed with variable sensitivity, but the potential clinical impact in the management of patients with deep-seated *S. aureus* infections is unclear.

Clinical impact of strains with increased vancomycin minimal inhibitory concentration. Several studies have reported a rise in the vancomycin MICs over time, a phenomenon also known as vancomycin "MIC creep," although the use of this terminology is still controversial. The increase in vancomycin MICs might be explained by replacement of local MRSA clones with strains with higher vancomycin MICs rather than by a vancomycin "creep" per se within an MRSA clone.[29] In fact, this vancomycin MIC creep phenomenon can be seen in centers where vancomycin is frequently prescribed and/or in the setting of a specific clone predominance with high vancomycin MIC; however, there does not appear to be increased resistance overall in *S. aureus* around the world.

There is evidence that VISA isolates (MICs, 4–8 μg/mL) are associated with therapeutic failure. In addition, poorer clinical outcomes have been associated with hVISA isolates compared with non-hVISA isolates among patients treated with vancomycin in many but not in all clinical studies. A decrease in the virulence properties of hVISA isolates has been suggested by some studies that reported lower rates of invasive infections and diminished risk for septic shock compared with VSSA strains.[30,31]

It is also important to note that a poor response to vancomycin has been documented in an experimental endocarditis model using hVISA strains and that decreased in vitro killing by vancomycin (likely to be seen with hVISA isolates) has been significantly associated with worse clinical outcome,[32,33] although time-kill experiments cannot be performed by most laboratories.

Several initial retrospective[32–35] and prospective[36,37] studies and meta-analysis[38] have reported unsatisfactory response to vancomycin in the treatment of invasive MRSA infections, including bacteremia caused by strains with vancomycin MICs >1.5 μg/mL. However, another meta-analysis[39] and some recent prospective studies[40,41] have failed to confirm such association. Part of the dilemma likely arises from the inherent variability in the results of MIC testing, with the CLSI criteria considering a result accurate to ± one twofold dilution. Moreover, vancomycin MICs measured by Etest and by some automated methods are generally one-half to one dilution higher and one to two dilutions lower than the gold standard broth microdilution method, respectively.[42] Thus the exact meaning of a high vancomycin MIC (but within the susceptible range) among invasive *S. aureus* isolates is still a matter of debate. Current Infectious Diseases Society of America (IDSA) practice guidelines for the treatment of MRSA infections suggest that, for strains with vancomycin MIC ≤2 μg/mL, a decision to continue vancomycin treatment should depend more on clinical response than on the MIC value.[43]

Vancomycin-resistant *Staphylococcus aureus*. Another mechanism of decreased susceptibility to vancomycin defined as "true" vancomycin resistance (MIC >16 μg/mL) was reported in 2002, primarily in the United States (mainly in the state of Michigan) with 14 VRSA clinical isolates reported to date.[44,45] These isolates display a median vancomycin MIC of 512 μg/mL, with a range of 32 to 1024 μg/mL. Most patients from whom VRSA were isolated had chronic underlying diseases, prior or current MRSA and VRE colonization or infection, and extensive exposure to vancomycin. All the strains had acquired the enterococcal *vanA* gene, and most of them belonged to the MRSA lineage USA100 containing SCC*mec* type II within clonal cluster 5.[44] However, a community-associated ST8 strain of VRSA was reported in Brazil,[46] with acquisition of the *vanA* gene cluster also by methicillin-susceptible *S. aureus* (MSSA).[47] Molecular studies of the transfer of the *vanA* cluster from enterococci to these MRSA isolates can result in replication of the actual enterococcal *vanA* plasmid in the new staphylococcal host after plasmid transfer by conjugation (less common) or transposition of the Tn*1546* element to a staphylococcal plasmid with subsequent loss of the enterococcal plasmid.[47,48] Infection control measures, with perhaps decreased transmissibility or fitness, appear to have controlled the spread of these isolates. VRSA strains have been reported, albeit very rarely, from other parts of the world, such as India, Iran, Portugal, Guatemala, and Brazil. Because cocolonization with MRSA and VRE strains is not a rare event and the population of *S. aureus* that can acquire the *vanA*-containing enterococcal plasmid is very widespread, it is likely that reports of VRSA strains will continue in the future.

Coagulase-Negative Staphylococci

Studies in the 1980s found high MICs of teicoplanin, sometimes within the resistance range, among methicillin-resistant *Staphylococcus haemolyticus*. Overall, MICs of teicoplanin against coagulase-negative staphylococci show a wide range, occasionally higher than the CLSI resistance breakpoint (MIC ≥32 μg/mL). For this group of organisms, MICs of vancomycin are generally less variable and within the susceptible range (susceptible at ≤4 μg/mL, intermediate at 8–16 μg/mL, and resistant at ≥32 μg/mL by CLSI, and susceptible at ≤4 μg/mL and resistant at >4 μg/mL by EUCAST). Overall, reduced vancomycin susceptibility due to heterogeneous resistance to glycopeptides has been reported between 7% and 18% of the studied coagulase-negative staphylococci isolates, most of which were associated with glycopeptide exposure.[49] As described with *S. aureus,* the mechanism for reduced glycopeptide susceptibility among coagulase-negative strains appears to be related to changes in cell wall homeostasis leading to thickened cell walls.

Other Gram-Positive Bacteria

Vancomycin-resistant pneumococci have not been reported, although some series have found reduced bactericidal activity of vancomycin, that is, tolerance, in up to 8.7% of isolates.[50,51] The first *S. pneumoniae* isolate showing this phenotype was isolated from a patient with meningitis and named the "Tupelo" strain. Tolerant strains appear to be more commonly resistant to other antibiotics and have been recovered as colonizers or causing invasive disease with similar frequency.[50] The clinical implications of this phenomenon are difficult to assess; an apparent vancomycin (with cefotaxime) therapeutic failure for pneumococcal meningitis caused by a vancomycin-tolerant strain has been reported and, in a retrospective analysis, vancomycin-tolerant isolates causing meningitis were associated with worse clinical outcome.[50] The mechanism for tolerance is not well understood but may involve a deficiency in LytA (a cell-wall hydrolase with major autolytic function) activity or changes in the CiaRH system, which has an established lysis protection role. Exposure of *S. pneumoniae* to vancomycin induces the transcription of a four-gene operon named *ptv* (phenotypic tolerance to vancomycin), which might act by modulating cell membrane properties.[52]

Although less often associated with human disease, the genera *Leuconostoc* and *Pediococcus,* and certain *Lactobacillus* spp. (*L. rhamnosus, L. casei,* and *L. plantarum*) are intrinsically resistance to glycopeptides. The mechanism of resistance also involves production of peptidoglycan precursors that terminate in D-alanyl-D-lactate. The D-alanyl-D-lactate ligase of these organisms, however, is only remotely related to the VanA or VanB ligase found in VRE strains. Another gram-positive organism, *E. rhusiopathiae,* is also typically vancomycin resistant.

Clinical Pharmacodynamics and Pharmacokinetics

A considerable number of studies have found that the bactericidal activity of vancomycin is concentration independent once a concentration of four to five times the MIC for the organism is reached. Finding the pharmacodynamic parameter able to predict vancomycin treatment success has not been straightforward,[53] but it seems that the 24-hour AUC/MIC ratio is the best predictor of efficacy in clinical studies.[54,55] For example, in patients with MRSA pneumonia, higher rates of clinical success and more rapid bacterial eradication were associated with achievement of an AUC_{24}/MIC ratio ≥400.[55] Of note, no relationship between percentage of time higher than the MIC and response was found in this study.[55]

For the correct interpretation of the data related to studies addressing the pharmacodynamics of vancomycin, the following considerations should be taken into account: (1) Because vancomycin susceptibility is determined by methods that significantly differ from the standard broth microdilution method (e.g., vancomycin MICs by Etest are onefold or 0.5–1.5 $\log_2$ dilution higher than broth microdilution MICs, whereas automated methods such as Sensititre [Thermo Scientific/TREK Diagnostic Systems; Oakwood, OH] and Vitek-2 [BioMérieux, Durham, NC], tend to underestimate the MICs value), small variations in the MIC will represent significant changes in the AUC/MIC ratio; (2) trough level is used as a surrogate marker for AUC because the latter is not calculated in clinical practice; (3) in patients with serious infections, especially those caused by MRSA, vancomycin levels may be used to modify the dose to attain the target serum level; (4) maximal optimization of the vancomycin dosing does not seem to be required for less serious MRSA infections, such as most acute bacterial skin and skin structure infections (ABSSSI), for which dosing based on renal function and actual patient weight is likely to be adequate; (5) measurement of the peak value is not recommended; and (6) low trough vancomycin levels (<10 μg/mL) have been associated with development of hVISA isolates.

For serious infections caused by MRSA, such as endocarditis, bacteremia, arthritis, osteomyelitis, meningitis, pneumonia, and severe ABSSSI, the consensus from the IDSA, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists published in 2009 recommends trough vancomycin concentration between 15 and 20 μg/mL.[56] In those receiving vancomycin as a continuous infusion, the recommended target plateau concentration has been 20 to 25 μg/mL. The range of recommended trough serum levels between 15 and 20 μg/mL has been correlated with a 24-hour AUC (±standard deviation) of 418 ±152,[46] which will achieve a vancomycin AUC/MIC ratio ≥400 if the MIC of the infecting strain is ≤1 μg/mL. To attain these levels, the vancomycin dose is usually 15 to 20 mg/kg every 8 to 12 hours based on actual body weight in patients with normal renal function. Indeed, a recent prospective study found that dosing vancomycin based on AUC estimation rather than on trough concentration was associated with lower rates of nephrotoxicity, shorter duration of therapy, and lower overall vancomycin exposure.[57]

The need to target an AUC/MIC ratio ≥400 was initially based on clinical studies in patients with MRSA lower respiratory tract infections reporting higher rates of clinical success and more rapid bacterial eradication in those patients with achievement of an AUC/MIC ratio ≥400, where vancomycin MICs were determined by broth microdilution.[55] In a single-center and retrospective study of 320 patients with MRSA bacteremia treated with vancomycin, the group of patients that did not reach an AUC/MIC ratio of at least 421 was associated with a significantly higher failure rate than those that did achieve this cutoff (61% vs. 49%, $P = .038$) (MIC measured by broth microdilution).[58] More recently, a group of researchers reported a retrospective and then a prospective study of patients with MRSA bacteremia treated with vancomycin, demonstrating a significant association between a low AUC/MIC ratio and treatment failure; in both studies and for broth microdilution and E-tests susceptibility tests, the AUC/MIC cut-off values were between 392 and 430.[59,60] In accordance, a systemic review of published studies, including 916 patients with different types of MRSA infections, found that a high AUC/MIC ratio was significantly associated with lower clinical failure and mortality; the authors proposed an AUC/MIC ratio of 400 as a reasonable target (MIC measured by either broth microdilution or by E-test).[61]

Even though vancomycin AUC is not measured in clinical practice, it can be estimated with the use of several computer programs having patient information such as the trough vancomycin level at steady state, the estimated volume of distribution, and renal function, among others. It has been shown that a significant proportion of patients can achieve an AUC/MIC ratio ≥400 with a trough concentration <15 μg/mL; therefore the target of at least 15 μg/mL may overexpose patients to vancomycin and its related nephrotoxicity risk.[62] In this regard, a Monte Carlo simulation model suggested that targeting a vancomycin trough level >15 μg/mL may not be necessary for MRSA strains with an MIC of 0.5 μg/mL.[63] On the other hand, and as previously shown[64] for strains with vancomycin MICs of 2 μg/mL, the probability of achieving the target AUC/MIC ratio is 57% and 15% for vancomycin dosing of 2 g and 1 g every 12 hours, respectively,[63] implying that many of these patients would be given vancomycin doses ≥4 g/day to achieve the AUC/MIC target for severe MRSA infections.

Analyzing the pharmacodynamic AUC_{24}/MIC parameter for vancomycin efficacy in infections caused by enterococci, a retrospective single-center study found that among 57 patients with enterococcal bacteremia (32 *E. faecium*, 21 *E. faecalis*, and 4 other enterococci) treated with vancomycin, the 30-day mortality rate was significantly lower in those with an AUC/MIC ratio (MIC measured by Etest) ≥389.[65]

Of interest, a recent retrospective study showed that *S. aureus* isolates tolerant to vancomycin (defined as an MBC/MIC ratio ≥32 by broth microdilution) were significantly associated with vancomycin failure in patients with *S. aureus* bacteremia. This association was even maintained in patients with MSSA bacteremia treated with β-lactams, suggesting some fundamental difference in the organisms' response to these antibiotics.[66]

Besides the management of serious staphylococcal infections, other special circumstances where it seems prudent to measure vancomycin concentrations include, for the most part, patients concomitantly receiving another nephrotoxic agent, especially aminoglycosides; patients receiving high-dose vancomycin (e.g., very obese patients); those with rapidly changing renal function; and subjects undergoing hemodialysis, especially if high-flux membranes are used. Other situations include the measurement of cerebrospinal fluid (CSF) levels in patients receiving vancomycin for central nervous system (CNS) infection, whether by intrathecal, intraventricular, or intravenous (IV) routes (see later); vancomycin administration in neonates; and in extremely ill patients or in the presence of possible therapeutic failure, to ensure adequate drug presence.

The in vitro postantibiotic effect of vancomycin against staphylococci and enterococci has been described mostly as of short duration. As with β-lactams (i.e., nafcillin), the in vitro bactericidal activity of vancomycin is reduced when a high inoculum of *S. aureus* is used. The activity of vancomycin is affected, at least to some degree, by the presence of biofilm, which is often seen in the setting of medical device–related infection.

A study comparing innovator vancomycin product with vancomycin generics raised concern that generic vancomycin was less potent, possibly due to higher amounts of crystalline degradation products (CDP-1).[67] However, the US Food and Drug Administration (FDA) laboratories tested six commercially available vancomycin generic products and found minimal amounts of CDP-1,[68] and no statistically significant differences were observed between these product and the innovator molecule in an endocarditis animal model.[69]

Distribution

Vancomycin pharmacokinetics in adults is best described by a two- or three-compartment model. After a single IV dose of 0.5 g and 1 g in normal volunteers, vancomycin concentrations achieved in serum at 2 hours are about 10 μg/mL and 25 μg/mL, respectively, which decrease to 2 μg/mL by 6 to 8 hours after 0.5 g and by 12 hours after 1 g.[70] The drug shows a short distribution phase of about 7 minutes and then an intermediate phase of serum decline (half-life of 30–90 minutes). This is followed by a highly variable elimination phase of 3 to 11 hours (averaging 6 hours) in subjects with normal renal function; in this phase the vancomycin concentration is inversely affected by the creatinine clearance. The volume of distribution of vancomycin at steady state ranges from 390 to 970 mL/kg in studies including adults, children, and infants; and the percentage protein binding in serum varies between 30% and 55%.

Trough vancomycin serum level should be obtained at steady state, usually before the fourth dose, although steady state may occur earlier if a loading dose is used. When obtaining a trough vancomycin level, it is important to collect the sample within 30 minutes before administration because drawing too early is a common cause of elevated vancomycin levels, which can lead to inappropriate dosing change.

Penetration of vancomycin into the CSF is minimal in the absence of meningeal inflammation,[71] which usually results in higher vancomycin passage into the CSF in patients with meningitis than in those with ventriculitis. In adults with ventriculitis CSF penetration ranges from 5% to 10% after IV administration, probably resulting in subtherapeutic levels; for this reason, it is important to send CSF for determination of vancomycin levels when using it to treat CSF infections. In children with meningitis the vancomycin concentration in CSF has ranged from 14% to 28% (mean, 21%) of that in serum after a vancomycin dose of 60 mg/kg/day in conjunction with dexamethasone; this concentration is considered adequate and predictable. Dexamethasone, through reduction of meningeal inflammation, may decrease vancomycin CSF penetration, which was associated with delayed CSF sterilization in experimental meningitis, although with higher doses, therapeutic CSF levels were achieved. Low vancomycin CSF levels have been associated with clinical failures in adults with pneumococcal meningitis, although it has been difficult to establish a clear correlation between vancomycin CSF concentration and cure.[72] To overcome the relatively poor vancomycin CSF penetration, high-dose vancomycin administered in continuous infusion (50–60 mg/kg/day after a loading dose of 15 mg/kg) has been evaluated in adults with meningitis, resulting in a CSF penetration rate of a mean of 30%[73] to 48%.[74]

Animal studies have documented high concentrations of vancomycin in kidney, liver, and spleen of rats, but data on concentrations in the equivalent human organs are limited. A relatively good concentration was found in kidney, liver, aorta, lung, heart tissue, and in abscess fluid in a patient after several vancomycin doses, and the concentration of vancomycin in soft tissue appears to be lower in diabetic than nondiabetic patients. Vancomycin concentrations are generally adequate to treat susceptible organisms in fluids from the pericardial, ascitic, pleural, and synovial fluids/spaces.[71] Concentrations in heart valve, subcutaneous tissue, and muscle were found to be 52%, 29%, and 27% of the concomitant serum level, respectively, 6 hours after a single vancomycin dose.[75] In patients undergoing vascular surgery receiving continuous vancomycin infusion after a loading dose, serum/tissue concentration ratios of 0.22 and 0.50 for fat and vessel wall, respectively, were reported.[76] These results appear to support adequate vancomycin penetration into vascular tissue but probably not into fat, at least with the mentioned dosing. Heterogeneous diffusion of vancomycin into vegetations has been demonstrated in experimental endocarditis models.

Studies addressing vancomycin concentrations in lung tissue found significant variability, depending mainly on the sample used and the presence or not of inflamed lung tissue. Moreover, indirect measurements of vancomycin concentrations have been used for distal airways and alveoli. Twenty percent to 30% of the serum concentration has been reported in lung tissue. Others have reported its penetration into the epithelial lining fluid as approximately 16% that of concomitant vancomycin serum levels. In another study vancomycin serum trough levels >20 μg/mL were required to have detectable concentration in the epithelial lining fluid in patients with MRSA pneumonia. In contrast, the vancomycin epithelial lining fluid concentrations were 50% of those obtained in serum in 10 healthy volunteers after a 1-g infusion; however, a high degree of variability was found among the pharmacokinetic results.[77] Patients with higher concentrations of albumin in the bronchoalveolar lavage had higher concentrations of vancomycin, probably linked to inflammation.

Although vancomycin appears to penetrate into bile, it is not concentrated there. Vancomycin, like many other antimicrobial agents, penetrates very poorly into the aqueous humor of the eye. Human studies evaluating the concentration of vancomycin in infected and uninfected bone have reported highly variable results. A mean concentration of vancomycin in the sternum of 10.4 μg/g 60 minutes after administration of 15 mg/kg has been documented in subjects undergoing cardiac surgery.[78] In another study the penetration of vancomycin appeared to be satisfactory and suboptimal into the cancellous and the cortical bone, respectively.[79] Of note, this study also reported higher vancomycin bone concentrations in association with increased local inflammatory markers, likely secondary to bone inflammatory conditions. More recently, adults undergoing total knee replacement receiving vancomycin as prophylaxis were evaluated, with solid tissue concentrations measured by microdialysis chips; a delayed and low concentration of vancomycin in bone was found, with lower levels in the cortical than in the cancellous bone, with a time to reach 2 μg/mL of 110 and 27 minutes, respectively.[80] Nonetheless, it has been difficult to find a correlation between antibiotic bone concentrations and clinical outcome.

Transplacental passage of vancomycin during the second trimester of pregnancy and at time of delivery has been documented, and the concentration of vancomycin in breast milk 4 hours after IV infusion was 12.7 μg/mL. This could lead to a potential infant oral dose of 1.9 mg/kg/day.

Excretion

Vancomycin is primarily excreted unchanged via the kidneys by glomerular filtration, with no direct evidence of tubular secretion or resorption.[71] A linear correlation between creatinine clearance and vancomycin levels was recognized early on in patients with varying degrees of renal dysfunction. Some investigators report a lower rate of vancomycin clearance in patients with hepatic dysfunction, and variable levels of vancomycin have been found in stool samples of patients on IV vancomycin only after 5 days of therapy, although vancomycin does not appear to have enterohepatic circulation. However, nonrenal clearance does not appear to account for >5% of the total drug clearance, and therefore dose adjustment in patients with hepatic dysfunction alone is unlikely to be necessary.

Administration

Vancomycin is given intravenously for the treatment of systemic infections caused by susceptible organisms. In certain circumstances vancomycin can be administered through oral, intraperitoneal, intrathecal or intraventricular, and intraocular routes, but intramuscular injection is not recommended because it causes severe local pain. Vancomycin is poorly absorbed when administered orally, yielding high fecal concentrations (1406 ± 1164 μg/g of feces) using doses of 125 mg every 6 hours; in the presence of diffuse colonic inflammation and renal insufficiency, detectable levels of vancomycin may be obtained in serum, but monitoring drug levels does not seem necessary.

For IV administration, vancomycin is generally diluted in 100 to 250 mL of 5% dextrose or 0.9% saline solution with a concentration ≤5 mg/mL and infused at a rate not exceeding 15 mg/min (i.e., 0.5 g and 1 g over 30 and 60 minutes, respectively) to minimize the occurrence of infusion-related toxicities. Antihistamines may be used to reduce the incidence of red man (or red neck) syndrome, characterized by an acute onset of an erythematous rash affecting the upper trunk and neck during or at the end of an infusion, which, when seen, is usually associated with rapid infusion or a high vancomycin dose. The usual recommended IV dose in adults with normal renal function is 30 mg/kg/day divided into two or four doses (typically, 500 mg every 6 hours or 1 g every 12 hours). Based on pharmacodynamics studies, the need for higher trough levels (between 15 and 20 μg/mL) in the setting of severe MRSA infections has been reflected in a dosing recommendation of 15 to 20 mg/kg every 8 to 12 hours; this dose should be based on actual body weight, not exceeding 2 g per dose (Table 30.1). Continuous infusion at a dose of 30 mg/kg/day after a loading dose of 15 mg/kg also has also been used. This mode of administration appeared to be associated with lower rates of nephrotoxicity but not with increased efficacy[81]; prospective randomized studies are needed.

A few studies have evaluated the use of a loading dose of 25 to 30 mg/kg (at an infusion rate of 500 mg/h) or of 2 g, particularly in suspected severe MRSA disease, such as endocarditis, meningitis, pneumonia, or sepsis, to achieve higher trough concentrations earlier in therapy,[82,83] which has been associated with better initial outcome.[34,64] Prospective studies to address this therapeutic issue would be needed to make firmer recommendation on clinical criteria but is a logical pharmacologic approach.

Because obese patients were found to have increased volumes of distribution, higher renal clearance, and probably lower levels of free vancomycin in serum,[84] these individuals should receive vancomycin based on their actual total body weight instead of their ideal weight. To avoid very high peak values, a more frequent dosing schedule should be considered, and serum concentration should be obtained routinely

TABLE 30.1 Route of Administration, Recommended Dosages, and Infusions of Vancomycin, Teicoplanin, Telavancin, Dalbavancin, and Oritavancin

DRUG	ROUTE OF ADMINISTRATION	RECOMMENDED DOSAGE (ADULTS)	INFUSION	COMMENTS
Vancomycin	Intravenous	The average dose is 15–20 mg/kg q8–12h. If continuous infusion is indicated, the daily dose is 30 mg/kg after a loading dose of 15 mg/kg.	Should use a concentration of ≤5 mg/mL and a rate of <15 mg/min (i.e., 1 g over 60 min)	For many infections, 15 mg/kg q12h is adequate. For severe MRSA infections, a loading dose (see text) should be considered and, although still debated, current recommendations for monitoring include a trough between 15–20 µg/mL or an AUC/MIC ratio of ≥400.
	Oral	125–500 mg q6h		Severe *Clostridioides difficile* (formerly *Clostridium difficile*) colitis
Teicoplanin	Intravenous or intramuscular	Loading dose: 400 mg (6 mg/kg) q12h for 3 doses Maintenance*:* 400 mg q24h	Can be administered in bolus	For serious infections: 800 mg (up to 12 mg/kg) q12h for 3 times and then q24h
	Oral	100–400 mg q12h		Severe *C. difficile* colitis
Telavancin	Intravenous	10 mg/kg/day	1-hour infusion	Supplied as a 25-mg or 750-mg vial to be reconstituted with 15 mL and 45 mL, respectively, for a concentration of about 15 mg/mL
Dalbavancin	Intravenous	Twice-weekly regimen: 1000 mg then 500 mg 1 week later. One-time dosing: 1500 mg	30-min infusion	Supplied in 500-mg vials to be diluted in 5% dextrose for a final concentration of 1–5 mg/mL
Oritavancin	Intravenous	1200-mg single dose	3 hours	Supplied in 400-mg vials to be diluted (only in 5% dextrose) to a concentration of 1.2 mg/mL

AUC/MIC, Area under the curve/minimal inhibitory concentration; *MRSA,* methicillin-resistant *Staphylococcus aureus.*

when high doses are used. Significantly higher vancomycin clearance has been shown in burn patients, suggesting also the need for higher and more frequent doses and monitoring of serum levels in this group of patients. Even though a significant decrease of serum vancomycin levels during cardiopulmonary bypass has been documented, concentrations were maintained within the therapeutic range after a 15-mg/kg dose of this drug administered intravenously 1 hour before skin incision. No dosage adjustment appears to be necessary during pregnancy.

The dose of IV vancomycin for children with non-CNS infections should be 10 mg/kg every 6 hours, and, for infections involving the CNS and other serious infections, it should be 15 mg/kg every 6 hours.[85] In children age 1 month to 12 years with normal renal function, an increase in the prescribing dose from 45 mg/kg/day divided every 8 hours to 60 mg/kg/day divided every 6 hours was correlated with higher initial trough levels. This decreased the percentage of patients with trough levels <5 µg/mL from 38% to 17%.[86] However, a retrospective study found that about 60% of children (median age, 6 years) receiving empirical treatment with vancomycin attained subtherapeutic level (<15 µg/mL) even when high doses such as 20 mg/kg every 6 to 8 hours were used, probably secondary to increased creatinine clearance in this population. In particular, age younger than 12 years was significantly associated with initial low trough levels (<10 µg/mL) compared with those older than 12 years, even after adjustment for creatinine clearance.[87]

Neonates and young infants appear to have a lower vancomycin clearance rate. For neonates younger than 1 week, the recommended dose is 15 mg/kg every 12 hours; and for those between age 1 week and 30 days, it is 15 mg/kg every 8 hours.[85]

In premature infants longer intervals may be required because the clearance of vancomycin correlates with postconceptional age.[88] The classic dosing schedule in premature neonates has been to dose vancomycin 15 mg/kg every 12 or 18 hours, and every 8 or 12 hours when the postconceptional age is 29 weeks or younger and 30 to 44 weeks, respectively. However, because this dosing guideline aimed for a trough concentration between 5 and 10 µg/mL, and in one study 30% of neonates had serum concentrations <5 µg/mL, higher doses have been suggested.[89] The percentage of neonates (average gestational age, 28.2 weeks) achieving a trough of 10 to 20 µg/mL has been only 25% after empirical vancomycin treatment in the intensive care unit (ICU); among those who achieved the therapeutic goal, the median daily dose was 30 mg/kg.[90] It is also recommended to closely monitor serum concentrations of vancomycin in these patients.

After intraperitoneal administration of vancomycin in patients on continuous ambulatory peritoneal dialysis (CAPD), the concentrations of vancomycin were still 7 ± 1.2 µg/mL and 3.6 ± 1.1 µg/mL for serum and dialysate, respectively, 7 days after the intraperitoneal administration of 30 mg/kg (in 2 L of dialysate, with 6 hours' retention/settling).[91] An intermittent dosing schedule (one exchange daily) targeting a serum trough level >15 µg/mL has been recommended using a intraperitoneal vancomycin dose of 15 to 30 mg/kg in long dwell (at least 6 hours) every 5 to 7 days (patients on automated peritoneal dialysis may require additional doses); the dosing interval will depend on patients' residual renal function and peritoneum permeability.[92] A continuous (in each dialysate exchange) dosing regimen (loading dose of 30 mg/kg, followed by a maintenance dose of 1.5 mg/kg/bag), has also proven to be efficacious in this setting.[92] Conversely, the peritoneal dialysate concentration of vancomycin after IV administration alone does not reliably provide adequate levels to treat peritonitis caused by susceptible organisms.[71] The pharmacokinetics of vancomycin in children undergoing CAPD appear to be similar to those described in adults.

Because of concern that CSF levels of vancomycin are inadequate to treat ventriculitis (which can be assessed by sending CSF fluid for level determination), even with active infection, intrathecal or intraventricular administration of vancomycin should be considered, particularly when vancomycin is used as monotherapy. The recommended initial intraventricular dose for the treatment of ventriculitis or shunt-related infections is 5 mg, 10 mg, and 15 to 20 mg in patients with slit, normal-sized, and enlarged ventricles, respectively.[93,94] Immunocompromised patients and those with difficult-to-treat infections might benefit from using the higher dosage of 20 mg/day. Considering the CSF volume in infants, the intraventricular dose should be reduced by about 60% in this population. The recommended dosing frequency of vancomycin depends on the CSF drainage volume; with daily CSF volume drainage of >100 mL, between 50 mL and 100 mL, and <50 mL, the doses should be given every 24, 48, and 72 hours, respectively. Nevertheless, further adjustments based on the CSF levels should be made because of unpredictable kinetics of this drug in the CSF. The recommended optimal vancomycin trough concentration (24 hours after last administration) should be high enough to exceed about 10 to 20 times the microorganism MIC, usually representing target concentrations between 10 and 20 μg/mL[95] However, it has been difficult to clearly find a correlation between levels, toxicity, and efficacy with the usual ventricular dosage of 5 to 20 mg/day[72] For administration of vancomycin into the CSF, the drug may be diluted in sterile 0.9% saline solution to a volume of 1 to 10 mL, at a concentration of 2.5, 5, or 10 mg/mL solution, depending on the dose.[94]

The use of IV vancomycin in patients with postoperative endophthalmitis results in subtherapeutic concentrations in the vitreous. However, after intraocular administration of 1 mg of vancomycin, vitreous concentrations are in the therapeutic range for at least 3 days.

Vancomycin for oral administration is formulated in capsules and oral solution and can be given by mouth or, as needed in case of ileus or toxic megacolon, by nasogastric tube and even via rectal tube (intracolonic administration) or ileostomy. The recommended oral dose for pseudomembranous colitis in adults ranges from 125 mg to 500 mg every 6 hours, depending on the severity of the colitis. In children the usual dose is 40 mg/kg/day (not exceeding 2 g/day) divided in three or four doses. For intracolonic administration, 500 mg of vancomycin dissolved in 1 to 2 L of 0.9% saline solution has been infused as a retention enema several times (two to six) a day.

Dosing in Renal Insufficiency

Dosing nomograms have been developed to reflect the more recent recommendation of targeting higher vancomycin trough concentration (between 15 and 20 μg/mL) for severe staphylococcal infections.[43,56] Despite the bedside calculation of the vancomycin dosing, individualized drug monitoring based on a patient's serum levels is required owing to the relatively high interindividual variability in patients with any degree of renal failure.

The recommended daily dose for patients with renal failure not on hemodialysis with a creatinine clearance between 60 to 89 mL/min, 30 and 59 mL/min, and 15 and 29 mL/min are 20 to 30 mg/kg, 10 to 20 mg/kg, and 7 to 10 mg/kg respectively. For those with <15 mL/min, the dose should be 10 mg/kg every 48 hours.[96]

The prediction of vancomycin pharmacokinetics in patients undergoing hemodialysis is difficult; actual body weight, timing of vancomycin administration, residual kidney function, and type of dialysis membranes are among the variables that affect this prediction.[97] The use of a loading dose of 20 to 25 mg/kg, followed by a fixed 500-mg dose during or after high-flux dialysis membranes, has been a commonly used dosing regimen.[98] However, only 28% of the patients were within the target trough vancomycin range of 15 to 20 μg/mL using this dosage. Another dosing schedule for patients on dialysis included a loading dose of 20 mg/kg, followed by 1 g of maintenance during the last hour of dialysis, which obtained a good mean trough of 19 ± 6.6 μg/mL, but 38% of the patients had levels >20 μg/mL.[99] More recently, also including patients on high-flux hemodialysis and using a Monte Carlo simulation method, a new protocol for vancomycin dosing was developed, considering a subject's weight: a 1-g loading dose, 500-mg maintenance (given during the last hour of each dialysis session) dose for patients weighing <70 kg; 1.25 g, followed by 750 mg for those weighing 70 to 100 kg; and 1.5 g, followed by 1 g for those weighing >100 kg; this dosing regimen was prospectively validated to achieve therapeutic serum troughs, with a mean of 17.3 ± 4.0 mg/L, and almost 90% of the maintenance troughs between 10 and 22 μg/mL.[100] The older low-flow membranes have lower ultrafiltration coefficients than high-flux membranes; after a loading dose (15–20 mg/kg), the dose to attain the vancomycin serum target is 15 mg/kg every 3 to 5 days and 7 mg/kg in the last hour of each hemodialysis session with low-flow cellulose acetate and polysulfone membranes, respectively.[101] In addition, trough levels before each dialysis session should be obtained to guide therapy.[97] Because CAPD can decrease the elimination half-life of vancomycin, a modest increase in the IV dose appears necessary in these patients.

It should also be considered that the administration of vancomycin during the last hour of dialysis renders lower serum levels than when administered after dialysis.

The pharmacokinetics of vancomycin in patients managed with intermittent hemodialysis is significantly different from those receiving continuous renal replacement therapy (CRRT). Clearance of vancomycin in patients with acute renal failure undergoing CRRT, such as continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodialysis (CVVHD), is significantly increased. This clearance depends on operational factors, such as the ultrafiltration flow rate and the type of hemofilter. Based on the study of 24 critically ill patients undergoing CVVHD and posterior Monte Carlo simulation, the recommended initial dosing regimen of vancomycin for a target attainment between 15 and 20 μg/mL was 15 mg/kg every 24 hours, after the loading dose.[102,103] However, attainment of desired target concentrations was low, suggesting the importance of therapeutic drug monitoring for further adequacy of vancomycin dosing. Because about 20% of the vancomycin dose is removed during a 12-hour period of CVVH, the recommended maintenance dose of vancomycin is 500 to 750 mg every 12 hours, targeting a steady-state trough concentration of 15 to 20 μg/mL.[104] More recently, vancomycin, in continuous infusion administered based on a nomogram that included the CVVH intensity, achieved therapeutic levels (15–25 μg/mL) in >80% of 52 critically ill adults.[105] Drug removal appears to be higher when continuous venovenous hemodiafiltration (CVVHDF) (≈50%) is used, requiring doses of 750 mg every 12 hours, although drug accumulation has been described. Measurements of vancomycin levels are generally needed for patients on any form of CRRT.

Adverse Reactions

One of the first reports of the clinical use of vancomycin included six patients who developed severe ototoxicity.[106] Most of them were receiving 1 to 2 g of vancomycin per day despite renal insufficiency; when vancomycin levels were measured, values between 80 and 100 μg/mL were observed.[106] After 50 years of clinical use of vancomycin, with more purified material and because of the relatively few cases of confirmed vancomycin-related ototoxicity reported and existing data from animal studies showing no evidence of vancomycin-induced hearing damage, many authors concluded that vancomycin-related ototoxicity was a rare reaction. However, a retrospective study evaluating patients receiving higher doses of vancomycin (mean trough level, 19 μg/mL) reported an overall occurrence of worsening audiogram of 12%, a rate that was higher in subjects older than 53 years.[107] When ototoxicity develops, it generally appears to be reversible after drug discontinuation. Vertigo and tinnitus are also rarely reported during vancomycin therapy and may precede hearing loss. Prospective studies addressing the true rate of vancomycin-related ototoxicity in the era of higher vancomycin target serum levels are needed.

Nephrotoxicity associated with vancomycin has been reported since the beginning of its clinical use, thought to be related, at least in part, to impurities in the early preparations. This nephrotoxicity is usually defined as an increase in serum creatinine concentration of 0.5 mg/dL or a ≥50% increase from the baseline serum creatinine level. The mechanism underlying vancomycin-related nephrotoxicity appears to be related to its oxidative effects on cells of the proximal renal tubule, leading to renal tubular ischemia.[108] Vancomycin, in an animal model, appeared to induce apoptosis in proximal tubular cells via mitochondrial production of reactive oxygen species with peroxidation of the mitochondrial phospholipid cardiolipin.[109]

Initial studies noted renal toxicity in animals when high doses of vancomycin were administered. However, and despite its prior reputation as a nephrotoxic agent, vancomycin use alone has been associated with a relatively low rate of renal dysfunction in clinical studies that avoided the inclusion of confounding factors. Most prospectively designed studies report an incidence of renal function impairment between 0% and 12%, which appeared associated with vancomycin trough levels ≥15 μg/mL,[34] concomitant use of nephrotoxic agents, and duration of vancomycin therapy.[34,110] A more recent meta-analysis found that vancomycin troughs concentrations >15 μg/mL and treatment duration more than 7 days were associated with nephrotoxicity (odds ratio, 2.67; 95% confidence interval [CI], 1.95-3.65).[111] Most of these studies found a relationship between trough levels and renal toxicity, with rates usually between 15% and 30% when trough levels were 15 to 20 μg/mL.[112] A prospective multicenter study conducted between 2008 and 2010 found nephrotoxicity rates of 29.6% and 8.9% in patients with vancomycin serum trough concentrations of ≥15 μg/mL and <15 μg/mL, respectively.[113] Lodise and associates[114] had previously reported a significantly higher rate of nephrotoxicity in patients receiving 4 g/day or more of vancomycin versus those receiving <4 g/day (34.6% and 6.7%, respectively). In the analysis of the relationship between vancomycin levels and nephrotoxicity, it should also be considered that levels may rise as result of a decreased renal clearance.

Other factors associated with increased vancomycin-related nephrotoxicity are weight ≥101.4 kg (224 lb), an estimated creatinine clearance ≤86.6 mL/min, critically ill patients,[114] and concomitant administration of other nephrotoxic agents, especially aminoglycosides.[115] The time to the onset of vancomycin-related nephrotoxicity has been between 4.3 and 17 days of therapy initiation.[111]

Even though vancomycin-associated nephrotoxicity is usually reversible, patients with nephrotoxicity tend to have worse outcomes with prolonged hospital stays, higher health care costs, and even higher mortality than those patients that did not developed nephrotoxicity.[112] Of note, use of a vancomycin loading dose has not been related to renal toxicity.

The coadministration of vancomycin (or an antistaphylococcal penicillin) plus gentamicin even at low dose (and for only the first 4 days of therapy) for *S. aureus* native valve endocarditis and bacteremia in a prospective randomized trial was associated with a significant decrease in creatinine clearance (≈25%) compared with those treated with daptomycin alone (≈8%).[116] An increased rate of acute kidney injury was reported with the association of vancomycin and piperacillin-tazobactam, both in adults and children.[117] The augmented risk of this association maintained its significance when compared not only with monotherapy with vancomycin or piperacillin-tazobactam but also to the combination of vancomycin plus cefepime or a carbapenem.[118] Rarely, acute interstitial nephritis has been associated with vancomycin use.

The overall risk for nephrotoxicity appears lower in the pediatric population than in the adult one. A rate of 14% has been noted in a retrospective study including patients from age 1 week to 19 years.[119] Trough levels >15 μg/mL, concomitant use of furosemide, and critically ill patients were the factors associated with decreased renal function.[119] Premature infants appear to have an even lower risk for developing vancomycin-related nephrotoxicity.

Several studies have assessed the nephrotoxicity associated with the mode of vancomycin administration as continuous infusion versus intermittent infusion. Different meta-analysis found that, overall, continuous infusion of vancomycin was associated with a lower risk for nephrotoxicity compared with intermittent infusion with no effect on treatment failure or mortality rates.[81,120] Specific biologic markers in blood, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, insulin-like growth factor-binding protein 7, and tissue inhibitor of metalloproteinases-2, among others, for early detection of vancomycin-induced renal damage have been developed and may become a useful tool for patients on vancomycin and at risk for nephrotoxicity.[108,121]

Infusion-related reactions are the most common side effects seen with vancomycin. A rapid onset of an erythematous rash or pruritus affecting the head, face, neck, and upper trunk, with or without associated angioedema and hypotension (anaphylactoid reaction), commonly known as red neck or red man syndrome, has been reported during the infusion of vancomycin with variable frequency, ranging from 3.4% to 14%. Vancomycin may cause histamine release from degranulation of cutaneous mast cells. A retrospective study done in children observed a red man syndrome incidence of 14%; factors associated with it were vancomycin concentration and dose, white ethnicity, age older than 2 years, and antecedent use of antihistamines; a single nucleotide polymorphism in the diamine oxidase gene may be associated with predisposition to this reaction.[122]

Severe hypotension and even cardiac arrest have also been reported during vancomycin infusion. The mechanism for these effects is probably related to histamine release from basophils and mast cells. These reactions usually subside soon after stopping the infusion without other measures. The incidence of these side effects can be reduced by decreasing the infusion rate or the concentration and by using antihistamines (histamine type 1 receptor antagonists). Local reactions, such as phlebitis, have been reported in 3% to 14% of patients receiving vancomycin.

Neutropenia is also observed with vancomycin with a frequency of 1% to 2%, although this increases to 12% to 13% in patients with long-term vancomycin therapy. Neutropenia usually resolves after discontinuation of the drug, and it is recommended to monitor the leukocyte count weekly in patients receiving vancomycin for more than 1 week. A case of agranulocytosis was described on rechallenge in a patient with prior vancomycin-induced neutropenia. Neutropenia can be a glycopeptide class effect because cross-reactivity with teicoplanin has been described.

Thrombocytopenia associated with vancomycin use is very rarely reported, although it may be unrecognized. Vancomycin-dependent, platelet-reactive antibodies have been found in a high proportion of patients with suspected vancomycin-induced thrombocytopenia, suggesting an immune-mediated platelet destruction.[123] Some cases can be associated with significant bleeding and, rarely, a significant drop in the platelet count can be seen within 24 hours after initiation of vancomycin administration.[123]

Presumptive vancomycin-induced maculopapular or erythematous rash and drug-related fever were noted in 3% and 2% of patients receiving vancomycin, respectively.

Vancomycin has been associated with a series of immune-mediated reactions, or hypersensitivity reactions that include maculopapular rash, drug rash eosinophilia and systemic symptoms (DRESS) syndrome, linear immunoglobulin A bullous dermatosis, and Stevens-Johnson syndrome/toxic epidermal necrolysis. The majority are nonimmediate reactions.[124] These immune-mediated reactions associated with vancomycin may show cross-reactivity with teicoplanin.

Despite the clinical efficacy of oral vancomycin for treating *C. difficile*–related diarrhea, cases of *C. difficile* colitis attributed to the use of IV vancomycin have been reported. Even though mild increases of transaminases have been reported in some patients receiving vancomycin, this antibiotic is not considered a drug with associated risk for severe liver injury.[125]

Intraventricular administration of vancomycin is regarded as safe, although an episode of reversible decreased consciousness and two cases of CSF eosinophilia have been reported. Intraperitoneal administration of vancomycin is rarely associated with chemical peritonitis.

Scarce published data exist on the use of vancomycin during pregnancy, and it is classified as pregnancy category C. Vancomycin was noted to show minimal maternal-fetus transplacental passage in an ex vivo human placental perfusion model, but it reaches therapeutic levels in fetal circulation in the setting of overt amnionitis. Infants born to mothers who received a course of vancomycin during the second or the third trimester of pregnancy had no nephrotoxicity or sensorineural hearing loss. However, because no reports exist on vancomycin use during the first trimester, it is unknown if this drug produces fetal harm. This drug should be used only in situations when it is needed, considering the maternal benefit and the possible fetal risk. Vancomycin is excreted in human milk, resulting in potential exposure of infants to this agent, with an expected substantial effect on the intestinal microbiota.

Drug Interactions

Precipitation has been noted when a highly concentrated solution of vancomycin was mixed with ceftazidime, and the use of different syringes for the intraocular administration of these two antibiotics for the treatment of endophthalmitis is recommended. Vancomycin has also been reported to be incompatible in IV solutions with other compounds, including chloramphenicol, methicillin, corticosteroids, aminophylline, barbiturates, thiazides, phenytoin, sodium bicarbonate, and sulfisoxazole. Precipitation with decreased activity of vancomycin was reported when infused together with heparin, although others were unable to detect an effect of heparin on vancomycin stability or activity. Anion-exchange resins, such as cholestyramine, can bind to vancomycin, decreasing the activity of vancomycin in the gut lumen when orally administered. In neonates with patent ductus arteriosus the use of indomethacin and ibuprofen has been associated with a 40% and 28% decreased clearance of vancomycin, respectively.

Clinical Uses

Skin and Soft Tissue Infections

During the past decade or so, vancomycin has been included as the comparator in numerous studies of ABSSSI caused by gram-positive bacteria when new agents with activity against MRSA were evaluated. None of these trials showed significant differences in the primary clinical outcome, although post hoc analysis done in some of these studies displayed some differences favoring the new drug. Thus, and because of its long experience and low cost, when an IV antibiotic is required, vancomycin is still considered the drug of choice for ABSSSI caused by MRSA.[43,126]

Bacteremia and Endocarditis

Although recently debated,[64,127] vancomycin is still the first treatment option for bacteremia, endocarditis, and other serious infections caused by methicillin-resistant staphylococci; the same indication applies for those infections caused by methicillin-susceptible strains in subjects with a history of significant allergic reactions to β-lactams who cannot be desensitized. Failures have been reported with this glycopeptide in the treatment of staphylococcal endocarditis, and its effectiveness has been questioned based on the high rate of unsatisfactory response among injection drug users with *S. aureus* endocarditis, the slow response (median duration of bacteremia, 7 days) in patients with MRSA endocarditis, and the higher failure rate for right-sided MSSA endocarditis when compared with cloxacillin. Because of studies showing worse outcomes in patients with MSSA bacteremia, vancomycin should not be used purely for its dosing convenience or in patients with MSSA endocarditis with a suspicious history of immediate hypersensitivity reaction to β-lactam antibiotics for whom skin testing for penicillin allergy should be performed and patients desensitized, as needed.

The addition of gentamicin to vancomycin was previously suggested for the treatment of MRSA native valve endocarditis.[128] However, owing to the lack of clinical studies showing improved outcome with this combination and the increase in nephrotoxicity with vancomycin plus aminoglycosides (which may be higher than previously appreciated),[129] the risks of adding gentamicin appear to exceed the presumed benefits.[130] The addition of rifampin to vancomycin in the treatment of native valve endocarditis caused by *S. aureus* was successful in a few reports and in an animal model, but not in a randomized clinical trial, done in an era before the documentation of emergence of hVISA. A retrospective study of patients with native valve *S. aureus* endocarditis, some of whom received rifampin, warned about the potential risks associated with the addition of rifampin, such as emergence of rifampin resistance, hepatotoxicity, and drug interactions. Even more, a recent randomized trial showed that adjunctive rifampin to standard therapy did not affect the *S. aureus* bacteremia–related mortality.[131]

Different studies have reported a median of 7 to 9 days of bacteremia in patients with MRSA endocarditis treated with vancomycin. The decision as to when a patient treated with vancomycin for a serious MRSA infection is a clinical failure is a matter of debate. Several factors might be involved in this determination, such as the patient's overall clinical response, the presence of adequate vancomycin levels and of eradicable foci of infection, and the vancomycin MIC of the infecting strain. Although some have promoted a move away from vancomycin use when the infecting organism's vancomycin MIC value is 1.5 μg/mL per Etest measurement, this needs to be carefully interpreted because of the limitations and variability of the available susceptibility methods, such as Etest, automated, and broth microdilution.[32,132] Even with MRSA strains having vancomycin MICs <2 μg/mL, clinical and microbiologic response should be closely monitored; if response is not considered adequate despite removal of foci of infection or foreign-body device, then another treatment might be indicated regardless of the vancomycin MIC of the infecting strain.[43] In any situation an alternative treatment to vancomycin is recommended for MRSA isolates with MIC >2 μg/mL (VISA strains).[43]

The combination of vancomycin with β-lactams has demonstrated enhanced in vitro activity against *S. aureus,* including MRSA, hVISA, and VISA isolates. Retrospective studies appear to show an advantage of this combination over vancomycin monotherapy in patients with MRSA bacteremia,[133,134] and a prospective randomized trial of vancomycin plus flucoxacillin (for the first 7 days) versus vancomycin monotherapy also demonstrated a shorter duration of MRSA bacteremia (mean of 1.94 versus 3 days in the combination and monotherapy group, respectively) with no differences in rates of mortality, metastatic infection, and nephrotoxicity.[135]

Studies from the 1990s have shown that vancomycin was ineffective for most infections caused by MRSA strains with a vancomycin MIC ≥4 μg/mL[136] However, there has been much debate on the clinical impact of infections caused by MRSA (and MSSA) strains with high vancomycin MICs but within the current susceptibility range (MIC ≤2 μg/mL). A meta-analysis published in 2012 found that infections caused by MRSA isolates with an MIC ≥1.5 μg/mL were associated with increased mortality[38]; however, another meta-analysis including 8291 episodes of *S. aureus* bacteremia did not find any relationship with an MIC ≥1.5 μg/mL and mortality.[39] A more recent study also failed to find an association between high MIC (≥1.5 μg/mL) and 30-day mortality among 1027 episodes of invasive *S. aureus* infections.[41] These discrepancies might be in part related to the innate variation among the tests used to determine the vancomycin MIC (i.e., broth microdilution, Etest, automated methods) and to the several other clinical, and even genetic, factors that might also impact the clinical outcome of patients with severe infections caused by MRSA and MSSA. Whether there is a relationship between clinical outcome and vancomycin MIC in patients with MSSA bacteremia/endocarditis treated with β-lactams is also unclear. Several retrospective and prospective studies looking for a possible effect have found an association between high vancomycin MIC (≥1.5 μg/mL) and clinical outcome, although others have not.[36,137] Thus clinical indicators rather than the vancomycin MIC per se should be the most important factor to guide therapeutic decisions in regard to vancomycin use.

For the treatment of enterococcal endocarditis, vancomycin may be considered if the infecting strain is highly ampicillin resistant (typically an *E. faecium* isolate) or the patient is truly allergic to β-lactam antibiotics (preferably confirmed by skin test) and cannot be desensitized. In these instances vancomycin could be combined with gentamicin or streptomycin to achieve bactericidal activity (if the organism does not display high-level resistance to the aminoglycoside).[138]

For native valve endocarditis caused by viridans streptococci, *Granulicatella* spp. and *Abiotrophia defectiva* (both formerly classified within the group of nutritionally variant streptococci), *Gemella* spp., and *S. bovis* (now *S. gallolyticus*), a 4-week course of vancomycin has been recommended for patients unable to tolerate β-lactams.[128,139] In the rare case of oral streptococci highly resistant to penicillin (MIC ≥4 μg/mL), vancomycin is the first therapeutic option.

For prosthetic valve endocarditis due to methicillin-resistant staphylococci, vancomycin in combination with rifampin for 6 weeks, together with gentamicin for the first 2 weeks (if the strain is susceptible), is the recommended regimen. This combination was derived from patients with *S. epidermidis* prosthetic valve endocarditis and has also been recommended for MRSA prosthetic valve endocarditis despite lack of proven clinical benefit,[128] because of the poor prognosis associated with this condition; also for the latter reason, surgical treatment should be undertaken if at all possible.

Vancomycin also plays an important role in the treatment of endocarditis caused by diphtheroids, including *Corynebacterium jeikeium,* which typically occurs in patients with prosthetic valves. The addition of rifampin has been suggested, although with a paucity of clinical evidence. Vancomycin has also been effective in a few reported cases of penicillin- and cephalosporin-resistant *S. pneumoniae* endocarditis and in the experimental model of endocarditis caused by this organism. Empirical treatment of central venous catheter–related infections should include a glycopeptide antibiotic because methicillin-resistant coagulase-negative staphylococci, MRSA, or other gram-positive organisms are frequently found, and clinical trials have shown the effectiveness of vancomycin in this setting. Please refer also to Chapter 80.

Meningitis and Ventriculitis

Vancomycin in combination with cefotaxime or ceftriaxone is the treatment of choice for empirical therapy of patients with suspected or proven pneumococcal meningitis until susceptibility data are available, in areas where infections caused by penicillin-resistant *S. pneumoniae* have been documented[140] or where the prevalence of isolates not susceptible to ceftriaxone is >3% in adult and 9% in children.[141] If pneumococcal meningitis is confirmed and the isolate shows an MIC of ceftriaxone/cefotaxime ≥1 μg/mL (considered nonsusceptible for meningeal isolates by the CLSI), the administration of the combination of vancomycin and ceftriaxone or cefotaxime should continue.[142] In children rifampin may be added to this regimen if the *S. pneumoniae* isolate shows an MIC of ceftriaxone/cefotaxime of >2 μg/mL.[140] In adults the addition of rifampin, if susceptible, to the regimen appears justified in cases caused by ceftriaxone-nonsusceptible *S. pneumoniae* strains when dexamethasone is also administered[142]; the clinical benefit of this approach has not been evaluated, but rifampin increased the activity of ceftriaxone and vancomycin in an experimental model using a highly ceftriaxone-resistant *S. pneumoniae* strain. Vancomycin as the only antimicrobial agent for which concomitant administration of dexamethasone has been associated with a high failure rate in adults with pneumococcal meningitis. Higher vancomycin doses appear to overcome the negative effect of dexamethasone on the vancomycin CSF concentration.

Vancomycin has a major role in the treatment of infections related to CSF shunts, the most common cause being *S. epidermidis.* IV with or without intraventricular vancomycin administration (see "Administration" for dosing suggestions), together with shunt hardware removal, followed by external drainage and placement of a new shunt after confirmed CSF sterility, appears to be the most appropriate treatment modality. Determination of vancomycin levels in the CSF is recommended to ensure adequate concentrations. The addition of rifampin to the regimen should be contemplated for susceptible organisms when bacterial eradication is not achieved with vancomycin alone. Vancomycin is also recommended for the empirical treatment of postsurgical meningitis.[142]

Owing to the poor prognosis and low therapeutic response to standard doses of vancomycin in patients with postsurgical MRSA meningitis, high-dose vancomycin (15–20 mg/kg every 8–12 hours) targeting a trough concentration of 25 to 30 μg/mL has been recommended.[43] Another option, especially in nonresponding cases, is to administer vancomycin by continuous infusion, also at a high dose (50–60 mg/kg/day after a loading dose of 15 mg/kg)[74]; the toxicity of both options is likely greater. Rifampin could be added to vancomycin despite the lack of clinical data supporting the combination, and intrathecal administration of vancomycin may also be another therapeutic approach.[142] In rare but severe cases of community-acquired meningitis caused by MRSA, the addition of rifampin or trimethoprim-sulfamethoxazole (TMP-SMX) to vancomycin has been used.[143] For more details in the management of meningitis, see Chapters 86, 87, and 92.

Pneumonia

Vancomycin has been considered the drug of choice for MRSA pneumonia, but high failure rates associated with its use have been consistently reported, which may be related to the fact that many of these patients are critically ill and, at least in part, to underdosing this agent, including lack of a loading dose. Indeed, clinical and bacteriologic success rates have been associated with higher AUC/MIC values (≥400) in patients with MRSA pneumonia.[55] In two randomized, double-blind trials of patients with nosocomial pneumonia, no significant differences in the response rate were observed in the vancomycin group compared with the linezolid group.[144,145] However, when a post hoc analysis of a subset of patients with MRSA ventilator-associated pneumonia was done, linezolid displayed significantly better cure rates. In a more recent randomized multicenter clinical trial, linezolid showed significantly better cure rates than vancomycin (15 mg/kg every 12 hours, with adjustment based on trough levels) in patients with nosocomial pneumonia caused by MRSA (57.6% vs. 46.6%, respectively; 95% CI, 0.5% to 21.6%; $P = .042$).[146] The group of patients treated with linezolid also experienced a significantly higher rate of eradication or presumed eradication at the end of the study. However, this trial had various shortcomings, including the fact that fewer than half of the patients had achieved the target trough level (15 μg/mL) on day 3, there was no vancomycin loading dose, more patients receiving vancomycin had concomitant bacteremia and kidney disease, about half of the patients received vancomycin for fewer than 10 days, and there was no difference in the 60-day mortality. Considering these caveats, linezolid is a good choice, if not better, for the treatment of documented MRSA nosocomial pneumonia than is standard vancomycin (without loading) dosing, particularly in patients at high risk for nephrotoxicity. The addition of rifampin to vancomycin appeared to improve the outcomes of ventilator-associated pneumonia caused by MRSA, compared with vancomycin alone, in a small randomized open-label trial[147]; this finding should be confirmed in other prospective studies.

More recently, vancomycin was the comparator arm in two large randomized clinical trials of hospital-acquired pneumonia caused by gram-positive pathogens in which telavancin was noninferior to vancomycin.[148] Another agent, such as TMP-SMX, was found superior to vancomycin, with significant lower clinical failure and 30-day mortality rate in a small, retrospective, case-control, and single-center study of patients with MRSA pneumonia[149]; prospective studies are needed.

Osteomyelitis

Vancomycin is the agent of choice for osteomyelitis caused by methicillin-resistant staphylococci, and it is an alternative for methicillin-susceptible strains in patients with intolerance or with allergic reactions to β-lactams agents.[43] Among serious MRSA infections, osteomyelitis is among those with highest relapse and failure rates.[150] Failure rates between 35% and 46% have been reported in retrospective studies of patients with osteomyelitis treated with vancomycin.[150,151] In accordance, animal models have shown poor results using vancomycin for the treatment of experimental MRSA osteomyelitis, whereas the coadministration of rifampin has been consistently associated with improved response. The duration of treatment of osteomyelitis has not been clearly defined; at least 8 weeks of therapy has been suggested for MRSA osteomyelitis, although the decision about the length of IV versus oral (or oral step-down after an IV course) has to be individualized.[43] Complete surgical débridement is critical for a successful outcome. Vancomycin has been used successfully in conjunction with rifampin as in some studies of prosthetic joint infection.

Pseudomembranous Colitis

Oral vancomycin was used historically for the treatment of pseudomembranous colitis caused by *C. difficile* and pseudomembranous enterocolitis caused by *S. aureus,* now a rare disease. Oral metronidazole and oral vancomycin, administered for 7 to 10 days, were found to have similar failure and relapse rates in the treatment of *C. difficile* colitis and, because of concern about selection of VRE, this drug was recommended for the treatment of *C. difficile* colitis only when there is no clinical response or intolerance to metronidazole or when the infected woman is pregnant.[152] However, since the emergence of an epidemic toxin-hyperproducing strain in North America and Europe (named BI/NAP1/027) associated with more severe disease, higher rates of metronidazole failures have been reported. Studies comparing oral metronidazole with oral vancomycin showed no differences in the outcome for mild disease but, for severe *C. difficile* colitis, the response rate was 76% and 97% for metronidazole and vancomycin, respectively ($P = .02$).[153] Therefore treatment with vancomycin should be considered in patients with severe *C. difficile* disease, defined as those having two or more of the following: age older than 65 years, fever, leukocyte count ≥15,000 cells/mm,[3] serum creatinine concentration increase ≥50% from baseline, and serum albumin concentration <2.5 mg/dL, or the presence of pseudomembranous colitis at endoscopy or hospitalization in an ICU.[153] Until 2011, when fidaxomicin was approved, oral vancomycin was the only FDA-licensed drug for the treatment of *C. difficile* colitis. It can be administered as a capsule formulation or by directly taking the IV form. Because of the poor concentration in stools after IV administration, vancomycin should not be used solely via this route. In cases of severe disease or in the presence of ileus or toxic megacolon, or both, IV metronidazole plus high doses of oral vancomycin (500 mg every 6 hours)[154] and intracolonic administration of this glycopeptide antibiotic[154] have been helpful, although, in some cases colectomy has been needed. Fecal transplantation has been successful in various reports, including for severe and/or relapsing disease. In two randomized trials the new macrocyclic nonabsorbable antibiotic fidaxomicin showed similar efficacy with fewer recurrence rates than oral vancomycin for the treatment of *C. difficile* colitis.[155] Vancomycin, as well as fidaxomicin, is also an option for secondary recurrences in a tapered or pulsed regimen.[156]

Please also see Chapter 243 for further discussion on treatment options.

Febrile Neutropenia

The use of vancomycin in febrile neutropenic patients has been a controversial issue for a number of years. No differences in morbidity and mortality have been detected with the use of vancomycin as part of the initial regimen, even if a gram-positive organism was initially isolated or in persistently febrile patients despite the use of piperacillin-tazobactam for 48 to 60 hours. The inclusion of vancomycin in the initial empirical treatment of patients with febrile neutropenia is recommended in certain clinical situations, such as presumptive serious catheter-related infection, prior colonization with resistant microorganisms (i.e., penicillin- and cephalosporin-resistant *S. pneumoniae* and viridans streptococci or MRSA), positive blood culture for a gram-positive microorganism, skin or soft tissue infection of any site, radiologically documented pneumonia, or evidence of hemodynamic instability.[157] Others advocate empirical initial use of vancomycin in the presence of severe mucositis and prior prophylaxis with quinolones, which could be associated with severe penicillin-tolerant viridans streptococci infections. However, carbapenems, cefepime, and piperacillin-tazobactam are considered effective monotherapy regimens in this situation. Empirical vancomycin, if used, should be stopped after 2 days if initial workup did not reveal a gram-positive organism resistant to the patient's antimicrobial regimen. See also Chapter 306.

Prophylaxis

Vancomycin is an alternative choice for prophylaxis against endocarditis in subjects with cardiac conditions considered at risk for endocarditis and who are allergic to ampicillin.[158] Vancomycin is also recommended as a prophylactic agent for β-lactam–allergic patients undergoing cardiovascular surgery or orthopedic procedures with hardware placement and for surgical procedures requiring prophylaxis in centers with a high prevalence of MRSA, although not all studies have shown the effectiveness of this approach.[159] In the setting of a cluster of infections by methicillin-resistant staphylococci at the institutional level, a switch from β-lactams to vancomycin, or the addition of vancomycin, as surgical prophylaxis may be recommended.[159]

A retrospective study of patients undergoing primary joint arthroplasty showed the addition of vancomycin to cefazolin did not decrease the surgical site infection rate.[160] And indeed, it was associated with significantly higher incidence of acute kidney injury than the cefazolin alone group.[161]

If vancomycin is chosen for prophylaxis of endocarditis or surgical site infections, the infusion should start within 120 minutes of the beginning of the procedure. Each hospital should develop institutional guidelines on the use of vancomycin for the prevention of surgical site infections.[159] The CDC guidelines have recommended the use of vancomycin for the prevention of perinatal group B streptococcal disease in the case of penicillin-allergic women at high risk for β-lactam anaphylaxis, in whom a streptococci isolate was resistant (or with inducible resistance) to clindamycin or with an unknown susceptibility pattern.[162]

The use of local vancomycin powder in adults undergoing spine surgery appears to be effective to prevent deep and superficial surgical site infections[163]; however, most of these data come from retrospective studies, and the form and dose of each application have not been clearly established. The presumptive benefit of this approach appears to be most appreciated in high-risk patients or in centers with high postsurgical infection rates. In those spine surgeries where vancomycin powder has been applied and surgical site infection still occurs, a predominance of gram-negative bacilli has been reported.[164]

Even though no major side effects have been associated with this route of vancomycin administration, in vitro damage of dural cell damage has been induced by vancomycin in a concentration-dependent manner.[165] More prospective studies are necessary in this field before a more concise recommendation can be made. For further details, see Chapter 313.

Other Uses

Vancomycin is active against the majority of bacteria that cause post-traumatic and postoperative endophthalmitis and is the recommended agent for empirical therapy for intraocular gram-positive organisms in this disease. Animal models of endophthalmitis have also demonstrated the usefulness of vancomycin in this setting. Administration of intraperitoneal vancomycin as an intermittent or continuous dosing schedule is recommended in patients undergoing CAPD with bacterial peritonitis.[92] For uncomplicated peritonitis caused by coagulase-negative staphylococci, the duration of treatment is usually 2 weeks; for enterococci and *S. aureus,* a 3-week course appears necessary. Many of the peritonitis cases caused by *S. aureus* are associated with exit site infection that required peritoneal catheter removal to resolve the infectious process.

In uncomplicated intraluminal bacteremia associated with a tunneled central venous catheter or implantable devices, especially those caused by coagulase-negative staphylococci, the use of antibiotic lock therapy appears to improve the rate of catheter salvage when added to the standard IV treatment. A lock solution containing vancomycin at a final concentration of 5 mg/mL plus normal saline or 50 to 100 units of heparin has been recommended.[166] The lock solution should have an indwelling time of no more than 48 hours, and the duration of the lock therapy is usually 2 weeks. If the isolated pathogen is *S. aureus,* because high failure rates have been described with antibiotic lock therapy, the catheter should be removed. The use of prophylactic antibiotic lock solution has also been recommended for the prevention of long-term central venous catheter infection for patients with recurrent catheter-related bacteremia and, in oncology patients, for those at high risk for severe infections or where the baseline central catheter infection rate is increased.[167] Prevention of central venous catheter infections in patients undergoing hemodialysis with antibiotic lock solutions also appears to be effective, although use of other agents may be more common.

Teicoplanin

Teicoplanin (formerly known as teichomycin A_2) was obtained from *Actinoplanes teichomyceticus* recovered from a soil sample in India in 1978. This glycopeptide antibiotic is currently available in many countries in Europe, Asia, and South America but not in the United States. The FDA has not approved it, probably because of no clear benefit over vancomycin (Fig. 30.2). Teicoplanin is actually a mixture of related glycopeptide analogues with a basic structure characterized by a linear heptapeptide, the distinct carbohydrates D-mannose and D-glycosamine, and an acyl residue that carries various fatty acids, which define the members of the teicoplanin complex. Teicoplanin has a molecular weight estimated as 1900 Da.

Antimicrobial Activity and Resistance

Teicoplanin inhibits cell wall synthesis by a mechanism similar to that described for vancomycin, although some differences in activity exist. For instance, MICs of teicoplanin against coagulase-negative staphylococci tend to be more variable. In one survey, 21% and 1% of coagulase-negative staphylococci and *S. aureus* strains, respectively, from bacteremic patients were nonsusceptible to teicoplanin based on the EUCAST breakpoint (MIC >4 μg/mL).[168] A more recent study done in France found that 33% of the coagulase-negative staphylococci isolates were nonsusceptible to teicoplanin (MIC >4 μg/mL).[169] High teicoplanin MICs appear to be more frequent among *S. haemolyticus* than other staphylococcal species.[170] On the other hand, the MICs of teicoplanin for *Enterococcus* spp., *S. pneumoniae, S. gallolyticus* (formerly *S. bovis*), viridans-group streptococci, and other streptococci are usually lower than those of vancomycin. The in vitro activity of teicoplanin seems to be similar to that reported with vancomycin against *L. monocytogenes, Corynebacterium* spp. (including *C. jeikeium*), and gram-positive anaerobes, such as *Clostridium* spp. (including *C. difficile*), *Peptostreptococcus* spp., *Actinomyces* spp., and *Propionibacterium* spp. No international consensus has been established for teicoplanin susceptibility breakpoints for *S. aureus,* but they have been set as ≤2 μg/mL and ≤8 μg/mL by the EUCAST and CLSI, respectively (www.eucast.org/clinical_breakpoints). The same breakpoints have been provided by both groups for *Enterococcus* spp. For coagulase-negative staphylococci, these values have been set as ≤4 μg/mL by the EUCAST and ≤8 μg/mL by the CLSI.

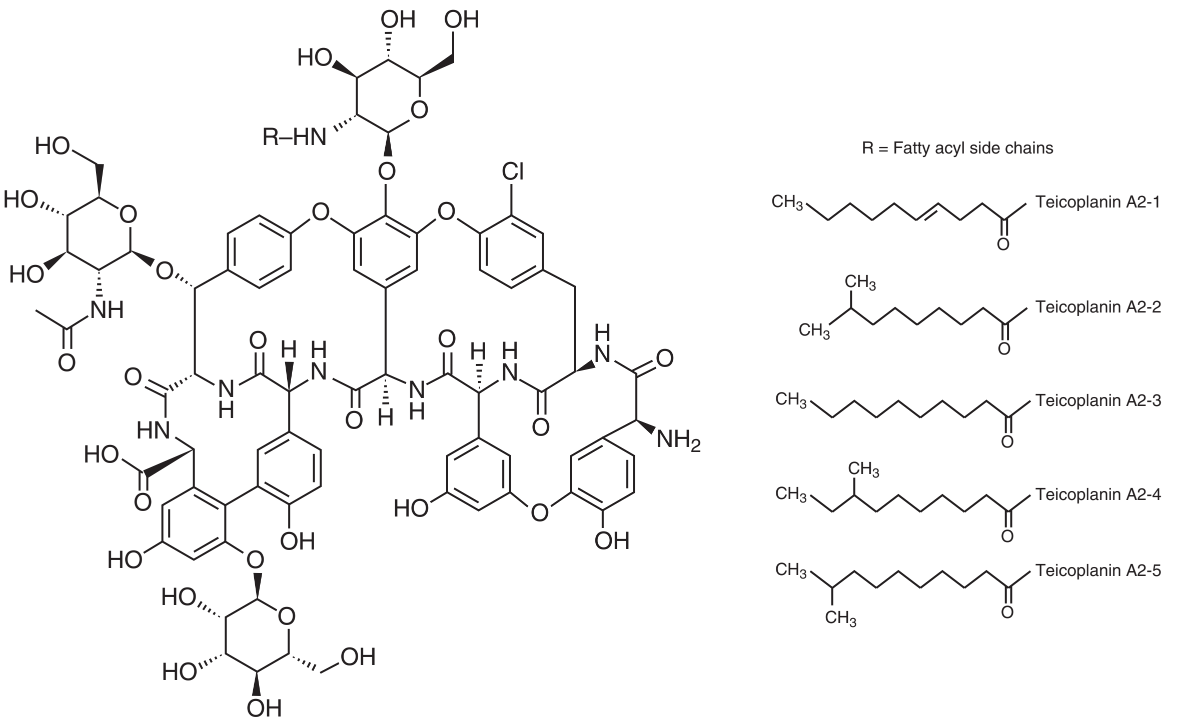

FIG. 30.2 **Chemical structure of teicoplanin.**

Strains of *S. aureus* susceptible to vancomycin but displaying higher MICs of teicoplanin were reported before the description of VISA isolates, and high MICs of teicoplanin were subsequently found in VISA isolates as well[10] (also called GISA). Almost all VISA strains are "cross-resistant" to teicoplanin. However, some teicoplanin-heteroresistant *S. aureus* strains may test susceptible to vancomycin, and specific cell wall changes may affect teicoplanin more so than vancomycin. Greater MIC increases for teicoplanin compared with vancomycin were found by inactivation of the *tcaA* gene in GISA strains, which encodes a transmembrane protein presumably associated with cell wall metabolism. As expected, decreased activity of teicoplanin and selection of subpopulations with higher glycopeptide MICs were observed in animal models infected with VISA strains. Because disk tests and some automated systems do not reliably recognize MRSA strains with decreased susceptibility to teicoplanin, Etest and agar dilution methods are recommended when needed. As described with vancomycin, MICs determined by Etest tend to be higher than those determined by broth microdilution. Most of the VRSA isolates carrying the enterococcal *vanA* gene cluster described in the United States also showed decreased susceptibility to teicoplanin (≥16 μg/mL).

In general, strains that produce peptidoglycan precursors ending in D-Ala-D-Lac, encoded by the *vanABDM* gene clusters, are likely to be resistant to teicoplanin (VanA, VanB, VanD, and VanM). However, VanB-type strains are usually susceptible in vitro because teicoplanin does not induce expression of the gene cluster. However, mutations that result in constitutive expression of the *vanB* operon can occur in vivo and lead to resistance. Thus, even if MICs are within the susceptible range, teicoplanin should probably not be used to treat infections caused by VRE strains due to the risk for development of resistance while on therapy. Other enterococci that synthesize peptidoglycan precursors ending in D-Ala-D-Ser (VanC, VanE, VanG, and VanN) show low teicoplanin MICs.

Clinical Pharmacokinetics

Teicoplanin has favorable pharmacokinetic properties that permit administration by IV bolus or intramuscular route. As with vancomycin, this agent is not significantly absorbed when administered orally. After an IV dose of 6 mg/kg, the mean peak (at 2 hours) and trough (at 24 hours) concentrations of teicoplanin in serum are 111.8 μg/mL and 4 μg/mL, respectively. At steady state, teicoplanin mean trough concentrations are 14 μg/mL after IV administration of 6 mg/kg/day and 23 μg/mL after 12 mg/kg/day. It appears that teicoplanin trough concentrations ≥10 μg/mL are required for clinical success in the majority of infections by susceptible organisms, although for serious staphylococcal infections (i.e., endocarditis), trough levels >20 μg/mL are recommended.[171]

The distribution of teicoplanin is best described by a three-compartment kinetic model, and its volume of distribution at steady state ranges from 800 to 1600 mL/kg.[172] Teicoplanin is approximately 90% bound to serum proteins (albumin) and highly bound in tissues, which may explain its low clearance and long half-life, which has ranged from 83 to 168 hours.[172] Animal studies have reported better bone concentrations with teicoplanin than with vancomycin after equivalent IV infusion. However, in patients with osteomyelitis, vancomycin achieved slightly higher levels in cortical and cancellous bone than teicoplanin.[79] The concentration of teicoplanin in cortical and cancellous bone, which has more abundant vascular supply, was 12% (mean, 2 μg/mL) and 49% (mean, 7.5 μg/mL) of concomitant plasma concentration at steady state (with a daily dose of 10 mg/kg), respectively.[79] Penetration into the heart; pericardium; mediastinal tissue; and synovial, pleural, peritoneal, and pericardial fluid is also considered adequate. The concentration of teicoplanin in the epithelial lining fluid at steady state was about 30% (mean concentration, 4.9 μg/mL) of the corresponding trough serum level in 13 patients with ventilator-associated pneumonia treated with 12 mg/kg/day.[173]

In experimental endocarditis teicoplanin appears to be concentrated only at the periphery of the vegetation. After IV infusion, significant concentrations of teicoplanin are generally not achieved in vitreous samples nor in the CSF, even in the presence of meningitis. A high concentration of teicoplanin in feces is achieved after oral administration of 100 mg.

Teicoplanin is almost entirely eliminated by renal mechanisms and, even though this agent used to be regarded as a nondialyzable drug, hemodialysis using high-flux membranes, CVVHD, CVVH, and CVVHDF remove significant quantities. Teicoplanin levels seem not to be significantly modified in subjects undergoing cardiopulmonary bypass surgery. Teicoplanin should not be used during pregnancy (pregnancy category B) or lactation unless the potential benefits outweigh the possible risks.

The oral dose of teicoplanin for the treatment of *C. difficile* pseudomembranous colitis ranges from 100 to 400 mg twice daily for 10 days. The parenteral teicoplanin dose depends on the patient's age and renal function, the suspected or known microorganism, and site of infection. Because of its long half-life, a loading dose of teicoplanin is required to achieve earlier optimal steady-state serum levels. For most infections the regimen recommended is 400 mg (6 mg/kg) every 12 hours for three doses and then once daily, which attains a trough level >10 μg/mL by the fourth day of treatment. The loading dose should be given to all patients regardless of the patient's creatinine clearance. Then, in adults with normal renal function, 400 mg (6 mg/kg) every 24 hours is the usual maintenance dose. A higher dose, 800 mg (up to 12 mg/kg) every 12 hours for three doses and then every 24 hours to target a trough concentration of more than 20 μg/mL, is recommended for more difficult infections, such as septic arthritis, osteomyelitis, and endocarditis, although some have recommended a trough >30 μg/mL for the latter[174] (see Table 30.1). However, teicoplanin trough levels of 28 μg/mL or greater have been associated with hepatotoxicity.[175]

Even though the recommended high trough levels of teicoplanin appear associated with better clinical outcome, reaching the target concentration is challenging. A recent retrospective study found that only 32% of patients with MRSA infections treated with teicoplanin achieved a desired trough ≥15 μg/mL on day 3 or 4 of therapy. Emphasizing the effect of the initial dosing, the trough target was readily achieved in those receiving a higher loading dose (1600 mg given as 800 mg on day 1 and on day 2) and in those with a creatinine clearance <56 mL/min receiving a lower loading dose (1200 mg, 800 mg/day on day 1).[176] Even more, an enhanced teicoplanin dosing regimen was evaluated in a prospective study of patients with a creatinine clearance <60 mL/min (10 mg/kg twice on the first day, followed by 10 mg/kg/day and 6.7 mg/kg/day on the second and third day, if the creatinine clearance was between 40 and 60 mL/min and <40 mL/min, respectively). The median minimum concentration (C_{min}) on day 4 and the proportion of patients with the target C_{min} between 15 and 30 μg/mL in the enhanced loading group versus those in the conventional regimen group were 18.1 μg/mL and 12.1 μg/mL, and 20.4% and 7.1% ($P < .001$), respectively.[177] In the same study, among 106 patients with MRSA infection, a significantly higher clinical success rate was observed in those achieving a C_{min} >15 μg/mL.

The recommended doses for neonates is 16 mg/kg initially, followed by 8 mg/kg daily and, for children older than 2 months, 10 mg/kg every 12 hours for three doses and then every 24 hours.[172] In the presence of renal insufficiency, teicoplanin dose adjustment is required only after the end of the loading doses. In subjects with creatinine clearance between 30 and 80 mL/min., the daily dose should be halved or given every 48 hours and, in those with more severe renal failure or on hemodialysis with conventional membranes, the daily dose should be one-third or be administered every 72 hours.[172,178] Others have suggested the administration of 10 mg/kg every 48 to 72 hours in patients on hemodialysis, which was consistently associated with trough levels >10 μg/mL.[179]

Teicoplanin is significantly removed by CVVH and CVVHDF but with high variability, depending on the operating conditions of the renal replacement therapy used and the patient's serum albumin concentration. A reasonable proposed dosing regimen to generate a trough teicoplanin level of 10 to 20 μg/mL is 6 mg/kg every 12 hours for three or four doses, followed by 3 to 6 mg/kg/day[180]; others have suggested higher daily doses (600–1800 mg/day), targeting 15 to 25 μg/mL in patients undergoing CVVH.[181] However, because teicoplanin serum levels in this setting can be affected by the serum albumin concentration, the presence of residual renal function, and the volume ultrafiltration rate, therapeutic drug monitoring is recommended in critically ill patients undergoing CRRT.[180]

Peritoneal administration of teicoplanin results in serum concentrations similar to those achieved by IV concentration; however, after IV administration, penetration of teicoplanin into the peritoneal dialysate does not achieve local therapeutic levels. Teicoplanin has been administered in doses of 20 mg/L in each bag for the first week, in alternate bags during the second week, and only in the overnight dwell bag in the third week. Another approach is to dose 20 mg/L in each exchange (four times daily) for 10 days or for 5 days after clearing of bacteria from the dialysate. Others have successfully used intermittent intraperitoneal dosage of teicoplanin (15 mg/kg every 7 days) in children with CAPD peritonitis.

Monitoring of teicoplanin serum levels is not generally needed with doses <12 mg/kg/day. IV drug abusers with endocarditis have a higher clearance rate of teicoplanin, thus suggesting a need for serum level measurements in this population. It has been suggested that a trough level should be drawn to ensure teicoplanin concentrations in serum of at least 20 μg/mL and even >30 μg/mL in patients with bone and joint infections and endocarditis, respectively,[171,178] especially if teicoplanin is administered as monotherapy. Other clinical scenarios in which measurement of teicoplanin serum levels might be appropriate include patients not responding to treatment, patients with severe burns, and patients with rapidly changing renal function or on CRRT.

As with vancomycin, some discrepancies exist on the clinical impact of teicoplanin MIC in patients with MRSA bacteremia because a teicoplanin MIC >1.5 μg/mL by Etest was associated with worse outcome in one retrospective study but not in others, including 101 and 270 patients treated with teicoplanin (6 mg/kg/day after loading dose), respectively.[182,183] Of interest, the in vitro combination of teicoplanin with various cephalosporins could decrease the teicoplanin MIC to ≤2 μg/mL of several hVISA and VISA isolates.[184]

Adverse Events

Teicoplanin is generally regarded as a safe drug. Rates of adverse events and nephrotoxicity have been reported more frequently in individuals receiving vancomycin than those receiving teicoplanin. Teicoplanin is nephrotoxic in animals, although at much higher doses than those used in humans. A lower rate of nephrotoxicity was reported with teicoplanin combined with aminoglycosides or with amphotericin B, compared with vancomycin combined with these agents.[185] The most common side effects associated with teicoplanin are maculopapular or erythematous rash and drug-related fever in about 7% and 6% of the patients, respectively.[186] These events are more frequent in patients receiving doses >12 mg/kg/day. Cases of allergic cross-reactions between vancomycin and teicoplanin have been reported, but vancomycin-allergic patients also have been successfully treated with teicoplanin. For example, in one study, cross-reaction in patients with vancomycin-induced fever or rash or both was seen in about 10%, whereas 50% of patients with vancomycin-related neutropenia developed neutropenia while on teicoplanin.[187] Compared with vancomycin, a meta-analysis showed that teicoplanin was associated with a lower rate of total adverse events, nephrotoxicity, and red man syndrome than vancomycin.[188]

The anaphylactoid reaction that has been described with vancomycin IV administration (known as red man or red neck syndrome) is extremely uncommon with the infusion of teicoplanin. Ototoxicity related to teicoplanin is also rare. Thrombocytopenia can occur at a rate similar to that found with vancomycin use and also appears to be more frequent at higher doses. Other hematologic effects, such as neutropenia and eosinophilia, are infrequently reported.

Clinical Uses

A failure rate of >50% in severe staphylococcal infections was found in initial studies using a low dose of teicoplanin (3 mg/kg/day). Even at higher doses (6 mg/kg/day and 10 mg/kg/day), teicoplanin was associated with a significantly lower response rates compared with vancomycin in patients with endocarditis or intravascular infection caused by *S. aureus*. Teicoplanin trough levels <20 μg/mL have been correlated with treatment failure.[171] Because a high failure rate was observed in patients with MSSA bacteremia treated with teicoplanin at 400 mg/day, if this agent is used for the treatment of *S. aureus* endocarditis or other serious staphylococcal infection, a high dose (probably 12 mg/kg/day) should be considered. For less serious infections, teicoplanin at standard doses appears as efficacious as vancomycin, as shown by a meta-analysis including 24 randomized clinical trials in which no difference in terms of 30-day mortality was found.[188] Also, for patients with hospital-acquired MRSA bacteremia (mostly catheter-related infections), teicoplanin showed similar outcomes to vancomycin in an observational prospective study.[189]

Teicoplanin might be an alternative in the treatment of native valve endocarditis caused by viridans streptococci and enterococci, in doses of 600 mg/day (or 6 mg/kg/day). Of interest, against *E. faecalis*, several patients were cured with teicoplanin monotherapy. In an experimental model of enterococcal endocarditis, teicoplanin was shown to be as effective as ampicillin and more effective than vancomycin. In this model the addition of an aminoglycoside to teicoplanin resulted in enhanced efficacy.

Teicoplanin has been shown to be effective in the treatment of susceptible organisms causing skin and soft tissue infections, lower respiratory tract infections, and catheter-related infections. Teicoplanin was equivalent to vancomycin in a study of neutropenic patients with persistent fever. Initial studies have shown similar response and relapse rates in patients with *C. difficile* infection who received oral teicoplanin, metronidazole, or vancomycin; however, a recent prospective, nonrandomized, observational study found a significantly lower rate of clinical failure and recurrence among 107 patients treated with oral teicoplanin versus 180 treated with oral vancomycin (100 mg and 200 mg every 12 hours and 125 mg and 500 mg every 6 hours, for noncomplicated and complicated infection, respectively).[190]

Intraperitoneal administration of teicoplanin has been successfully used for the treatment of CAPD-related peritonitis. Teicoplanin does not penetrate into the CSF; a small case series of CSF shunt-related infections treated with intraventricular teicoplanin have been reported, using doses of 10 to 20 mg every 24 to 48 hours. Teicoplanin (400 mg IV dose at the time of anesthesia induction) is as effective as first-generation cephalosporins in the prevention of hip or knee implant-related infections, although it was not as effective as standard of care in patients undergoing cardiac and prosthetic vascular surgeries. In a retrospective study of 1896 patients undergoing hip or knee arthroplasty, the addition of one dose of teicoplanin (800 mg) to cefuroxime was able to significantly decrease the rate of surgical site infections at this center.[191] Teicoplanin, like vancomycin, is recommended as an option for prophylaxis of infective endocarditis in patients allergic to penicillin.

Overall, it appears that in countries where both antibiotics are available, teicoplanin is infrequently used in place of vancomycin, at least in the acute phase of the infection under treatment. The main reasons for this approach are that teicoplanin appears to have overall lower response rates when compared with vancomycin in patients with severe MRSA infections. As such, high doses (12 mg/kg/day) are recommended for this type of infection, leading to possible toxicities and that teicoplanin is expensive.

In some situations teicoplanin could be considered for mild-to-moderate enterococcal infections or, as outpatient therapy, to continue the treatment of certain MRSA infections (e.g., osteoarticular infections) after vancomycin, once the patient has improved. In other instances teicoplanin could be chosen as a prophylactic antibiotic for selected surgical procedures, such as cardiovascular surgery in centers with a high prevalence of MRSA. Teicoplainin may also be useful as outpatient therapy for some streptococcal infections (e.g., viridans) that require prolonged therapy when there is documented β-lactam allergy.

LIPOGLYCOPEPTIDES

Lipoglycopeptides are semisynthetic derivatives of naturally occurring glycopeptides produced by changes of glycopeptide molecules. These three new agents—ritavancin, dalbavancin, and telavancin—contain lipophilic side chains, which appears to increase the ability to kill bacteria by also binding to the cell membrane, producing important disruptions in the physicochemical properties of this cell component, leading to cell death. Furthermore, the lipophilic chain confers a longer half-life and converts these agents (with the exception of dalbavancin) into concentration-dependent bactericidal antibiotics.[192] Lipoglycopeptides display similar spectrum of activity to that of glycopeptides, but their additional chemical modifications seem to increase their potency. Of importance, the hydrophobicity of these compounds has made it difficult to standardize susceptibility testing because the drugs diffuse poorly in agar media and tend to bind to plastic surfaces. These properties led to important modifications in the method for MIC determination with the addition of the nonionic surfactant polysorbate-80 at a final concentration of 0.002%.[193] Indeed, using this methodology, isolates with MICs higher than the breakpoint for susceptibility for each lipoglycopeptide have been extremely rare, although both in vitro and in vivo selection of resistant strains has been observed.[194,195]

Telavancin

Structure and Mechanism of Action

Telavancin (Vibativ; Theravance Biopharma, South San Francisco, CA) was the first of the lipoglycopeptides to be available on the market and is approved in the United States and Canada for the treatment of adults with ABSSSI due to gram-positive pathogens. In addition, telavancin has an indication in the United States and Europe for hospital-acquired pneumonia, including ventilator-associated pneumonia caused or believed to be caused by MRSA when other options are not suitable (Fig. 30.3).

Telavancin, a derivative of vancomycin, is produced by alkylation of the vancosamine nitrogen with a hydrophobic (decyl-aminoethyl) side chain and a hydrophilic (phosphonomethyl aminomethyl) group linked on the 4′ position of amino acid 7 of the cyclic peptidic core.[192] The mechanism of action of telavancin is similar to that of glycopeptides and involves binding to peptidoglycan precursors (D-alanine-D-alanine

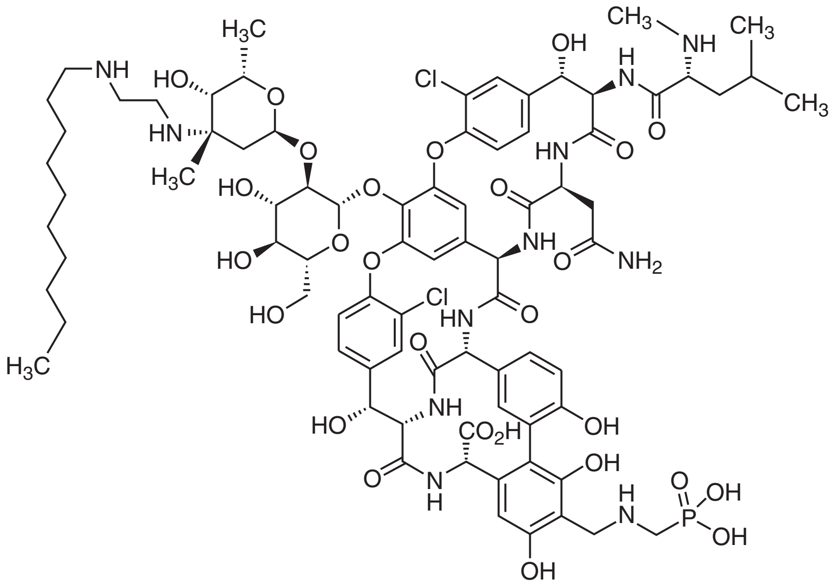

FIG. 30.3 Chemical structure of telavancin.

termini) at the outside of the bacterial cell, as they emerge from the cytoplasm. Of interest, the resulting inhibition of transglycosylase activity achieved by telavancin is about 10-fold greater on a molar basis than that observed with vancomycin.[196] However, a second mechanism of action is likely to play an important role in the bactericidal activity of the drug.[196a–196c] This mechanism is appears to be related to the rapid and concentration-dependent disruption of bacterial cell membrane homeostasis (e.g., *S. aureus*).[196] The alterations in membrane physiology have been associated with leakage of important ions such as potassium, alteration of adenosine triphosphate turnover, increased cell permeability, and eventually, cell death. Even though the interaction between telavancin and lipid II seems crucial for membrane depolarization, the nature of such interaction with this peptidoglycan precursor is unknown.[197]

Antimicrobial Activity and Resistance

As mentioned earlier, potent, concentration-dependent bactericidal activity has been described with telavancin,[196b] which also occurs in stationary phase of growth. The increased in vitro activity of telavancin observed since the inclusion of polysorbate-80 in its dilution MIC testing led to changes in the susceptibility breakpoints. Current breakpoints are as follows: *S. aureus*, *Streptococcus pyogenes*, and *Streptococcus agalactiae* are all ≤0.12 μg/mL; *Streptococcus anginosus* group, ≤0.06 μg/mL; and *Enterococcus faecalis* (vancomycin-susceptible strains), ≤0.25 μg/mL. EUCAST only has breakpoints available for *S. aureus* (MIC ≤0.125 μg/mL) and does not provide breakpoints for streptococci or enterococci due to insufficient data available (www.eucast.org/clinical_breakpoints).

The MIC_{90} of telavancin for *S. aureus* and coagulase-negative staphylococci isolates (independent of methicillin susceptibility) is 0.06 μg/mL.[198] Telavancin is very potent against *S. pneumoniae* with all isolates inhibited at concentrations ≤0.03 μg/mL and displays comparable activity to that of penicillin against β-hemolytic streptococci, including *S. pyogenes* and *S. agalactiae*.[198] Overall, telavancin MICs are onefold to twofold higher for hVISA and VISA isolates, and those with higher telavancin MICs also display higher vancomycin MICs. Against VRSA strains, telavancin exhibits decreased bactericidal activity, which is likely due to the change in composition of peptidoglycan precursors in these strains (D-alanine-D-lactate instead of D-alanine-D-alanine).[198a] Telavancin displays good in vitro bactericidal activity against MSSA, MRSA, and VISA strains with MBCs within twofold of the MIC.[196b] Telavancin has also been reported to retain bactericidal activity against daptomycin-nonsusceptible *S. aureus* isolates, including those that also exhibit decreased susceptibility to vancomycin.[198b]

In a recent study with more than 10,000 strains from a worldwide collection of gram-positive cocci, telavancin inhibited all *S. aureus* at a concentration ≤0.125 μg/mL.[199] For *S. aureus* isolates with a vancomycin MIC of 2 μg/mL, the MICs of telavancin were 0.06 μg/mL (lower than the susceptibility breakpoint), but these MICs were higher than those observed for isolates with vancomycin MIC <2 μg/mL (0.03 μg/mL).[199] In the same study the MIC_{90} of telavancin for coagulase-negative staphylococci was 0.06 μg/mL; for *E. faecalis,* 0.12 μg/mL; for vancomycin-susceptible *E. faecium* (VSE)*,* 0.03 μg/mL; for *S. pneumoniae,* ≤0.015 μg/mL; and for viridans-group streptococci and β-hemolytic streptococci, 0.03 μg/mL.

A variety of gram-positive anaerobes are susceptible to telavancin concentrations <2 μg/mL,[200] including *Actinomyces* spp., *C. difficile* (and other *Clostridium* spp.), *Eubacterium* group, *Lactobacillus* spp., *Propionibacterium* spp., *Peptostreptococcus* spp., and *Corynebacterium* spp. *L. monocytogenes* and *B. anthracis* are also highly susceptible to telavancin. Organisms that produce peptidoglycan precursors ending in D-Ala-D-Lac, including vancomycin-resistant enterococci, *Pediococcus, Leuconostoc,* and *Lactobacillus* are considered nonsusceptible, with telavancin MICs ≥2 μg/mL.[200] Selection of telavancin resistance in vitro among gram-positive isolates has been difficult to achieve, and clinical resistance has not been fully characterized. A recent patient appeared to have developed in vivo resistance to telavancin while on treatment with this compound for mediastinitis and persistent bacteremia caused by an MRSA/hVISA strain in the setting of a left ventricular assist device infection. Of note, the telavancin MIC increased to 1.5 μg/mL with concomitant increases in vancomycin and daptomycin MICs.[194]

Clinical Pharmacodynamics and Pharmacokinetics

Telavancin is supplied as a 250-mg or 750-mg single vial of a lyophilized powder that should be reconstituted with 15 mL and 45 mL, respectively, of 5% dextrose, sterile water, or 0.9% sodium chloride, leading to a final concentration of 15 mg/mL. The approved IV dose of telavancin is 10 mg/kg daily, which should be administered as a 1-hour infusion (see Table 30.1).[200a] This dosing schedule has resulted in peak plasma concentrations of 93.6 ± 14.2 μg/mL and an AUC of 666 ± 107 μg•hr/mL. The elimination half-life of telavancin ranges from 6.1 to 9.1 hours, and serum levels of telavancin are linear and predictable with minimal accumulation in patients with normal renal function. The percentage of drug bound to protein is relatively high (90%),[192,200b] and the tissue distribution of telavancin is similar to that of vancomycin.[192] The concentration of telavancin in blister fluid was 40% that of serum.[200c] In healthy adults telavancin concentrations in the epithelial lining fluid displayed a mean peak of 3.7 μg/mL and a trough of 1 μg/mL, 8 hours and 24 hours after infusion, respectively.[200d] The concentration in alveolar macrophages was 45 μg/mL and 42 μg/mL at 12-hour and 24-hour time points, respectively. Using population pharmacokinetic modeling, it has been reported that telavancin concentrations achieved in lung tissue are higher than the MICs for MRSA isolates for the majority of the time interval between two doses.[200e]

Dose adjustment of telavancin is required in the presence of renal dysfunction because clearance of the drug occurs via the kidneys. Thus the telavancin dose should be reduced to 7.5 mg/kg/day and 10 mg/kg every 48 hours in patients with creatinine clearances 30 to 50 mL/min and 10 to 30 mL/min, respectively.[200f] These recommendations were validated using a population pharmacokinetic model derived from 749 subjects enrolled in clinical trials.[200g] Insufficient information has been collected to make dosing recommendations in patients with creatinine clearance <10 mL/min, including those receiving hemodialysis. The European Medicines Agency (EMA) has advised against its use in patients with acute renal failure and with severe renal impairment.[201] Telavancin is coformulated with hydroxypropyl-β-cyclodextrin to improve its solubility. The latter compound might accumulate in patients with renal dysfunction. Of note, no drug adjustment is required for subjects with mild and moderate (Child-Pugh class B) hepatic impairment, and no significant drug interactions are expected to occur with telavancin through hepatic metabolism.

Efficacy of Telavancin in Animal Models

The efficacy of telavancin has been evaluated in various animal models. In the neutropenic murine thigh infection and subcutaneous infection models, telavancin showed significant concentration-dependent decreases in the bacterial titers of *S. aureus* and compared favorably with vancomycin and linezolid (MRSA) and nafcillin (MSSA).[200b] In a rabbit model of *S. aureus* endocarditis, telavancin yielded a significantly greater reduction in CFUs per gram of vegetation than vancomycin against two MRSA strains.[201a] In the same model, telavancin decreased bacterial counts in vegetations to a greater degree than vancomycin against two VISA isolates, although the difference was not statistically significant.[201b] In an experimental animal model of MRSA pneumonia, telavancin and vancomycin showed similar efficacies against MRSA strains with vancomycin MICs <2 μg/mL, but telavancin produced significantly greater reduction than vancomycin in bacterial counts in lung tissue in three out of four VISA isolates tested.[201c] In the rabbit model of meningitis caused by a penicillin-resistant *S. pneumoniae* strain (telavancin MIC, 0.06 μg/mL), telavancin exhibited a statistically significant reduction of CFUs in CSF compared with ceftriaxone plus vancomycin despite penetrating only 2% into CSF with inflamed meninges.

Adverse Reactions

Initial studies of telavancin infusions in healthy volunteers showed minor increases in the QTc interval; however, in advanced-phase clinical trials no significant differences in QTc interval were found compared with vancomycin.[148] Nonetheless, telavancin should be used with caution in patients taking medications that are known to cause QTc prolongation and avoided in patients with known long QTc interval, uncompensated heart failure, and severe left ventricular hypertrophy because these patients were excluded from the clinical trials. A pooled analysis of all side effects in the phase II and phase III ABSSSI and hospital-acquired pneumonia trials showed that nausea, vomiting, taste disturbance, chills, and creatinine elevation were significantly more frequent in the telavancin group than in the comparator arm of the trials.[201d] The most common adverse events that led to discontinuation of telavancin were nausea, vomiting, and renal dysfunction.[148,202] Nephrotoxicity was reported to be greater in patients with concomitant medications that might affect kidney function (e.g., diuretics, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors) and in those older than 65 years. The rate of significant creatinine increase (>50% increase from baseline and a maximum value >1.5 mg/dL) was significantly higher in patients receiving telavancin than those treated with vancomycin, both in the ABSSSI trials (6% vs. 2%, respectively)[202] and in the hospital-acquired pneumonia trials (16% vs. 10%, respectively).[148] In a retrospective analysis of the use of telavancin postmarketing, creatinine increase was found in 33% of the patients after a median of 9 days of treatment, although these patients had different comorbidities, were receiving other potentially nephrotoxic agents, and telavancin was prescribed for nonapproved indications.[202a] The renal toxicity, the most worrisome telavancin side effect, appears to be reversible, but cautious monitoring is required. Of interest, a recent updated meta-analysis of the published clinical data available from the telavancin trials showed no significant difference in clinical and microbiologic outcomes compared with other therapies. However, patients receiving telavancin had significantly higher rates of serum creatinine increases and hypokalemia.[203] Moreover, in the trials of hospital-associated pneumonia, lower survival rates (all-cause mortality at day 28) were observed among patients treated with telavancin than those receiving vancomycin when the patient had baseline moderate-to-severe renal impairment (creatinine clearance ≤50 mL/min) (59% and 70%, respectively; difference 11%; 95% CI, −19.9% to −1.3%).[204]

Telavancin has been associated with laboratory interference in quantification of urine protein (when tested by reagent strip and dye methods), prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time, and factor Xa coagulation tests. Because these effects appear to be minimal at drug trough, it is recommended to draw blood for these tests before the next dose of telavancin. As a derivative of vancomycin, telavancin has been associated with infusion-related reactions, such as red man syndrome–like reaction, flushing, pruritus, and rash. Slowing the infusion rate tends to mitigate these reactions.

There are no available data on the use of telavancin in pregnant women, lactating mothers, or pediatric patients. Telavancin is considered pregnancy drug class C and should be avoided in pregnant women unless the potential benefits outweigh the fetal risks. Increased rates of limb and digit malformations were seen in three animal species exposed to telavancin. As many other antibiotics, diarrhea caused by *C. difficile* occurred in patients receiving telavancin.

Clinical Uses

Skin and Soft Tissue Infections

Telavancin is currently approved for the treatment of ABSSSI caused by gram-positive pathogens. Two phase II studies and a large phase III study with telavancin in patients with ABSSSI have been published.[202,204a,204b] The first phase II study used a daily dose of 7.5 mg/kg, but thereafter the dose was 10 mg/kg/day. MRSA was the most common isolated pathogen. The cure rates for telavancin and vancomycin were 88.3% and 87.1% and 90.6% and 86.4% in the clinically evaluable patient group and those infected with MRSA, respectively.[202] A meta-analysis of the ABSSSI clinical trials found that, if the infected organism was MRSA, the microbiologic eradication rate was more favorable in those receiving telavancin than those treated with vancomycin.[201d] However, among patients with renal insufficiency (creatinine clearance <50 mL/min), decreased efficacy was seen in the telavancin group.

Hospital-Acquired Pneumonia

Telavancin was noninferior to vancomycin (1 g every 12 hours) in two large randomized trials of hospital-acquired pneumonia caused by gram-positive pathogens.[148] Ninety percent of the patients in the microbiologic evaluable population had an *S. aureus* strain isolated from respiratory samples, of which >55% were MRSA. The observed cure rates for telavancin- and vancomycin-treated patients were 82.4% and 80.7%, respectively. Telavancin performed better than vancomycin in those with monomicrobial *S. aureus* pneumonia and in those infected with MRSA, although the difference only reached statistical significance for monomicrobial hospital-acquired pneumonia caused by *S. aureus* isolates, with a vancomycin MIC ≥1 μg/mL.[205]

Other Clinical Uses

Telavancin was tested in a phase II randomized, double-blind trial of uncomplicated *S. aureus* bacteremia versus vancomycin or anti–staphylococcal penicillins, showing no differences in efficacy at 84 days of follow-up.[206]

Postmarketing use of telavancin has included 14 patients with refractory MRSA bacteremia (most of whom had endocarditis), 8 of whom were successfully treated.[207] Other reports of success include a case of pacemaker lead–related infective endocarditis due to a VISA/non–daptomycin-susceptible strain,[208] a few cases of MRSA osteomyelitis,[209] and prosthetic joint infections.[210]

Dalbavancin

The in vitro activity of dalbavancin was initially assessed in the late 1990s. Clinical development was pursued thereafter based on its antibacterial activity and favorable pharmacokinetic behavior. In 2014 in the United States and in 2015 in the European Union, dalbavancin was approved for treatment of adults with ABSSSI, initially as a two-weekly IV regimen of 1000 mg, then 500 mg 1 week later and more recently as a single 1500-mg dose regimen.

Structure and Mechanism of Action

Dalbavancin (Dalvance/Xydalba; Allergan; Dublin, Ireland) is a semisynthetic lipoglycopeptide derived from the semisynthetic derivative of the teicoplanin-like glycopeptide A40926, with a half-life of about 8.5 days and that allows once-weekly dosing. It is synthesized from a fermentation product of *Nonomuraea* spp., and comprises five related active components.

Dalbavancin, as other lipoglycopeptides, forms a stable complex with the C-terminal D-alanyl-D-alanine of the pentapeptide in the nascent cell wall peptidoglycan; dalbavancin's lipophilic side chain enhances its affinity to the target site. However, dalbavancin appears to adopt a closed conformation upon ligand binding, an interaction with cell wall precursors called noncooperative, which does not contribute to its own activity.[211,212] This differs from vancomycin and the other lipoglycopeptides, telavancin and oritavancin.

Antimicrobial Activity and Resistance

Dalbavancin shows in vitro activity against almost all significant gram-positive bacteria except those intrinsically resistant to glycopeptides, such as some *Lactobacillus* spp. and those having the VanA phenotype of vancomycin-resistance. The current FDA breakpoints for susceptibility of dalbavancin are ≤0.25 μg/mL for *S. aureus* (including MRSA), *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, viridans group streptococci (*S. anginosus* group only), and *E. faecalis* (vancomycin-susceptible isolates only). The breakpoint for these microorganisms determined by the EUCAST is one dilution lower (≤0.125 μg/mL).

Against susceptible species, dalbavancin displays significantly greater potency than vancomycin. Despite this, the in vitro activity of dalbavancin has been characterized as slowly bactericidal against *S. aureus* and *S. pyogenes*,[213] similar to the effect of vancomycin. Against hVISA isolates, dalbavancin displayed bacteriostatic activity.[214] For VRE, dalbavancin lacks useful activity against VanA-type strains and appears to be active against VanB type (presumably due to lack of induction of resistance, similar to teicoplanin). However, mutants that express VanB resistance constitutively are readily selected during drug exposure (as seen with teicoplanin). Dalbavancin is also active in vitro against the VanC-type enterococci (*E. gallinarum* and *E. casseliflavus*). The dalbavancin MIC_{90} for VRE type A is >4 μg/mL and for VanB and VanC is between ≤0.06 μg/mL and 2 μg/mL.[215]

Against more than 60,000 *S. aureus* isolates collected from the United States and Europe in a surveillance program over a decade (2002–12), dalbavancin demonstrated activity with MIC_{90} of 0.06 g/mL against strains including those nonsusceptible to daptomycin, linezolid, and tigecycline.[216] Analyzing strains from pediatric patients with skin and skin structure infections in the United States (2014–15), dalbavancin also displayed similar in vitro activity against *S. aureus* (MRSA and MSSA strains) (MIC_{90}, 0.06 µg/mL), coagulase negative staphylococci (MIC_{90}, 0.06 µg/mL), and β-hemolytic streptococci (MIC_{90}, 0.03 µg/mL).[217]

Dalbavancin shows good in vitro activity against many anaerobic gram-positive bacteria, including most *Clostridia* spp. (except *Clostridium clostridioforme*), *Propionibacterium* spp., *Peptostreptococcus* spp., *Eubacterium* spp., and *Actinomyces* spp.; some species of *Lactobacillus* displayed MICs >32 µg/mL.[218] Dalbavancin is also active against other gram-positive organisms, such as *Bacillus* spp., *Corynebacterium* spp., and *Micrococcus* spp. Selection of dalbavancin nonsusceptible variants from fully susceptible isolates in vitro has not been successful; however, a recent case report described the emergence of a dalbavancin-nonsusceptible VISA strain isolated from a patient who had received dalbavancin and vancomycin treatment for a catheter-related MRSA bacteremia.[195]

Clinical Pharmacodynamics and Pharmacokinetics

The current approved doses of dalbavancin in patients with normal renal function (creatinine clearance ≥30 mL/min) or on regular hemodialysis include a single administration of 1500 mg or 1000 mg, followed by 500 mg 1 week later, infused in 30 minutes for adults with ABSSSI. When IV dalbavancin was given as 1000 mg on day 1, followed by 500 mg weekly for 7 weeks in healthy volunteers, there was no accumulation, and mean serum concentrations >30 µg/mL from day 8 to 50 were found. The mean peak serum concentration (C_{max}) after a dose of 1000 and 1500 mg is 287 µg/mL and 423 µg/mL, respectively; the terminal half-life of dalbavancin is 8 to 9 days, with a high volume of distribution (between 9 and 15 L), suggesting extravascular distribution. The plasma protein binding of dalbavancin is approximately 93%, mainly to albumin. A mean of 45% is excreted in urine (33% unchanged and 12% as the metabolite hydroxyl-dalbavancin) and 20% in feces.

The penetration of dalbavancin in skin blister fluid is ≈60%, with a mean concentration ≈30 µg/mL by day 7, following a dose of 1000 mg.[219] The cortical bone, synovial tissue, skin, and plasma concentrations at 2 weeks after a single dose of 1000 mg of dalbavancin were 4.1 µg/g, 15.9 µg/g, 13.8 µg/g, and 15.3 µg/mL, respectively.[220] Based on a population pharmacokinetic modeling, two 1500-mg IV infusions given 1 week apart have been proposed for 6 to 8 weeks as a potential treatment of *S. aureus* osteomyelitis because this would provide free dalbavancin exposure higher than the *S. aureus* MIC_{90} for the treatment period.[220]

Even though dalbavancin is not approved for use in children, a model based on plasma concentrations from 43 pediatric patients (3 months–11 years of age), to simulate one-dose and two-dose adult regimens, respectively, yielded the following eventual dosing recommendations: from 6 to <18 years of age: 18 mg/kg (1500 mg maximum), and 12 mg/kg (up to 1000 mg) on day 1 and 6 mg/kg (500 mg maximum) on day 8; and from 3 months to <6 years of age: 22.5 mg/kg (up to 1500 mg), and 15 mg/kg (1000 mg maximum) and 7.5 mg/kg (500 mg maximum) on day 8.[221] The pharmacokinetic parameters of dalbavancin was similar to those described in adults among 10 healthy adolescents (between 12 and 17 years of age) receiving 1000 mg (or 15 mg/kg if the participant weighed <60 kg) infused in 30 minutes.[222]

The pharmacodynamic parameter that best describes the activity of dalbavancin is the 24-hour AUC/MIC. The efficacy of this compound was dose dependent in animal models against *S. aureus* and pneumococci; for the latter the drug exposure for similar efficacy was much lower than for *S. aureus*. The estimated target 24-hour AUC/MIC for *S. aureus* was between 100 and 300.[223]

Dalbavancin clearance is affected in patients with severe renal impairment.[224] Therefore doses should be adjusted in patients not on hemodialysis with a creatinine clearance <30 mL/min; in this case, the dose of dalbavancin should be 1125 mg as a single dose or 750 mg on day 1, followed by 375 mg on day 8 in the two-dose regimen. Patients on hemodialysis can receive the regular dose without considering the timing of dialysis. No need for dose adjustment is required in patients with hepatic insufficiency, even though drug exposure has been 27% to 36% lower in those with severe liver impairment.[224]

Dalbavancin is supplied in 500-mg powder vials that should be reconstituted with 25 mL sterile water or 5% dextrose, to be further diluted in 5% dextrose to a final dalbavancin concentration of 1 to 5 mg/mL. The time from reconstitution to administration should be <48 hours and can be stored either at 2°C to 8°C or at 20°C to 25°C. The IV infusion time is 30 minutes (more rapid infusions can cause red man syndrome–type of reactions), and it should not be coadministered with other medications or saline-containing infusions; lines should be cleared with 5% dextrose solution before and after use.[225]

Adverse Reactions

In phase III clinical trials that compared the two-dose regimen of dalbavancin (1000 mg on day 1 and 500 mg on day 8) with vancomycin, followed by oral linezolid, the most common adverse events in the dalbavancin arm were nausea (2.5%), diarrhea (0.8%), and pruritus (0.6%); these latter two were significantly less frequent than in the comparator arm. Reactions associated with infusion were seen in 1.4% of the patients in the dalbavancin group, although the majority of them occurred during the placebo infusions required in the trial.[226]

Hypersensitivity and skin reactions have been described, and cross-reactions might occur in patients with prior history of glycopeptide allergy. *C. difficile*–associated diarrhea has been described in patients receiving dalbavancin. Increases in alanine transaminase (ALT) levels have been reported in 0.8% of dalbavancin-treated patients compared with 0.2% of those in the comparator arm, although most of these patients had hepatic underlying conditions; these increased ALT levels were reversible. Dalbavancin in single doses of 1000 mg or 1500 mg showed no significant effect on heart rate, PR, QRS, and QTc intervals in a thorough study including 200 volunteers.[227]

Dalbavancin is classified as pregnancy category C because delayed fetal maturation was observed in rats receiving high doses of this compound, and there are no data about pregnant women. The excretion of dalbavancin in human milk has not been addressed, and the risk of drug-drug interactions appears minimal because it does not interfere with CYP450 isoenzymes or P-glycoprotein.

Clinical Uses

Dalbavancin showed similar outcomes as the comparator arm in phase II trials[228] of adults with ABSSSI. These studies were followed by phase III double-blind randomized trials that confirmed the noninferiority of dalbavancin administered as 1000 mg infused on day 1, followed by 500 mg vancomycin on day 8, with the option of oral linezolid on day 3. These studies led to the approval by the FDA and EMA of dalbavancin for ABSSSI caused by various susceptible organisms. More recently a 1500-mg single-dose of dalbavancin infused in 30 minutes showed similar outcome to the two-dose regimen in adults with ABSSSI, with a similar rate of adverse events,[229] leading to the FDA and EMA approval of this new dosing. A two-dose regimen of dalbavancin is currently under study in a phase III open-label and randomized trial (identifier NCT02814916) of pediatric patients (3 months–17 years of age) with ABSSSI compared with standard of care. Dalbavancin, administered as two 1500-mg weekly doses, showed good clinical outcomes and no serious related adverse events in a recently published, open-label, phase II clinical trial, of patients with chronic osteomyelitis caused by gram-positives.[229a] Of concern, a recent failure of dalbavancin has been reported in a pregnant patient with MRSA right-sided endocarditis treated with this drug, having relapsed with a VISA and lipoglycopeptide nonsusceptible isolate.[230] More clinical data on the potential use of dalbavancin in staphylococci bacteremia and/or endocarditis and osteomyelitis would be particularly interesting, considering its intrinsic antibacterial activity and its favorable pharmacokinetic profile that allows weekly administration.

Oritavancin

Oritavancin was selected for clinical development in 1994 based on its in vitro activity and its advantageous dosing profile; however, its development was slow due to ownership transference among pharmaceutical companies and the presence of an in vitro phenomenon that overestimated the MICs. Oritavancin finally was granted approval for use in adults with ABSSSI caused by susceptible gram-positive organisms in the United States and Europe in 2014 and 2015, respectively.

Update: Oritavancin in Osteomyelitis

Structure and Mechanism of Action

Oritavancin (Orbactiv) is a semisynthetic derivative of the lipoglycopeptide chloroeremomycin structurally similar to vancomycin, with the addition of an aminated sugar (4-epi-vancosamine) and a hydrophobic side chain, responsible for the amphipathic property of the drug and the membrane anchoring characteristic, also documented for telavancin. Oritavancin has three known mechanisms of action, including inhibiting transglycosylation, inhibiting transpeptidation, and disrupting the cell membrane.[231] First, like vancomycin, oritavancin binds to the D-alanyl-D-alanine peptidoglycan termini of lipid II, inhibiting the glycan chain extension (transglycosylation). Second, probably through its lipophilic side chain, oritavancin also interacts at another level of the pentapeptide terminus of lipid II (the pentaglycyl bridge and the D-iso-glutamine residue in position 2),[232] allowing a significant inhibition of the transpeptidase activity; this might explain its activity against vancomycin-resistant organisms. And third, oritavancin was shown to produce membrane depolarization and permeabilization, which appears independent of cellular growth and division.

Antimicrobial Activity and Resistance

Oritavancin has in vitro activity against staphylococci (including MRSA), streptococci, and enterococci (including VRE).[233,234] As with other lipoglycopeptides, the CLSI recommends performing oritavancin MIC testing using 0.002% polysorbate-80, to inhibit the adherence of the compound to test tube walls. The oritavancin CLSI and EUCAST breakpoints for susceptibility against staphylococci, streptococci, and VSE (only CLSI) are ≤0.12 μg/mL, ≤0.25 μg/mL, and ≤0.12 μg/mL, respectively.

Oritavancin has low MIC_{90} values against vancomycin-susceptible and VanB-mediated vancomycin-resistant strains, whereas the MICs for VanA strains tend to be slightly higher. For example, oritavancin MIC_{90} against enterococcal isolates from Europe and the United States, collected between 2011 and 2013, were 0.06 μg/mL and 0.12 μg/mL for vancomycin-susceptible *E. faecalis* and VanA *E. faecium*, respectively.[235] In addition, oritavancin exhibited in vitro bactericidal activity for both VRE and VSE in time-kill experiments; however, an increased concentration was required for bactericidal activity against VRE.[236,237]

Oritavancin also showed good in vitro activity against 1008 *S. aureus* clinical isolates from patients with invasive infections in the United States between 2013 and 2014, with an MIC_{90} of 0.06 μg/mL.[238] Oritavancin also displays in vitro activity against *C. difficile*, even more potent than that of vancomycin against most of the isolates.

In vitro studies including time-kill curves have shown a synergistic activity of oritavancin when combined with cefazolin and with nafcillin against MRSA strains, possibly secondary to the seesaw effect in which the glycopeptide (and lipopeptide) MICs are inversely proportional to the β-lactam MICs. The combination of oritavancin with ceftaroline was also synergistic against MRSA and was the most effective combination against the MRSA, daptomycin-nonsusceptible MRSA, and hVISA isolates tested. In the same study the synergistic effect of the combination of oritavancin with ampicillin, ertapenem, and ceftaroline against vancomycin-resistant *E. faecalis* and *E. faecium* isolates was limited and strain dependent.[239]

Clinical Pharmacokinetics and Pharmacodynamics

Oritavancin is administered as a single dose of 1200 mg over 3 hours, after which an average peak of 138 mg/L in serum is obtained.[240] Oritavancin is widely distributed, fitting a dose-linear, three-compartment model with a high volume of distribution of almost 100 L and a slow release from tissue absorption sites. This increased volume of distribution, together with high protein binding (85%–90%), may explain, in part, the prolonged terminal half-life of about 240 hours, supporting the one-time dosing strategy for ABSSSI.[240] Oritavancin accumulates intracellularly in the liver, kidneys, spleen, lymphoid tissue, and lungs, from where it is subsequently released; only trace amounts of the administered dose are found in urine and feces. An adequate penetration of oritavancin into skin blister fluid of approximately 19% of the plasma concentration has been reported.[241]

Oritavancin displays a rapid bactericidal and concentration-dependent activity against a wide variety of gram-positive organisms. In the neutropenic murine thigh infection model using *S. aureus* isolates, the activity is best predicted by the C_{max}:MIC ratio and the AUC/MIC ratio.[242] It has also been observed that a greater bactericidal effect is seen when a single full dose of oritavancin is given than when it is administered in fractioned doses. Oritavancin also exhibits concentration-dependent bactericidal activity against stationary phase and biofilm culture of *S. aureus* in vitro.[243]

Oritavancin is supplied in 400-mg vials that should be reconstituted and further diluted in dextrose 5% (1000 mL) to a concentration of 1.2 mg/mL to be infused over 3 hours. This compound is not compatible with normal saline and should only be diluted in dextrose 5%.

Adverse Reactions and Drug Interactions

Among the ABSSSI phase III trials,[244,245] the most common side effects were headache, nausea, vomiting, and diarrhea; rates of discontinuation were not different from the comparator arm. Transient and mild ALT elevations were also observed. Infusions reactions, such as flushing and pruritus, may occur but less frequently than with vancomycin and also resolve after slowing the infusion rate. Hypersensitivity reactions were unusual (<1.5%), but some evidence suggests they may develop more frequently in those patients with prior reactions to glycopeptides. In clinical trials the median duration of the hypersensitivity reactions was 2.4 days. Oritavancin is classified as pregnancy category C, and its use in nursing mothers has not been studied.

Oritavancin, unlike other lipoglycopeptides, has a potential for drug-drug interaction through the inhibition of several cytochrome P450 enzymes. In this regard, a recent study showed no effect of oritavancin on S-warfarin C_{max} or AUC, although patients receiving these drugs concomitantly should still be observed for possible bleeding.[246] In addition, as with telavancin, oritavancin can affect laboratory phospholipid-dependent coagulation tests, such as PT/international normalized ratio (INR) and aPTT, whereas anti-FXa assay and thrombin time remain unaffected. The duration of the interference with these tests depends on the commercial reagents used. The maximum time to resolution of these test abnormalities has been 12 hours for PT/INR and 120 hours for aPTT; hence the use of IV unfractionated heparin sodium is contraindicated for 5 days after the administration of oritavancin. Surprisingly, about 30% of the healthy subjects receiving oritavancin experienced increased levels of D dimer that returned to normal in up to 72 hours.[247] In patients with mild to moderate liver or renal impairment, adjustment of oritavancin dosage is not required, although its use in those with severe hepatic or renal insufficiency has not been evaluated.

Clinical Uses

Oritavancin showed evidence of efficacy in a phase II trial of patients with complicated skin and soft tissue infections[248] and in another study of patients with *S. aureus* bacteremia administered in four different daily doses.[249] In two identical phase III randomized trials of adult patients with ABSSSI, oritavancin, as a single-dose of 1200 mg, was noninferior to 7 to 10 days of vancomycin.[244,245] These trials enrolled 1987 patients, and the primary end point was cessation (or reduction) of spread of baseline skin lesion, absence of fever, and no need for other antibiotics after 48 to 72 hours of therapy initiation. In both trials MRSA was found in ≈20% of all patients and in ≈0% of those with a positive culture. With these results the FDA approved this agent in 2014 for the treatment of adult patients with ABSSSI caused by susceptible isolates of the following gram-positive microorganisms: *S. aureus* (including MRSA), *S. pyogenes, S. agalactiae, S. dysgalactiae, S. anginosus* group, and *E. faecalis* (vancomycin-susceptible isolates only). Oritavancin is not currently approved in the pediatric population, although it is being evaluated in an ABSSSI clinical trial of children age 3 months to 18 years (clinicaltrials.gov identifier NCT02134301). Based on its significant in vitro activity and its ease of administration, studies of oritavancin for infections such as bacteremia, endocarditis, and osteomyelitis caused by susceptible gram-positive organisms, including VRE, MRSA, VISA, hVISA, and VRSA, seem warranted.

CONCLUSIONS

Among the drugs reviewed in this chapter, vancomycin is still the most important option for severe skin infections requiring hospitalization and the usual choice for parenteral therapy for osteomyelitis, bacteremia, and endocarditis caused by MRSA. This view reflects the long experience with and confidence in its use, along with its relatively low cost; however, the recommendation of targeting higher serum levels in severe disease has reduced the therapeutic window. Telavancin has been approved for the treatment of ABSSI and hospital-acquired pneumonia caused by gram-positive pathogens when other agents are unsuitable; however, its current use is probably jeopardized in view of the lower efficacy observed in patients with moderate-to-severe renal failure and its higher rate of creatinine increase than the comparator in the ABSSI and hospital-acquired pneumonia trials. Due to its favorable pharmacokinetic properties, dalbavancin and oritavancin appear as attractive agents for the treatment of ABSSI caused by gram-positive pathogens, allowing the administration of only a single dose. This strategy might be particularly useful to avoid hospitalization of a significant proportion of patients with ABSSI; however, the cost of these compounds might be a limitation for more extensive use. Further efficacy studies on drug-resistant gram-positive infections are expected.

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The complete reference list is available online at Expert Consult.

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UPDATE

Oritavancin in Osteomyelitis

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Because of its long half-life, oritavancin can be used as a single injection in patients who have difficulties with repetitive dosing regimens. Although randomized clinical trials are lacking, real world data on the safety and efficacy of oritavancin is accumulating.[1,2] These two small case series include a total of 17 patients with chronic osteomyelitis of whom 16 had clinical cure after 1-10 doses of oritavancin (usually 1-2 doses). These results are promising, but randomized studies are warranted.

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