eliminated in feces by way of biliary excretion and possibly transintestinal elimination.[206] Biliary concentrations of azithromycin are higher than in the serum, and most of the drug in the bile is unchanged.[206] There are no data available on dose adjustments required with severe renal or hepatic failure.

Clarithromycin is well absorbed after oral administration, with or without food, and is approximately 55% bioavailable.[184] Mean peak serum concentrations at steady state with oral doses of 250 and 500 mg every 12 hours are 1 and 2 to 3 μg/mL, respectively. The elimination half-lives for those two regimens are 3 to 4 and 5 to 7 hours, respectively. Clarithromycin is appreciably metabolized in the liver by oxidation and hydrolysis to a number of compounds, accounting for a recovery of 78%. The major metabolite, 14-hydroxyclarithromycin, has antibacterial activity and accounts for 20% of the metabolites.[184] With the 250-mg and 500-mg oral doses given every 12 hours, about 20% to 30%, respectively, of the drug is excreted into the urine unchanged and 10% to 15% as the hydroxy metabolite. At higher doses, there is some nonlinearity of half-life, apparently because of saturation of metabolic mechanisms with a higher proportion of unchanged drug eliminated in the urine.[184] About 65% to 70% of the drug is bound to protein in the serum. With renal insufficiency involving creatinine clearances of less than 30 mL/min, there is a marked increase in the half-life of clarithromycin.[191] Dose adjustment is suggested in patients with severe renal failure, including recommendations for a 500-mg loading dose, followed by 250 mg once or twice daily depending on the type of infection.[191] No dosage adjustment is recommended at present for severe hepatic dysfunction.[191]

Clarithromycin is widely distributed and penetrates well into various tissues, generally exceeding peak maximum serum levels by severalfold.[191] Concentrations of clarithromycin and its 14-hydroxy metabolite in middle ear fluids of children with acute otitis media exceeded the plasma concentrations by approximately ninefold and fourfold, respectively, 12 hours after the sixth dose when the drug was given every 12 hours.[212] Concentrations generally exceed the MIC of most strains of middle ear pathogens, except for highly penicillin-resistant *S. pneumoniae*. Data indicate minimal penetration of clarithromycin and its 14-hydroxy metabolite into CSF in patients without meningitis.[213] The levels achieved were below the MIC for the usual pathogens associated with bacterial meningitis and were 1% to 2% of the corresponding plasma levels. Clarithromycin, like the other macrolides, penetrates well into phagocytic cells.[214]

Adverse Reactions

Adverse reactions to clarithromycin and azithromycin at the usual doses have been rare.[183,184,215] The most common complaints are gastrointestinal (diarrhea, nausea, abdominal pain), and discontinuance of therapy is rarely required. Azithromycin has also been shown to have a profound effect on the gastrointestinal microbiome. When compared to household contacts who did not receive antibiotics, patients who received either azithromycin or amoxicillin experienced substantial decreases in microbiota diversity that were sustained throughout the 6-month study period.[216] Studies in mice show long-term effects on the microbiome from macrolides, especially in young animals,[217,218] and studies in schoolchildren in Finland confirm the more profound and prolonged perturbation compared to β-lactam antibiotics.[219]

Acute psychosis or "mania" has been noted in a few patients receiving clarithromycin.[125,126] High doses of clarithromycin in animals have been associated with teratogenic effects, and therefore that drug is not recommended for use in pregnancy.[109] Azithromycin is classified as pregnancy category B.

Abnormalities in liver function are occasionally encountered in patients treated with these drugs, and reversible cholestatic hepatitis has been reported with azithromycin.[220] With the high doses of these drugs used in the treatment of *M. avium* complex, tinnitus, dizziness, and reversible hearing loss have been reported.[221,222] Rarely, severe allergic reactions have occurred with the use of azithromycin.

The risk of macrolide-associated torsades de pointes (a polymorphic ventricular tachycardia) has been associated with increasing age, female sex, chronic use, and concomitant drug use, especially with cisapride.[223,224] Chronic exposure to azithromycin in an animal model promoted intracellular sodium loading, which could lead to proarrythmia.[224] A retrospective study reported that patients taking a 5-day course of azithromycin had a 2.88 increased risk of cardiovascular death compared with those taking no antibiotics, with risk being most pronounced among patients at high risk for cardiovascular disease.[225] Additionally, in an observational case series of patients who received treatment for *H. pylori* with either clarithromycin or amoxicillin, there was an increased risk of myocardial infarction, arrhythmia, and cardiac mortality during or shortly after clarithromycin therapy. However, clarithromycin use was not associated with cardiovascular risks long term.[226] After following patients for a year or longer in a large randomized, multicenter study an increased number of deaths were observed among patients with underlying coronary artery disease who received 2 weeks of clarithromycin.[227] Conversely, a recent retrospective cohort study found that macrolide antibiotics were not associated with a higher 30-day risk of ventricular arrhythmia or all-cause mortality compared to nonmacrolide antibiotics.[228] Although these conflicting observations are of concern, definitive association of increased cardiovascular-related death and exposure to azithromycin or clarithromycin cannot be based on a retrospective cohort design, given residual confounding that may have influenced the outcome.[229] However, as a result of that study, the US Food and Drug Administration has required changes in the labeling of azithromycin warning about the risk of QT interval prolongation and cardiac arrhythmias, as well as changes in the labeling of clarithromycin warning about the increased risk of death among patients with underlying heart disease even in the setting of short courses of therapy based on the study by Jespersen and coauthors.[227,230] It now seems prudent not to use a macrolide antibiotic together with another drug known to prolong the QT interval and to exercise caution in the use of a macrolide antibiotic, even alone, in patients with underlying heart disease.

Drug Interactions

Azithromycin minimally inhibits CYP3A4 and therefore appears to be the safest macrolide derivative from a drug interaction perspective.[231]

Clarithromycin has been reported to be associated with increased concentrations of several drugs that undergo hepatic metabolism by the CYP3A subclass of the cytochrome P-450 enzyme system (see Table 29.3).[134] As with erythromycin, these interactions can lead to serious toxicity. It is not yet clear whether the clarithromycin interactions can occur with all the drugs that interact with erythromycin, but a conservative clinical approach would be to consider that potential. These interactions with the hepatic metabolism of other drugs have not been documented with azithromycin, which does not appear to induce or bind and inactivate the cytochrome P-450 enzymes, probably because of its different azalide structure.[133,232]

Clarithromycin may decrease the serum concentration of zidovudine by unknown mechanisms when the two drugs are taken at the same time.[233] However, in another study with a somewhat different design, there was no significant alteration of zidovudine bioavailability in volunteers with acquired immunodeficiency syndrome (AIDS) who took the two drugs 2 hours apart.[234]

Clarithromycin, like erythromycin, may occasionally lead to digoxin toxicity, possibly by diminishing the bacterial metabolism of digoxin in the gut.[235]

Uses of Clarithromycin and Azithromycin

Clarithromycin and azithromycin have several indications for use as the drug of choice and some important applications as an alternative drug (see Table 29.4).[6,75,109,135–146] Clarithromycin and azithromycin were as effective as other commonly used antimicrobial agents when employed in randomized multicenter trials for the treatment of pharyngitis, sinusitis, community-acquired pneumonia (including *M. pneumoniae* and *C. pneumoniae* pneumonia), and skin infections.[147,183,184,236] Clarithromycin and azithromycin have been considered alternatives to penicillin in treating group A β-hemolytic streptococcal pharyngitis in patients with penicillin allergies.[237] Treatment with a 10- to 14-day course of either clarithromycin (250 mg twice daily) or penicillin VK (250 mg every 6 hours) is equally effective.[184,238] Azithromycin administered for 5 days (500 mg on day 1, followed by 250 mg daily for 4 days) is effective in

eradicating group A streptococci from the pharynx,[239] although shorter courses of 3-day treatment with azithromycin were associated with lower levels of bacteriologic eradication when compared with a 10-day course of penicillin V.[240] One study demonstrated that a 10-day course of treatment with clarithromycin (250 mg twice daily) led to more bacteriologic eradication compared with a 5-day course with azithromycin (500 mg on day 1, followed by 250 mg daily).[241] Clinical studies have demonstrated equal or superior tolerability as well as clinical and bacterial efficacy of azithromycin (12 mg/kg, once daily for 5 days) compared with a 10-day therapy with penicillin V in the treatment of pediatric streptococcal pharyngitis.[242,243] However, the effectiveness of short-course azithromycin in preventing acute rheumatic fever is unknown.[244] Moreover, with the variable prevalence of macrolide resistance by group A streptococci, the effectiveness of these agents in treating such infections when the susceptibility of the organism is unknown should be questioned.

Azithromycin administered for 5 days or clarithromycin for 7 to 10 days for the treatment of acute otitis media in children has been effective,[245,246] but use is limited due to increasing macrolide resistance amongst *S. pneumoniae* isolates, and cases of meningitis have been reported during oral therapy.[247]

Guidelines available for the treatment of adult outpatients with community-acquired pneumonia include the use of a macrolide alone as a first-line agent in patients with no significant medical problems and without the recent use of antimicrobial agents or as combination therapy with a β-lactam or respiratory fluoroquinolone in patients with comorbidities such as chronic heart, lung, or liver disease; diabetes; or immunosuppressing conditions.[147] The aforementioned guideline is now further complicated for patients with heart disease by the concern for potentiating cardiac arrhythmias with either a macrolide or a fluoroquinolone. All three macrolides have good activity against most pathogens that commonly cause community-acquired pneumonia, including many strains of *S. pneumoniae* and almost all strains of *M. pneumoniae, C. pneumoniae, Legionella* species, and *Moraxella catarrhalis* (see Table 29.1).[34] However, the rising prevalence, already discussed, of macrolide resistance by strains of *S. pneumoniae,* especially those that are penicillin resistant, requires caution in the use of any of the macrolides as a sole agent when that organism may be causing pneumonia. That concern would be greatest for older adults or persons with underlying medical conditions. A study by Martinez and colleagues[248] suggested lower mortality benefit with combination therapy including a macrolide in community-acquired pneumonia associated with *S. pneumoniae,* including penicillin-susceptible strains, although sample size was small and the study was retrospective in design. Macrolides, with their ability to concentrate intracellularly, are effective against intracellular pathogens, including *C. pneumoniae, Legionella* species, and *Coxiella burnetii* (the agent of Q fever).[249] Treatment with macrolides of lower respiratory tract infection with *M. pneumoniae* and *C. pneumoniae* in children shortens the clinical course of infection.[250] In the treatment of patients with nonpneumococcal pneumonia, erythromycin and azithromycin were equally effective (76% and 79%, respectively) in achieving clinical and radiologic resolution.[198] The longer half-life of azithromycin allows a shorter duration of therapy, and in one retrospective study, a 3-day course of azithromycin (daily dose, 500 mg) was as effective as a 5-day course (500 mg in a single dose the first day, followed by 250 mg daily for 4 days) in the treatment of atypical pneumonia.[251]

The generally recommended empirical therapy for community-acquired pneumonia requiring hospitalization includes the combination of a macrolide and a β-lactam,[147] which was associated with briefer hospital stays and a lower mortality rate than treatment with a cephalosporin alone.[252,253] In addition, two retrospective studies found that in cases of bacteremic pneumococcal pneumonia, dual antimicrobial therapy, including a macrolide, reduced mortality.[254,255]

B. pertussis is susceptible in vitro to azithromycin and clarithromycin. Furthermore, data from a multicenter randomized trial in North America demonstrated that azithromycin was as effective as erythromycin, better tolerated, and associated with improved compliance.[256] The Centers for Disease Control and Prevention (CDC) recommends that azithromycin should be used for all neonates younger than 1 month and erythromycin, clarithromycin, or azithromycin are noted to be acceptable for the treatment of pertussis in persons age 1 month or older.[257] Resistance to azithromycin has been rarely reported, but limited studies are available on its clinical effectiveness.[258] In a study involving a small number of children with pertussis in Japan, a 5-day course of azithromycin and a 7-day course of clarithromycin were as effective in eradicating *B. pertussis* from cultures 1 week after treatment as in historical control subjects who had been treated with erythromycin for 2 weeks.[137] Until more data from clinical studies evaluating clarithromycin and azithromycin are available, the American Academy of Pediatrics recommends erythromycin as the antimicrobial agent of choice for treatment of and prophylaxis against pertussis and clarithromycin (15 mg/kg/day orally in two divided doses, with a maximum of 1 g/day, for 7 days) and azithromycin (10 mg/kg/day orally in one dose, with a maximum of 500 mg/day, for 5 days) as alternatives for patients who cannot tolerate erythromycin.[259]

Clarithromycin (500 mg orally twice daily) or azithromycin (500–600 mg orally once daily) in addition to ethambutol with or without rifabutin are now considered the drugs of choice in the treatment of disseminated *M. avium* complex infections in patients with AIDS.[109] Relatively few mutations are associated with macrolide resistance in mycobacteria, and all are in genes encoding the peptidyl transferase region of the 23S rRNA.[260] Therefore the use of macrolides alone is often associated with clinical relapse and the emergence of macrolide-resistant organisms.[261] In AIDS patients with $CD4^+$ T-lymphocyte counts lower than 100 cells/mm^3, prophylaxis of disseminated *M. avium* complex infection with clarithromycin (500 mg orally twice daily) or azithromycin (1200 mg orally once weekly) is effective.[262,263] Clarithromycin prophylaxis of this condition has been demonstrated to increase survival.[262] Discontinuation of a macrolide-based prophylaxis for *M. avium* complex infection may be possible in patients who have been given prophylaxis for at least 1 year and whose $CD4^+$ counts have increased to greater than 100 cells/μL on highly active antiretroviral therapy.[264] In patients who develop disseminated infection despite prophylaxis, macrolide-resistant isolates are frequently found.[262]

A single oral dose of azithromycin (1-g single dose oral dose) is a highly effective treatment for trachoma and has become the treatment of choice for *C. trachomatis*.[109,265] In fact, in a recent study conducted in trachoma endemic areas, such as sub-Saharan Africa, it was hypothesized that biannual mass distributions of azithromycin to children ages 1 to 59 months would reduce mortality. While limitations of the study and the downstream effects of mass distribution of antibiotics should be considered, it is interesting to note that childhood mortality was 13.5% lower (P <.001) among children in communities who received azithromycin than in those who received placebo.[266] A single oral 1-g dose of azithromycin has been as effective as a 1-week course of doxycycline in the treatment of *C. trachomatis* urethritis and cervicitis[141] and acute nongonococcal urethritis (caused by *C. trachomatis* or *U. urealyticum*) in men.[267] Azithromycin (1-g single oral dose) is as effective as ceftriaxone (250-mg intramuscular dose) in treating chancroid and is considered first-line treatment.[155] A single 2-g dose of azithromycin is not recommended as treatment for *N. gonorrhoeae* infection because of gastrointestinal side effects, expense, and concern for the induction of resistance.[268]

Clarithromycin (500 mg orally twice daily) combined with amoxicillin (1 g twice daily) or metronidazole (500 mg two to three times daily) and a proton pump inhibitor for 14 days is recommended as a first-line therapy for the treatment of *H. pylori* in areas where clarithromycin resistance for this pathogen is <15% and in patients without a history of macrolide exposure.[269] Failure is often associated with primary resistance by *H. pylori* strains to one of these antimicrobials[270] or with the emergence of secondary resistance, which occurs more frequently if only one antimicrobial agent is used or if two are used in the presence of primary resistance to one of them.[271,272] Sequential therapy involving 5 days of use of a proton pump inhibitor together with amoxicillin, followed by another 5 days of the proton pump inhibitor plus clarithromycin and a nitroimidazole, is associated with high cure rates (approximately 90%)[270] and is a suggested first-line therapy.[269]

Azithromycin is effective in the treatment of *Campylobacter* enteritis, but in some areas macrolide-resistant strains are common.[138,273] Because of its lower toxicity, azithromycin should be used instead of erythromycin

when therapy is indicated and cost not a major factor. Azithromycin treatment for 5 days was found to be as effective as ciprofloxacin in the treatment of shigellosis in a randomized controlled trial and can be considered an alternative therapy for that condition, especially for children and pregnant women.[109,143]

Clarithromycin has been used effectively as the central drug or as an alternative in a variety of mycobacterial infections, including *M. tuberculosis, M. avium* complex, *Mycobacterium chelonae,*[274] *Mycobacterium fortuitum, Mycobacterium genavense,* and *Mycobacterium kansasii.*[109] In deep-seated infections and in immunocompromised patients with these infections, combination therapy with more than one active agent is suggested to decrease the chance for the emergence of resistant strains.[275] Limited data suggest the effectiveness of clarithromycin in treating leprosy, for which it can serve as an alternative drug.[109,276]

Clarithromycin (500 mg twice daily for 14–21 days) or azithromycin (500 mg for 7–10 days) is an alternative treatment of early Lyme disease[277,278]; however, it is less effective than doxycycline, amoxicillin,[278] and cefuroxime.[279] In some situations, such as allergy to β-lactam antibiotics in pregnant women or allergy to both β-lactam and tetracycline antibiotics, azithromycin may be an effective alternative treatment for Lyme disease. However, present guidelines do not recommend macrolides as first-line therapy for Lyme disease.[279]

Azithromycin (when given with atovaquone) is as effective as clindamycin and quinine for the treatment of *Babesia microti* infections, a frequent coinfecting agent with *B. burgdorferi.*[146] Although clindamycin plus quinine remains the preferred treatment regimen in severe cases of babesiosis, atovaquone plus azithromycin is an effective regimen for non–life-threatening babesiosis in immunocompetent adult patients.[146,279]

Azithromycin has been shown to have antimalarial activity similar to that of doxycycline in animal models.[280] Two human volunteer studies suggested that azithromycin has potential in the prevention of chloroquine-resistant *Plasmodium falciparum* infection.[280,281] Two field trials on the use of azithromycin as a single agent for malaria prophylaxis demonstrated only moderate efficacy (70%–90%) for *P. falciparum* compared with high efficacy for *Plasmodium vivax.*[282,283] Azithromycin in combination with other antimalarial agents, such as chloroquine, quinine, or sulfadoxine-pyrimethamine in pregnant women, produces synergistic interactions in vitro and may be effective for the treatment of uncomplicated *P. falciparum* malaria in adults.[284–286]

There has been great interest in the potential role of chronic infections (especially those caused by *C. pneumoniae*), and more recently in the role of inflammation per se, in potentiating atherosclerosis and vascular thromboses, including coronary artery disease.[287] In this regard, azithromycin has been investigated because of its activity against *C. pneumoniae* and its ability to accumulate in high concentrations in atherosclerotic plaques.[288] One study in a small number of men who had survived myocardial infarction, had substantial *C. pneumoniae antibody* titers, and were given azithromycin (500 mg daily for 3 or 6 days) demonstrated a significant decrease in subsequent adverse cardiovascular events compared with a similar group of men who were not treated with azithromycin.[289] However, clinical trials have not shown a benefit of macrolide use in preventing recurrent events in patients with acute coronary syndromes.[290,291] Assuming a real effect of the macrolide on such cardiac events, it is uncertain whether the result is related to its antimicrobial activity, its antiinflammatory activity on atheromata or thrombogenesis (as discussed earlier in the "Antimicrobial Activity" section under "Erythromycin"), both of these activities, or other unknown effects. A large randomized, placebo-controlled trial of stable patients with previous myocardial infarction and immunoglobulin G antibodies to *C. pneumoniae* treated with azithromycin for 12 weeks and followed for a median of 14 months did not demonstrate a significant reduction of clinical sequelae of coronary heart disease.[292] A randomized, placebo-controlled trial of clarithromycin 500 mg once daily for 2 weeks in several thousand Danish patients with stable coronary artery disease followed over 3 years showed no benefit of treatment and a significant increase in cardiovascular mortality in those receiving clarithromycin (5.1% vs. 3.5%, $P = .01$).[227] Potential reasons for the increase in cardiovascular mortality found in those who received clarithromycin include a nonspecific random effect, unknown inequalities in risk between the two randomized groups, and proarrhythmic and drug interaction effects of clarithromycin (though cardiovascular mortality did not differ during the first month of follow-up).

Efficacy of azithromycin has been evaluated for treatment of patients with cystic fibrosis (CF). Four randomized, placebo-controlled trials comparing placebo with azithromycin administered for a period of 3 to 12 months found considerable improvement of lung function as assessed by increase of forced expiratory volume in 1 second from baseline, and reduced risk of bacterial exacerbations among patients receiving azithromycin.[293–296] The use of daily azithromycin at a dose of 250 mg once daily for 1 year was found to decrease exacerbations among patients at high risk for acute exacerbations of chronic obstructive pulmonary disease (COPD). However, patients were also more likely to have hearing loss and harbor macrolide-resistant organisms.[297] Beneficial effects demonstrated in CF, COPD, and ventilator-associated pneumonia[298,299] are likely related not only to the bacterial growth-inhibiting effects of the macrolide but also to the general antiinflammatory activities of the macrolides, the downregulating effects of the drug on the production of bacterial virulence factors of *P. aeruginosa* (already discussed), or both.[300] The use of azithromycin chronically in patients with COPD requires prior screening for QT interval prolongation and hearing loss and should not be used in those needing the administration of other drugs that are known to prolong the QT interval. Caution is also advised for such use in those with underlying heart disease.[225] When azithromycin is used chronically for those with COPD, it seems likely that administration three time per week rather than daily may be sufficient, given the long half-life of the drug in macrophages. Another caution comes from a recent study reporting that long-term use of azithromycin by adults with CF was associated with the development of infection with nontuberculous mycobacteria, particularly multidrug-resistant *Mycobacterium abscessus.* A suggested possible mechanism was that azithromycin can block autophagosomal clearance by preventing lysosomal acidification, thereby attenuating killing of intracellular mycobacteria.[301]

The potentially useful antiinflammatory actions of the macrolides (aside from their antimicrobial activity) were discussed earlier under "Erythromycin."

KETOLIDES

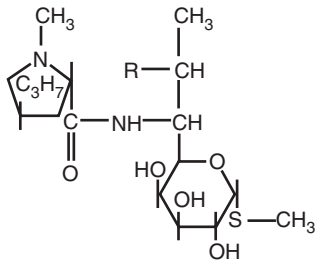
Ketolides are a class of semisynthetic agents derived from erythromycin A that have increased acid stability and increased antibacterial potency against many bacteria resistant to macrolides. They are unable to induce the MLS_B methylase type of resistance. Telithromycin (HMR 3647, or Ketek), which was approved for clinical use in the United States in April 2004 and had been in use in Europe since 2001 and in some Latin American countries, was the first member of this new class. However, its potential (although rare) for serious, even fatal, hepatotoxicity was recognized in 2006, which severely and appropriately limited its use, and the drug has now been removed from the market in the United States.

LINCOMYCIN AND CLINDAMYCIN

Derivation, Chemistry, and Preparations

Lincomycin was isolated in 1962 from an organism, *Streptomyces lincolnensis,* obtained from soil near Lincoln, Nebraska. Many of its biologic properties are similar to those of erythromycin, but it is chemically unrelated, consisting of an amino acid linked to an amino sugar (Fig. 29.4). Chemical modification provided clindamycin (7-chloro-7-deoxylincomycin) (see Fig. 29.4) with increased antibacterial potency and absorption after oral administration.[302] Because there are no therapeutic advantages for lincomycin over clindamycin, the discussion here concentrates on the latter, although both are still marketed as pharmaceuticals. Both are weak bases that are readily water soluble when provided as salts.

Although lincomycin (Lincocin) is available in the United States as the hydrochloride salt in solution (300 mg/mL) for parenteral use, it is rarely used. Clindamycin is prepared as the hydrochloride salt of the base in 75-, 150-, and 300-mg capsules and of the palmitate ester as a powder for pediatric suspension (75 mg/5 mL). It is supplied as the phosphate ester for IM use (150 mg/mL) and for IV use



trans-L-4-n propylhygrinic acid

FIG. 29.4 The lincosamide antibiotics. In lincomycin, R = OH; in clindamycin, R = Cl.

(150 mg/mL, 300 mg/mL, 600 mg/mL, 900 mg/mL). It is also available in topical solution, gel, lotion, foam, and pad (all at 1%) for the treatment of acne vulgaris and in a concentration of 2% in a vaginal cream and as a vaginal suppository (100 mg) for the treatment of bacterial vaginosis. A relatively new lincosamide, pirlimycin, is a *cis*-4-ethyl-L-picecolic acid amide of clindamycin that is exclusively approved for veterinary applications.[303]

Mechanism of Action

The lincosamide antibiotics have, in susceptible organisms, the same or overlapping 50S ribosomal binding sites as those for the macrolides and chloramphenicol, and they may compete with these drugs for binding.[3] Protein synthesis is inhibited primarily in early chain elongation by interference with the transpeptidation reaction,[303] possibly by blocking of the P (peptidyl donor) site. Like the macrolides, the lincosamide antibiotics may also stimulate the dissociation of peptidyl-tRNA from ribosomes.

Mechanisms of Resistance

There are several mechanisms of resistance to the lincosamide antibiotics. First, and most important, is the alteration in the 23S rRNA of the 50S ribosomal subunit by methylation of adenine,[3,304] which has been discussed earlier in the "Target Site Alterations" section under "Erythromycin". It is usually plasmid mediated and provides the MLS_B type of resistance, which includes that exhibited by some strains of *S. aureus*, *S. pyogenes,* and *B. fragilis* to clindamycin. This type of resistance in *S. aureus* is encoded by the *ermA* or *ermC* genes and, when of the macrolide-inducible variety, is characterized by a positive erythromycin-clindamycin "D test"—a double-disk diffusion test in which the zone of inhibition around the clindamycin disk is blunted on the side facing the erythromycin disk.[305] The MLS_B resistance mechanism in staphylococci more frequently manifests clindamycin resistance when the strain possesses the *ermA* gene as compared with the *ermC* gene.[306] With that type of resistance in *S. aureus,* exposure to clindamycin (which is not an inducer) in vitro or in vivo may result in clindamycin resistance due to selection of preexisting constitutive *erm* mutants, especially when the organism is at high inoculum.[306,307] An additional methyltransferase enzyme, cfr, was found to cause multidrug resistance in *S. aureus* to chloramphenicol, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A (PhLOPSA) through the methylation of the 23S ribosomal RNA nucleotide.[308–310] Second mutations in the bacterial ribosomal RNA may confer resistance to clindamycin as demonstrated in some strains of *Mycobacterium smegmatis.*[311] Third, alteration in particular 50S ribosomal proteins of the receptor site confers resistance to erythromycin and often to the lincosamides[3]; this mechanism was previously discussed for erythromycin. Fourth, resistance is conferred through inactivation of lincomycin and clindamycin by a few isolates of staphylococci (including *S. aureus*) and *Bacteroides* spp. that possess a plasmid-mediated 3-lincomycin 4-clindamycin *O*-nucleotidyltransferase that catalyzes the nucleotidylation of the hydroxyl group in position 4 of clindamycin.[8,312,313] This adenylation of the lincosamides is associated with high-level resistance to lincomycin, but clindamycin resistance may not be detected by routine methods. The adenylation of clindamycin is associated with impaired bactericidal activity and decreased activity at high inoculum levels. The *lnu* genes (formerly known as *linA* and *linA´*), include *lnu(A), lnu(B), lnu(C),* and others, which can be chromosomal or plasmid-carried.[303] Plasmids carrying *lnu(A)* are found in *S. aureus* and coagulase-negative staphylococci, and *lnu(B)* has been identified in staphylococci, enterococci, and *Erysipelothrix,* while *lnu(C)* was first found in *Streptococcus agalactiae.*[303]

Finally, Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp. are intrinsically resistant to clindamycin, apparently because of poor permeability of the cellular outer envelope to the drug.[8]

TABLE 29.5 In vitro Susceptibilities to Clindamycin

ORGANISM	MINIMAL INHIBITORY CONCENTRATION (μg/mL) Range	MIC_{50}
Streptococcus pneumoniae	≤0.25–≥128	≤0.25
Streptococcus pyogenes	≤0.06–>64	≤0.06
Viridans-group streptococci	≤0.06–>256	≤0.06–0.12
Enterococcus	0.12–>8	>8
Staphylococcus aureus	≤0.06–>8	0.25
Staphylococcus epidermidis	<0.12–>8	0.12
Clostridium perfringens	≤0.06–>4	1
Neisseria gonorrhoeae	0.01–6.3	3.1
Haemophilus influenzae	0.4–50	12.5
Bacteroides fragilis group	0.03–>128	1–3
Bacteroides melaninogenicus	≤0.1–1	<0.1
Bacteroides thetaiotaomicron	0.06–>128	1.7–4
Fusobacterium spp.	≤0.008–>16	0.25
Peptococcus spp.	≤0.1–>100	≤0.5
Peptostreptococcus spp.	≤0.06–>32	0.125
Prevotella sp.	0.03–>128	0.12
Mycoplasma pneumoniae	1.6–3.1	3.1

MIC_{50}, Minimal inhibitory concentration for 50% of isolates (μg/mL).

Antimicrobial Activity

In vitro susceptibilities to clindamycin are given in Table 29.5.[a] Clindamycin is more potent than lincomycin but similar in potency to erythromycin against staphylococci, pneumococci, *S. pyogenes,* and streptococci of the viridans group when strains are sensitive to both. However, although erythromycin demonstrates at least moderate activity against *Enterococcus, H. influenzae,* and *N. meningitidis,* clindamycin is generally inactive against these organisms at clinically achievable concentrations. In contrast, clindamycin has shown significantly greater activity than erythromycin against most clinically significant anaerobic bacteria, particularly *B. fragilis.*[78] Clindamycin is not active against *Nocardia* species, most aerobic gram-negative bacilli, or mycobacteria.

Clindamycin used to be one of the most active antibiotics available against *B. fragilis;* however, resistance is increasing to high levels (from approximately 30% to 60%).[318] With other agents available that are more reliably active (metronidazole, piperacillin-tazobactam, and carbapenems), empirical therapy with clindamycin for an anaerobic infection should be started with caution.[319,320] Estimates of resistance to clindamycin by anaerobes also include nearly 20% to 25% of clostridial species other than *C. perfringens,*[321,322] 15% to 20% of peptostreptococci,[323] 10% of *Fusobacterium* species,[323] and 30% to 40% of *Prevotella* strains.[321–323] All the Enterobacteriaceae are resistant to clindamycin.

[a]References 48, 50, 55, 67, 314–317.

Clindamycin provides high activity against pneumococci and group A streptococci; however, clinical isolates showing resistance to clindamycin and erythromycin have been increasingly reported from different areas, as already discussed under "Erythromycin". The majority of strains of *S. pneumoniae* remain clindamycin-susceptible, with resistance rates approaching 10% in some areas of the United States.[324] In the United States, most surveys conducted on macrolide-resistant *S. pneumoniae* and *S. pyogenes* strains isolated through the 1990s found them to be of the M phenotype, which does not show cross-resistance to clindamycin.[41] However, a survey of 1885 clinical strains of *S. pyogenes* isolated in 2002 and 2003 from 45 medical centers in the United States showed that almost 7% were macrolide resistant and 0.5% were clindamycin resistant, with 56% of the macrolide-resistant strains demonstrating the MLS_B phenotype (almost all of the inducible type) and 44% having the M phenotype.[16] Emergence of resistance might be expected during clindamycin treatment of macrolide-resistant *S. pyogenes,* initially showing clindamycin susceptibility, when the strain possesses the MLS_B-inducible phenotype. It is therefore suggested that the D test be performed on macrolide-resistant *S. pyogenes* to determine clindamycin susceptibility.[16] A recent study of *S. pyogenes* isolates from the United States predicted 12.7% resistance to erythromycin and clindamycin based on whole-genome sequencing.[325]

The antibacterial activity of clindamycin against *S. pyogenes* displays several characteristics that have the potential to be clinically advantageous and are less prominently demonstrated or absent in the penicillin family. In contrast to β-lactam drugs, clindamycin acts on stationary growth–phase bacteria, suppressing the production of bacterial proteins such as *S. pyogenes* superantigens,[326] supported by an observational clinical study finding that clindamycin treatment improved survival of patients with streptococcal toxic shock syndrome.[327] In vitro studies suggest that subinhibitory concentrations of clindamycin paradoxically induce virulence mechanisms in *S. pyogenes*, suggesting that therapeutic dosing is important.[326]

Group B *Streptococcus* (*S. agalactiae*) used to be predictably sensitive to clindamycin but that is no longer the case, with nearly one-third of strains resistant to clindamycin.[328] Both constitutive and inducible resistance are important issues in group B *Streptococcus*, which is now on the CDC's list of antibiotic-resistant threat agents.[328] Clindamycin continues to have substantial activity against methicillin-sensitive *S. aureus* but against fewer strains that are methicillin resistant.[329] Cross-resistance of *S. aureus* between lincomycin and clindamycin is complete. The MICs of clindamycin and erythromycin in vitro are generally similar for *S. aureus* strains that are sensitive to both agents; however, resistance can be selected in vitro by serial subculture in the presence of subinhibitory concentrations of either drug, and it occurs slowly for clindamycin and more rapidly for erythromycin.[302,330] In contrast, strains that are sensitive to clindamycin and resistant to erythromycin can be rapidly selected for clindamycin resistance by serial subculture on clindamycin. Consistent with these in vitro observations, the emergence of clindamycin-resistant *S. aureus* has been noted in clindamycin-treated patients, in particular when the organisms had demonstrated erythromycin resistance at the onset of treatment (i.e., the dissociated resistance of Garrod [inducible MLS_B]).[302,330] The bacterial strains possessing the inducible MLS_B resistance mechanism can often be detected in the laboratory with the D test, as discussed earlier. That test should be performed when clindamycin treatment is being considered for the treatment of *S. aureus* or *S. pyogenes* infections when the bacterial strain shows macrolide resistance. A positive D test suggests that emergence of resistance to clindamycin will often occur if that drug is used in treatment. A survey of nasal strains of *S. aureus* isolated in 2003 and 2004 showed that, among 237 that were methicillin sensitive, 2% were resistant to clindamycin with only a constitutive MLS_B phenotype, and 22.4% were resistant when including both inducible and constitutive MLS_B phenotype strains.[331] In the same study, among 134 strains that were methicillin resistant, 33.6% were resistant to clindamycin with only a constitutive MLS_B phenotype, and 62.4% were resistant when including both inducible and constitutive MLS_B phenotype strains. When methicillin-resistant *S. aureus* strains are of the community-associated variety, clindamycin resistance has been less common than among hospital-associated methicillin-resistant strains[332]; however, the proportion of the community-associated strains that are clindamycin resistant, often of the MLS_B inducible phenotype, has been increasing.[333] The antibacterial activity of lincomycin and clindamycin has been shown, in limited in vitro studies, to be bactericidal for *S. pneumoniae, S. pyogenes,* and *S. aureus.* Its killing activity is similar to that of erythromycin and therefore probably varies with the concentration, bacterial species, and inoculum. It is more slowly bactericidal for *S. aureus* than are the penicillins,[334] and it is inconsistently bactericidal for *B. fragilis.*[335] Studies in vitro have demonstrated that clindamycin is capable of suppressing the production of some *S. aureus* extracellular toxin proteins.[336]

Clindamycin has substantial in vitro activity against *T. gondii* in infected human fibroblasts.[337] Clindamycin and its three major metabolites are inhibitory against *P. falciparum.*[338]

Clinical Pharmacology

Peak serum levels achieved after oral administration of clindamycin occur earlier and are at least twice as high as those of lincomycin. Absorption of clindamycin is about 90% and is slightly delayed, but not decreased, by ingestion of food, whereas that of lincomycin is markedly decreased.[302] Mean peak serum concentrations of clindamycin in adults after single oral doses of 150 and 300 mg occur at 1 hour and are 2.5 and 3.6 μg/mL, respectively; at 6 hours, they are 0.7 and 1.1 μg/mL, respectively. The esters clindamycin palmitate in suspension for oral use and clindamycin phosphate for parenteral use are absorbed as the inactive ester and are rapidly hydrolyzed in the blood to the active base. After IM administration, which causes little pain, mean peak serum levels are reached in 3 hours and are about 6 μg/mL after a 300-mg dose and 9 μg/mL after a 600-mg dose; at 12 hours, they are 0.7 and 0.9 μg/mL, respectively.[339] In adult healthy volunteers, immediately after 20- to 45-minute intravenous infusions of 600, 900, or 1200 mg of clindamycin phosphate, serum levels of base are 10, 11, and 14 μg/mL, respectively. Higher levels after intravenous infusion have been reported in infected patients under treatment.[340] Dose regimens of IV clindamycin using 900 mg every 8 hours or 600 mg every 6 hours are considered acceptable.[341]

Limited studies have demonstrated good penetration of most tissues by the lincosamides, except for clinically insignificant entry of clindamycin into the CSF, even with meningitis.[342] Thus clindamycin should not be used to treat infections of the central nervous system. The concentration in bone compared with serum is particularly high.[343] Clindamycin administered to pregnant women readily passes the placental barrier and enters fetal blood and tissues.[104] Clindamycin is actively transported into polymorphonuclear leukocytes and macrophages[344] and is present in relatively high concentrations, compared with peak serum levels, in experimental abscesses.[345]

The normal half-life of clindamycin is 2.4 hours. Most of the absorbed drug is metabolized, probably by the liver, to products with variable antibacterial activity, including *N*-demethyl-clindamycin (more active than the parent compound) and clindamycin sulfoxide (less active), which have been detected in bile and urine but not in serum.[339] High bioactivity is found in bile, mostly as the *N*-demethyl metabolite; this represents a minor route of excretion and accounts for the activity assayed in feces after parenteral administration.[339,346] Clindamycin activity in feces persists for at least 5 days after 48 hours of parenteral administration and is associated with a major reduction in the population of sensitive bacteria in the colon that lasts for up to 14 days.[347] Clindamycin concentration in bile is markedly diminished or absent when the common bile duct is obstructed.[348] High clindamycin bioactivity, also mostly in the *N*-demethyl form, is found in the urine and persists for up to 4 days after a single dose, suggesting slow release from tissues.[340] Accurate data on the proportion of absorbed clindamycin that is excreted in the urine are not available because of the variable activity of the metabolites and their unknown proportions in urine.

The half-life of clindamycin is increased from 2.4 to about 6 hours in patients with severe renal failure, and peak blood levels after parenteral administration are about twice those in healthy people.[349] If modified at all, parenteral doses should be halved in such patients. Some prolongation of clindamycin activity in serum is noted in patients with severe liver disease.[350] Appreciable dose modification should be made when a patient exhibits concomitant severe renal and hepatic disease. Neither

hemodialysis nor peritoneal dialysis removes significant amounts of clindamycin.

Adverse Reactions

In a report from the CDC of emergency department visits in 2004 to 2006 for antibiotic-associated adverse events, those associated with clindamycin use were among the highest, with 18.5 emergency department visits per 10,000 outpatient prescription visits.[351] Cutaneous reactions are common adverse responses to clindamycin, including delayed maculopapular eruptions, urticaria, erythema multiforme, fixed drug eruptions, drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis.[352] Recent data from China suggest a genetic predisposition to cutaneous adverse events in persons with an HLA-B*51:01 genotype.[352]

Diarrhea occurs in up to 20% of clindamycin-treated patients and is more common with oral administration. However, the major toxicity of lincomycin and clindamycin that now appreciably limits their use is the occurrence of pseudomembranous colitis caused by toxins secreted by *C. difficile* that overgrows in the presence of these antibiotics.[353] In the early reports of that infection, it was noted in 0.01% to 10% of clindamycin-treated patients.[354] The infection may occur in association with the administration of other antibiotics or occasionally without a history of recent antibiotic use, and it has become more frequent and severe.[355] Antibiotics other than clindamycin—particularly cephalosporins and the fluoroquinolones, which have less potency than clindamycin to change the normal balance of intestinal microbiota and thereby allow the overgrowth of *C. difficile*—have become more frequently involved as inducers of the infection because they are now used more frequently than clindamycin.[356,357] *C. difficile* infection has been reported after the use of clindamycin vaginal cream in a patient being treated for bacterial vaginosis.[358]

Minor reversible elevation of transaminase levels, unassociated with other evidence of liver abnormality, has commonly been observed in patients receiving clindamycin, especially by the parenteral route. Some of these may have been false-positive reactions associated with colorimetric rather than specific enzymatic measurements.[302] However, rare cases of frank hepatotoxicity, including jaundice associated with hepatocellular damage, have been observed.[359]

Isolated cases of reversible neutropenia, thrombocytopenia, and agranulocytosis associated with lincomycin or clindamycin therapy have been reported; their relation to the administration of the antibiotic was uncertain.

Hypotension and electrocardiographic changes have occasionally been reported. Cardiopulmonary arrest has occurred rarely, when large intravenous doses of lincomycin were given rapidly. These effects have not been reported with clindamycin.

Local irritative reactions are rare with these drugs. Intramuscular or intravenous administration is generally well tolerated.

Drug Interactions

Clindamycin may block neuromuscular transmission and may enhance the action of other blocking agents.[134] Clindamycin may decrease the effect of cyclosporine.[134] Clindamycin phosphate in solution is physically incompatible with ampicillin, diphenylhydantoin, barbiturates, aminophylline, calcium gluconate, and magnesium sulfate.

Uses of Clindamycin

The higher activity and absorption properties of clindamycin compared with lincomycin, along with no greater potential for toxicity, favor the former in all indications for use of these antibiotics. The lincosamides have been used in a variety of infections, often with good effect; however, appreciation of the potential for serious or even fatal toxicity with pseudomembranous colitis and the availability of safer alternative antibiotics should now generally limit the use of clindamycin to a few indications as an alternative-choice antibiotic.[109]

Clindamycin is largely used for gram-positive or anaerobic bacterial infections of the soft tissues, or both, though increasing resistance among pathogens has limited its utility.[360] While clindamycin has been known as an alternative choice for the treatment of infections outside of the central nervous system that are likely to involve *B. fragilis* or other penicillin-resistant anaerobic bacteria, it has lost favor as an empirical agent for polymicrobial intraabdominal infections.[361,362]

Clindamycin may offer some advantage over penicillin G in the treatment of anaerobic bronchopulmonary infections[363]; in addition, it may serve as an alternative in patients who are allergic to penicillin. In a prospective, randomized study of 39 patients with community-acquired putrid lung abscess, clindamycin was more effective than penicillin in the time until eradication of fever and fetid sputum and in the "overall response" to treatment.[364] The study involved small numbers of patients and had some flaws in the analysis[365]; however, the superiority of clindamycin for some patients was demonstrated and may relate to observations that 15% to 25% of anaerobic pulmonary infections involve β-lactamase–producing strains of *B. fragilis, B. melaninogenicus, Prevotella ruminicola,* and *B. ureolyticus,* which are resistant to penicillin.[365] Another similar study also demonstrated a higher failure rate with penicillin than with clindamycin and attributed it to penicillin-resistant anaerobes.[366] That study was problematic in that penicillin oral therapy was used to complete the course of treatment of some patients in the penicillin group. Nevertheless, clindamycin may be preferable for treatment of this condition,[367] particularly in seriously ill patients and in those who have responded poorly to penicillin.

Clindamycin is useful as an alternative to penicillin in treatment of infections with *C. perfringens,* which is generally susceptible to this drug.[321] Clindamycin was more effective than penicillin in reducing mortality in a mouse model of *C. perfringens* gas gangrene and in vitro in suppressing the α-toxin activity produced by that organism.[368,369]

Depending upon susceptibilities, clindamycin can be useful in the treatment of staphylococcal infections, especially when therapy is appropriate by the oral route for a methicillin-resistant strain and when there is a history of β-lactam allergy for a methicillin-sensitive strain. However, the more limited bactericidal rate with clindamycin for staphylococci compared with that of the β-lactams, the real potential for the emergence of clindamycin-resistant strains in treated patients, and the substantial potency of clindamycin for sometimes inducing *C. difficile* colitis are disadvantages. The problem of emergence of clindamycin resistance, as discussed earlier and noted especially, but not only with erythromycin-resistant strains, appreciably limits its effectiveness as therapy for deep-seated, high-bacterial-density staphylococcal infections, particularly endocarditis.[370] The use of the D test (discussed earlier) is recommended to detect the likelihood of emergence of resistance to clindamycin when a strain is resistant to erythromycin. In general, vancomycin, daptomycin (not for pneumonia), or linezolid for methicillin-resistant strains or β-lactams for methicillin-sensitive strains are better choices for treatment of staphylococcal infections. Although high concentrations of clindamycin are achieved in bone, an advantage of clindamycin for the treatment of osteomyelitis has not been established.[343]

The topical clindamycin/benzoyl peroxide gel is more effective in the treatment of acne vulgaris than topical clindamycin alone.[371] However, pseudomembranous colitis associated with the use of topical clindamycin has been reported.[372] In the treatment of bacterial vaginosis, clindamycin vaginal cream (2% for 3–7 days) appears to be similar in efficacy and in the incidence of side effects to oral metronidazole (both used for 7 days).[373] Alternative dosing regimens, including oral clindamycin (300 mg twice daily for 7 days) or intravaginal clindamycin ovules (100 mg once daily for 3 days), can also be used for this condition. A case report of *C. difficile* colitis associated with clindamycin vaginal cream has already been noted, but this appears to be exceedingly rare.[358] Bacterial vaginosis is a risk factor for preterm delivery, and studies of clindamycin treatment for bacterial vaginosis have shown mixed results with respect to preventing preterm labor. Thus opinions differ as to the capacity of clindamycin to prevent preterm birth in women being treated for bacterial vaginosis.[374,375]

Clindamycin is an effective alternative regimen in treating animals experimentally infected with toxoplasma and when combined with pyrimethamine (and leucovorin) in treating patients with toxoplasmosis of the central nervous system.[376] This is a preferred alternative regimen for patients with cerebral toxoplasmosis who cannot tolerate sulfadiazine or do not respond to first-line therapy.[377] This combination, however,

does not prevent *Pneumocystis jirovecii* infection; therefore additional prophylaxis must be administered when it is used.

Clindamycin in combination with primaquine is an effective and well-tolerated regimen for the treatment of mild and moderately severe *P. jirovecii* pneumonia in patients with AIDS. In a comparative trial, this combination showed an efficacy similar to that of trimethoprim with sulfamethoxazole or trimethoprim with dapsone.[378] An analysis of 82 AIDS cases with *P. jirovecii* pneumonia from Copenhagen, London, and Milan, which had previously been reported in observational studies and had initial treatment regimens that were switched to other regimens after at least 5 days because of poor clinical response, showed that in 22 cases in which the switch was made to clindamycin with primaquine the response rate was 73% and was comparable with that for trimethoprim-sulfamethoxazole (68%) and superior to that for intravenous pentamidine (44%).[379]

Clindamycin in combination with quinine is effective in the treatment of falciparum malaria.[109] That regimen used for 4 days was found to be superior to quinine used alone for 7 days in a randomized trial in Gabonese children with severe disease.[380] The same combination has also been reported to be useful in the treatment of babesiosis.[109,381] A randomized controlled trial conducted in sub-Saharan Africa involving 100 Gabonese children with uncomplicated *P. falciparum* malaria showed that a 3-day oral regimen of artesunate with clindamycin was highly successful and at least comparable in efficacy and safety with a 3-day oral regimen of quinine with clindamycin.[382]

The coexistence of β-lactamase–producing *S. aureus* or *Bacteroides* species and group A streptococci may be associated with the failure of penicillin to eradicate the latter, resulting in recurrent tonsillitis. Limited evidence suggests that recurrence rates may be lowered when clindamycin is used.[383] In another study, patients with group A streptococcal pharyngitis that recurred after 10 days of treatment with phenoxymethyl penicillin were randomly allocated to re-treatment for 10 days with phenoxymethyl penicillin or clindamycin.[384] Group A streptococci were not recovered from any of the patients receiving clindamycin, but the same (or similar) strain was cultured from 64% of those re-treated with the penicillin. However, widespread use of clindamycin for this common problem is likely to lead to a substantial number of cases of *C. difficile* colitis, as well as selection for clindamycin-resistant strains of group A streptococci.

Although penicillin has been the traditional drug of choice for the treatment of group A streptococcal infections, clindamycin must be considered as potentially more effective in serious soft tissue infections, on the basis of data, already discussed, from the treatment of experimental infections in mice and the effectiveness of that agent compared with penicillin in decreasing the in vitro production of several of the virulence factors of the pathogen. Data from retrospective clinical studies do support such an advantage for clindamycin[385]; however, because some strains of *S. pyogenes* may be resistant to clindamycin, that drug should be used *in combination* with penicillin for the empirical treatment of life-threatening group A streptococcal infections, until sensitivity data are available.[386] Limited in vitro data suggest that the addition of penicillin to clindamycin does not antagonize the bactericidal effects of the latter.[387]

The dosage of clindamycin for adults depends on the site and severity of infection and the condition of the patient. Oral doses are usually 150 to 450 mg every 6 hours, and parenteral doses, given every 6 to 12 hours, usually total 600 to 2700 mg/day, occasionally higher.

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Key References

The complete reference list is available online at Expert Consult.

3. Leclercq R, Courvalin P. Resistance to macrolides and related antibiotics in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 2002;46:2727–2734.
8. Leclercq R, Courvalin P. Intrinsic and unusual resistance to macrolide, lincosamide, and streptogramin antibiotics in bacteria. *Antimicrob Agents Chemother*. 1991;35:1273–1276.
14. Leclercq R. Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. *Clin Infect Dis*. 2002;34:482–492.
17. Richter SS, Hellman KP, Beekmann SE, et al. Macrolide-resistant *Streptococcus pyogenes* in the United States, 2002-2003. *Clin Infect Dis*. 2005;41:599–608a.
19. Haight T, Finland M. Observations on mode of action of erythromycin. *Proc Soc Exp Biol Med*. 1952;81:188–193.
21. Sabath L, Gerstein DA, Loder PB, et al. Excretion of erythromycin and its enhanced activity in urine against gram-negative bacilli with alkalinization. *J Lab Clin Med*. 1968;72:916–923.
33. Pfaller MA, Farrell DJ, Sader HS, et al. AWARE Ceftaroline Surveillance Program (2008-2010): trends in resistance patterns among *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* in the United States. *Clin Infect Dis*. 2012;55(suppl 3):S187–S193.
35. Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *JAMA*. 2001;286:1857–1862.
44. Farrell DJ, File TM, Jenkins SG. Prevalence and antibacterial susceptibility of mef(A)-positive macrolide-resistant *Streptococcus pneumoniae* over 4 years (2000-2004) of the PROTEKT US Study. *J Clin Microbiol*. 2007;45:290–293.
51. Green MD, Beall B, Marcon MJ, et al. Multicentre surveillance of the prevalence and molecular epidemiology of macrolide resistance among pharyngeal isolates of group A streptococci in the USA. *J Antimicrob Chemother*. 2006;57:1240–1243.
52. Villasenor-Sierra A, Katahira E, Jaramillo-Valdivia AN, et al. Phenotypes and genotypes of erythromycin-resistant pyogenes strains isolated from invasive and non-invasive infections from Mexico and the USA during 1999-2010. *Int J Infect Dis*. 2012;16:e178–e181.
57. Sader HS, Flamm RK, Farrell DJ, et al. Activity analyses of Staphylococcal isolates from pediatric, adult and elderly patients: AWARE Ceftaroline surveillance program. *Clin Infect Dis*. 2012;55:S181–S186.
59. Haight TH, Finland FM. Laboratory and clinical studies on erythromycin. *N Engl J Med*. 1952;247:227–232.
97. Osono T, Umezawa H. Pharmacokinetics of macrolides, lincosamides and streptogramins. *J Antimicrob Chemother*. 1985;16(supplA):151–166.
109. Handbook of Antimicrobial Therapy. New Rochelle, NY: The Medical Letter on Drugs and Therapeutics; 2011.
115. Braun P. Hepatotoxicity of erythromycin. *J Infect Dis*. 1969;119:300–306.
127. Ray WA, Murray KT, Meredith S. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med*. 2004;351:1089–1096.
133. Amsden GW. Macrolides versus azalides: a drug interaction update. *Ann Pharmacother*. 1995;29:906–917.
152. Fields BS, Benson RF, Besser RE. *Legionella* and Legionnaires' disease: 25 years of investigation. *Clin Microbiol Rev*. 2002;15:506–526.
167. Catnach SM, Fairclough PD. Erythromycin and the gut. *Gut*. 1992;33:397–401.
173. Kudoh S, Azuma A, Yamamoto M, et al. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med*. 1998;157:1829–1832.
174. Keicho N, Kudoh S. Diffuse panbronchiolitis: the role of macrolides in therapy. *Am J Resp Med*. 2002;1:119–131.
177. Aoki Y, Kao PN. Erythromycin inhibits transcriptional activation of NF-kappaB, but not NFAT, through calcineurin-independent signaling in T cells. *Antimicrob Agents Chemother*. 1999;43:2678–2684.
183. Bahal N, Nahata MC. The new macrolide antibiotics: azithromycin, clarithromycin, dirithromycin, and roxithromycin. *Ann Pharmacother*. 1992;26:46–55.
209. Drehobl MA, De Salvo MC, Lewis DE, et al. Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. *Chest*. 2005;128:2230–2237.
216. Abeles SR, Jones MB, Santiago-Rodriquez TM, et al. Microbial diversity in individuals and their household contacts following typical antibiotic courses. *Microbiome*. 2016;4:39.
225. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med*. 2012;366:1881–1890.
228. Trac MH, McArthur E, Jandoc R, et al. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. *CMAJ*. 2016;188:E120–E129.
229. In brief: FDA azithromycin warning. *Med Lett Drugs Ther*. 2013;55:28.
237. Bisno AL, Gerber MA, Gwaltney JM Jr, et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America. *Clin Infect Dis*. 2002;35:113–125.
239. Hooton TM. A comparison of azithromycin and penicillin V for the treatment of streptococcal pharyngitis. *Am J Med*. 1991;91:23S–26S.
297. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365:689–698.
300. Healy DP. Macrolide immunomodulation of chronic respiratory diseases. *Curr Infect Dis Rep*. 2007;9:7–13.
302. McGehee R, Smith CB, Wilcox C, et al. Comparative studies of antibacterial activity in vitro and absorption and excretion of lincomycin and clindamycin. *Am J Med Sci*. 1968;256:279–292.
305. Siberry GK, Tekle T, Carroll K, et al. Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible clindamycin resistance in vitro. *Clin Infect Dis*. 2003;37:1257–1260.
330. Duncan IB. Development of lincomycin resistance by staphylococci. *Antimicrob Agents Chemother (Bethesda)*. 1967;7:723–729.
335. Nastro LJ, Finegold SM. Bactericidal activity of five antimicrobial agents against *Bacteroides fragilis*. *J Infect Dis*. 1972;126:104–107.
339. DeHaan RM, Metzler CM, Schellenberg D, et al. Pharmacokinetic studies of clindamycin phosphate. *J Clin Pharmacol*. 1973;13:190–209.
342. Panzer JD, Brown DC, Epstein WL, et al. Clindamycin levels in various body tissues and fluids. *J Clin Pharmacol New Drugs*. 1972;12:259–262.
343. Nicholas P, Meyers BR, Levy RN, et al. Concentration of clindamycin in human bone. *Antimicrob Agents Chemother*. 1975;8:220–221.
346. McCall CE, Steigbigel NH, Finland M. Lincomycin: activity in vitro and absorption and excretion in normal young men. *Am J Med Sci*. 1967;254:144–155.
351. Shehab N, Patel PR, Srinivasin A, et al. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008;47735–47743.
353. Bartlett JG. Historical perspectives on studies of *Clostridium difficile* and *C. difficile* infection. *Clin Infect Dis*. 2008;46(suppl 1):S4–S11.
370. Watanakunakorn C. Clindamycin therapy of *Staphylococcus aureus* endocarditis: clinical relapse and development of resistance to clindamycin, lincomycin and erythromycin. *Am J Med*. 1976;60:419–425.

References

1. Jain R, Danziger LH. The macrolide antibiotics: a pharmacokinetic and pharmacodynamic overview. *Curr Pharm Des*. 2004;10:3045–3053. Review.
2. Lin H, Dyar OJ, Rosales-Klintz S, et al. Trends and patterns of antibiotic consumption in Shanghai municipality, China: a 6 year surveillance with sales records, 2009-14. *J Antimicrob Chemother*. 2016;71:1723–1729.
3. Leclercq R, Courvalin P. Resistance to macrolides and related antibiotics in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother*. 2002;46:2727–2734.
4. Allen N. Effects of macrolide antibiotics on ribosome function. In: Schonfeld W, Kirst HA, eds. *Macrolide Antibiotics*. Boston: Birkhauser Verlag; 2002:261–280.
5. Edelstein PH. Pneumococcal resistance to macrolides, lincosamides, ketolides and streptomycin B agents: molecular mechanisms and resistance phenotypes. *Clin Infect Dis*. 2004;38(suppl 4):5322–5327.
6. Sutcliffe J, Leclercq R. Mechanisms of resistance to macrolides, lincosamides, and ketolides. In: Schonfeld W, Kirst HA, eds. *Macrolide Antibiotics*. Boston: Birkhauser Verlag; 2002:281–317.
7. Chittum HS, Champney WS. Erythromycin inhibits the assembly of the large ribosomal subunit in growing *Escherichia coli* cells. *Curr Microbiol*. 1995;30:273–279.
8. Leclercq R, Courvalin P. Intrinsic and unusual resistance to macrolide, lincosamide, and streptogramin antibiotics in bacteria. *Antimicrob Agents Chemother*. 1991;35:1273–1276.
9. Mao JC, Putterman M. Accumulation in gram-positive and gram-negative bacteria as a mechanism of resistance to erythromycin. *J Bacteriol*. 1968;95:1111–1117.
10. Taubeneck U. Susceptibility of *Proteus mirabilis* and its stable L-forms to erythromycin and other macrolides. *Nature*. 1962;196:195–196.
11. Xu X, Cai L, Xiao M, et al. Distribution of serotypes, genotypes, and resistance determinants among macrolide-resistant *Streptococcus pneumoniae* isolates. *Antimicrob Agents Chemother*. 2010;54:1152–1159.
12. Prunier AL, Malbruny B, Laurans M, et al. High rate of macrolide resistance in *Staphylococcus aureus* strains from patients with cystic fibrosis reveals high proportions of hypermutable strains. *J Infect Dis*. 2003;187:1709–1716.
13. Farrell DJ, Douthwaite S, Morrissey I, et al. Macrolide resistance by ribosomal mutation in clinical isolates of *Streptococcus pneumoniae* from the PROTEKT 1999-2000 Study. *Antimicrob Agents Chemother*. 2003;47:1777–1783.
14. Leclercq R. Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. *Clin Infect Dis*. 2002;34:482–492.
15. Leclercq R, Courvalin P. Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. *Antimicrob Agents Chemother*. 1991;35:1267–1272.
16. Shain CS, Amsden GW. Telithromycin: the first of the ketolides. *Ann Pharmacother*. 2002;36:452–464.
17. Richter SS, Hellman KP, Beekmann SE, et al. Macrolide-resistant *Streptococcus pyogenes* in the United States, 2002-2003. *Clin Infect Dis*. 2005;41:599–608a.
18. Sutcliffe J, Grebe T, Tait-Kamradt A, et al. Detection of erythromycin-resistant determinants by PCR. *Antimicrob Agents Chemother*. 1996;40:2562–2566.
19. Haight T, Finland M. Observations on mode of action of erythromycin. *Proc Soc Exp Biol Med*. 1952;81:188–193.
20. Haight T, Finland M. The antibacterial action of erythromycin. *Proc Soc Exp Biol Med*. 1952;81:175–183.
21. Sabath L, Gerstein DA, Loder PB, et al. Excretion of erythromycin and its enhanced activity in urine against gram-negative bacilli with alkalinization. *J Lab Clin Med*. 1968;72:916–923.
22. Pankuch GA, Visalli MA, Jacobs MR, et al. Susceptibilities of penicillin- and erythromycin-susceptible and -resistant pneumococci to HMR 3647 (RU 66647), a new ketolide, compared with susceptibilities to 17 other agents. *Antimicrob Agents Chemother*. 1998;42:624–630.
23. Canton R, Loza E, Morosini MI, et al. Antimicrobial resistance amongst isolates of *Streptococcus pyogenes* and *Staphylococcus aureus* in the PROTEKT antimicrobial surveillance programme during 1999-2000. *J Antimicrob Chemother*. 2002;50(supplS1):9–24.
24. Aracil B, Minambres M, Oteo J, et al. Susceptibility of strains of *Streptococcus agalactiae* to macrolides and lincosamides, phenotype patterns and resistance genes. *Clin Microbiol Infect*. 2002;8:745–748.
25. Zhanel GG, Walters M, Noreddin A, et al. The ketolides: a critical review. *Drugs*. 2002;62:1771–1804.
26. Alcaide F, Benitez MA, Carratala J, et al. In vitro activities of the new ketolide HMR 3647 (telithromycin) in comparison with those of eight other antibiotics against viridans group *Streptococci* isolated from blood of neutropenic patients with cancer. *Antimicrob Agents Chemother*. 2001;45:624–626.
27. Hoban DJ. Prevalence and characterization of macrolide resistance in clinical isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes* from North America. *J Chemother*. 2002;14(suppl 3):25–30.
28. Samra Z, Rosenberg S, Soffer Y, et al. In vitro susceptibility of recent clinical isolates of *Chlamydia trachomatis* to macrolides and tetracyclines. *Diagn Microbiol Infect Dis*. 2001;39:177–179.
29. Edelstein PH, Edelstein MA. In vitro activity of the ketolide HMR 3647 (RU 6647) for *Legionella* spp., its pharmacokinetics in guinea pigs, and use of the drug to treat guinea pigs with *Legionella pneumophila* pneumonia. *Antimicrob Agents Chemother*. 1999;43:90–95.
30. Critchley IA, Jones ME, Heinze PD, et al. In vitro activity of levofloxacin against contemporary clinical isolates of *Legionella pneumophila, Mycoplasma pneumoniae* and *Chlamydia pneumoniae* from North America and Europe. *Clin Microbiol Infect*. 2002;8:214–221.
31. Ednie LM, Jacobs MR, Appelbaum PC. Comparative antianaerobic activities of the ketolides HMR 3647 (RU 66647) and HMR 3004 (RU 64004). *Antimicrob Agents Chemother*. 1997;41:2019–2022.
32. Bermudez LE, Inderlied CB, Kolonoski P, et al. Telithromycin is active against *Mycobacterium avium* in mice despite lacking significant activity in standard in vitro and macrophage assays and is associated with low frequency of resistance during treatment. *Antimicrob Agents Chemother*. 2001;45:2210–2214.
33. Pfaller MA, Farrell DJ, Sader HS, et al. AWARE Ceftaroline Surveillance Program (2008-2010): trends in resistance patterns among *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* in the United States. *Clin Infect Dis*. 2012;55(suppl 3):S187–S193.
34. Thornsberry C, Sahm DF, Kelly LJ, et al. Regional trends in antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* in the United States: results from the TRUST Surveillance Program, 1999-2000. *Clin Infect Dis*. 2002;34(suppl 1):S4–S16.
35. Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *JAMA*. 2001;286:1857–1862.
36. Hsueh PR, Liu CY, Luh KT. Current status of antimicrobial resistance in Taiwan. *Emerg Infect Dis*. 2002;8:132–137.
37. Martin JM, Green M, Barbadora KA, et al. Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. *N Engl J Med*. 2002;346:1200–1206.
38. Jones RN, Sader HS, Mendes RE, et al. Update on antimicrobial susceptibility trends among *Streptococcus pneumoniae* in the United States: report of ceftaroline activity from the SENTRY Antimicrobial Surveillance Program (1998-2011). *Diagn Microbiol Infect Dis*. 2013;75:107–109.
39. Thornsberry C, Ogilvie PT, Holley HP Jr, et al. Survey of susceptibilities of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* isolates to 26 antimicrobial agents: a prospective U.S. study. *Antimicrob Agents Chemother*. 1999;43:2612–2623.
40. Ednie LM, Visalli MA, Jacobs MR, et al. Comparative activities of clarithromycin, erythromycin, and azithromycin against penicillin-susceptible and penicillin-resistant pneumococci. *Antimicrob Agents Chemother*. 1996;40:1950–1952.
41. Sutcliffe J, Tait-Kamradt A, Wondrack L. *Streptococcus pneumoniae* and *Streptococcus pyogenes* resistant to macrolides but sensitive to clindamycin: a common resistance pattern mediated by an efflux system. *Antimicrob Agents Chemother*. 1996;40:1817–1824.
42. Gay K, Baughman W, Miller Y, et al. The emergence of *Streptococcus pneumoniae* resistant to macrolide antimicrobial agents: a 6-year population-based assessment. *J Infect Dis*. 2000;182:1417–1424.
43. Corso A, Severina EP, Petruk VF, et al. Molecular characterization of penicillin-resistant *Streptococcus pneumoniae* isolates causing respiratory disease in the United States. *Microb Drug Resist*. 1998;4:325–337.
44. Farrell DJ, File TM, Jenkins SG. Prevalence and antibacterial susceptibility of mef(A)-positive macrolide-resistant *Streptococcus pneumoniae* over 4 years (2000-2004) of the PROTEKT US Study. *J Clin Microbiol*. 2007;45:290–293.
45. Jenkins SG, Brown SD, Farrell DJ. Trends in antibacterial resistance among *Streptococcus pneumoniae* isolated in the USA: update from PROTEKT US Years 1-4. *Ann Clin Microbiol Antimicrob*. 2008;7:1.
46. Lagrou K, Peetermans WE, Verhaegen J, et al. Macrolide resistance in Belgian *Streptococcus pneumoniae*. *J Antimicrob Chemother*. 2000;45:119–121.
47. Wang M, Zhang Y, Zhu D, et al. Prevalence and phenotypes of erythromycin-resistant *Streptococcus pneumoniae* in Shanghai, China. *Diagn Microbiol Infect Dis*. 2001;39:187–189.
48. Gordon KA, Beach ML, Biedenbach DJ, et al. Antimicrobial susceptibility patterns of beta-hemolytic and viridans group streptococci: report from the SENTRY Antimicrobial Surveillance Program (1997-2000). *Diagn Microbiol Infect Dis*. 2002;43:157–162.
49. Avanzini C, Bosio K, Volpe G, et al. *Streptococcus pyogenes* collected in Torino (northwest Italy) between 1983 and 1998: survey of macrolide resistance and trend of genotype by RAPD. *Microb Drug Resist*. 2000;6:289–295.
50. Alos JI, Aracil B, Oteo J, et al. High prevalence of erythromycin-resistant, clindamycin/miocamycin-susceptible (M phenotype) *Streptococcus pyogenes:* results of a Spanish multicentre study in 1998. Spanish Group for the Study of Infection in the Primary Health Care Setting. *J Antimicrob Chemother*. 2000;45:605–609.
51. Green MD, Beall B, Marcon MJ, et al. Multicentre surveillance of the prevalence and molecular epidemiology of macrolide resistance among pharyngeal isolates of group A streptococci in the USA. *J Antimicrob Chemother*. 2006;57:1240–1243.
52. Villasenor-Sierra A, Katahira E, Jaramillo-Valdivia AN, et al. Phenotypes and genotypes of erythromycin-resistant pyogenes strains isolated from invasive and non-invasive infections from Mexico and the USA during 1999-2010. *Int J Infect Dis*. 2012;16:e178–e181.
53. Hsueh PR, Teng LJ, Lee LN, et al. Increased prevalence of erythromycin resistance in streptococci: substantial upsurge in erythromycin-resistant M phenotype in *Streptococcus pyogenes* (1979-1998) but not in *Streptococcus pneumoniae* (1985-1999) in Taiwan. *Microb Drug Resist*. 2002;8:27–33.
54. Westh H, Rosdahl VT, Friis H. Erythromycin resistance in Danish *Staphylococcus aureus* hospital strains with emphasis on erythromycin consumption. *APMIS*. 1989;97:1121–1124.
55. Pfaller MA, Jones RN, Doern GV, et al. Survey of blood stream infections attributable to gram-positive cocci: frequency of occurrence and antimicrobial susceptibility of isolates collected in 1997 in the United States, Canada, and Latin America from the SENTRY Antimicrobial Surveillance Program. SENTRY Participants Group. *Diagn Microbiol Infect Dis*. 1999;33:283–297.
56. Schmitz FJ, Verhoef J, Fluit AC. Prevalence of resistance to MLS antibiotics in 20 European university hospitals participating in the European SENTRY surveillance programme. Sentry Participants Group. *J Antimicrob Chemother*. 1999;43:783–792.
57. Sader HS, Flamm RK, Farrell DJ, et al. Activity analyses of Staphylococcal isolates from pediatric, adult and elderly patients: AWARE Ceftaroline surveillance program. *Clin Infect Dis*. 2012;55:S181–S186.
58. Lepper M, Dowling HF, Jackson GG, et al. Effect of antibiotic usage in the hospital on the incidence of antibiotic-resistant strains among personnel carrying staphylococci. *J Lab Clin Med*. 1953;42:832.
59. Haight TH, Finland FM. Laboratory and clinical studies on erythromycin. *N Engl J Med*. 1952;247:227–232.
60. Pfaller MA, Mendes RE, Sader HS, et al. Telavancin activity against gram-positive bacteria isolated from respiratory tract specimens of patients with nosocomial pneumonia. *J Antimicrob Chemother*. 2010;65:2396–2404.
61. Engler KH, Warner M, George RC. In vitro activity of ketolides HMR 3004 and HMR 3647 and seven other antimicrobial agents against *Corynebacterium diphtheriae*. *J Antimicrob Chemother*. 2001;47:27–31.
62. Hof H, Nichterlein T, Kretschmar M. Management of listeriosis. *Clin Microbiol Rev*. 1997;10:345–357.
63. Finland M, Bach MC, Garner C, et al. Synergistic action of ampicillin and erythromycin against *Nocardia asteroides:* effect of time of incubation. *Antimicrob Agents Chemother*. 1974;5:344–353.
64. Goldstein EJ, Citron DM, Merriam CV, et al. Activities of telithromycin (HMR 3647, RU 66647) compared to those of erythromycin, azithromycin, clarithromycin, roxithromycin, and other antimicrobial agents against unusual anaerobes. *Antimicrob Agents Chemother*. 1999;43:2801–2805.
65. Sutter VL, Finegold SM. Susceptibility of anaerobic bacteria to 23 antimicrobial agents. *Antimicrob Agents Chemother*. 1976;10:736–752.
66. Brazier JS, Levett PN, Stannard AJ, et al. Antibiotic susceptibility of clinical isolates of clostridia. *J Antimicrob Chemother*. 1985;15:181–185.
67. Citron DM, Appleman MD. Comparative in vitro activities of ABT-773 against 362 clinical isolates of anaerobic bacteria. *Antimicrob Agents Chemother*. 2001;45:345–348.

68. Berryman DI, Rood JI. Cloning and hybridization analysis of *ermP*, a macrolide-lincosamide-streptogramin B resistance determinant from *Clostridium perfringens*. *Antimicrob Agents Chemother*. 1989;33:1346–1353.
69. Ackermann G, Degner A, Cohen SH, et al. Prevalence and association of macrolide-lincosamide-streptogramin B (MLS(B)) resistance with resistance to moxifloxacin in *Clostridium difficile*. *J Antimicrob Chemother*. 2003;51:599–603.
70. Ilchmann C, Zaiss NH, Speicher A, et al. Comparison of resistance against erythromycin and moxifloxacin, presence of binary toxin gene and PCR ribotypes in *Clostridium difficile* isolates from 1990 and 2008. *Eur J Clin Microbiol Infect Dis*. 2010;29:1571–1573.
71. Wilson KE, Cassiday PK, Popovic T, et al. *Bordetella pertussis* isolates with a heterogeneous phenotype for erythromycin resistance. *J Clin Microbiol*. 2002;40:2942–2944.
72. Pankuch GA, Hoellman DB, Lin G, et al. Activity of HMR 3647 compared to those of five agents against *Haemophilus influenzae* and *Moraxella catarrhalis* by MIC determination and time-kill assay. *Antimicrob Agents Chemother*. 1998;42:3032–3034.
73. Angyo IA, Okpeh ES. Changing patterns of antibiotic sensitivity and resistance during an outbreak of meningococcal infection in Jos, Nigeria. *J Trop Pediatr*. 1998;44:263–265.
74. Nilius AM, Bui MH, Almer L, et al. Comparative in vitro activity of ABT-773, a novel antibacterial ketolide. *Antimicrob Agents Chemother*. 2001;45:2163–2168.
75. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2001 Supplement: Gonococcal Isolate Surveillance Project (GISP) Annual Report, 2001. Atlanta, Georgia: U.S. Department of Health and Human Services; 2002.
76. Arthur M, Brisson-Noel A, Courvalin P. Origin and evolution of genes specifying resistance to macrolide, lincosamide and streptogramin antibiotics: data and hypotheses. *J Antimicrob Chemother*. 1987;20:783–802.
77. Centers for Disease Control and Prevention. National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Human Isolates Final Report, 2004. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2007.
78. Ednie LM, Spangler SK, Jacobs MR, et al. Antianaerobic activity of the ketolide RU 64004 compared to activities of four macrolides, five beta-lactams, clindamycin, and metronidazole. *Antimicrob Agents Chemother*. 1997;41:1037–1041.
79. Kenny GE, Cartwright FD. Susceptibilities of *Mycoplasma hominis, M. pneumoniae,* and *Ureaplasma urealyticum* to GAR-936, dalfopristin, dirithromycin, evernimicin, gatifloxacin, linezolid, moxifloxacin, quinupristin-dalfopristin, and telithromycin compared to their susceptibilities to reference macrolides, tetracyclines, and quinolones. *Antimicrob Agents Chemother*. 2001;45:2604–2608.
80. Roblin PM, Reznik T, Kutlin A, et al. In vitro activities of gemifloxacin (SB 265805, LB20304) against recent clinical isolates of *Chlamydia pneumoniae*. *Antimicrob Agents Chemother*. 1999;43:2806–2807.
81. Segreti J, Meyer P, Kapell K. In vitro activity of macrolides against intracellular *Legionella pneumophila*. *Diagn Microbiol Infect Dis*. 1996;25:123–126.
82. Jao RL. Susceptibility of *Mycoplasma pneumoniae* to 21 antibiotics in vitro. *Am J Med Sci*. 1967;253:639–650.
83. Peuchant O, Menard A, Renaudin H, et al. Increased macrolide resistance of *Mycoplasma pneumoniae* in France directly detected in clinical specimens by real-time PCR and melting curve analysis. *J Antimicrob Chemother*. 2009;64:52–58.
84. Ferguson GD, Gadsby NJ, Henderson SS, et al. Clinical outcomes and macrolide resistance in *Mycoplasma pneumoniae* infection in Scotland, UK. *J Med Microbiol*. 2013;62(Pt 12):1876–1882.
85. Zheng X, Lee S, Selvarangan R, et al. Macrolide-Resistant *Mycoplasma pneumoniae,* United States. *Emerg Infect Dis*. 2015;21:1470–1472.
86. Zhao F, Liu G, Wu J, et al. Surveillance of macrolide-resistant *Mycoplasma pneumoniae* in Beijing, China, from 2008 to 2012. *Antimicrob Agents Chemother*. 2013;57:1521–1523.
87. Kawai Y, Miyashita N, Kubo M, et al. Nationwide surveillance of macrolide-resistant *Mycoplasma pneumoniae* infection in pediatric patients. *Antimicrob Agents Chemother*. 2013;57:4046–4049.
88. Rapp RP, McCraney SA, Goodman NL, et al. New macrolide antibiotics: usefulness in infections caused by mycobacteria other than *Mycobacterium tuberculosis*. *Ann Pharmacother*. 1994;28:1255–1263.
89. Yew WW, Piddock LJ, Li MS, et al. In-vitro activity of quinolones and macrolides against mycobacteria. *J Antimicrob Chemother*. 1994;34:343–351.
90. Kucers A. Chloramphenicol, erythromycin, vancomycin, tetracyclines. *Lancet*. 1982;2:425–429.
91. Bechtol L, Stephens VC, Pugh CT, et al. Erythromycin esters: comparative in vivo hydrolysis and bioavailability. *Curr Ther Res*. 1976;20:610–622.
92. Malmborg AS. Effect of food on absorption of erythromycin: a study of two derivatives, the stearate and the base. *J Antimicrob Chemother*. 1979;5:591–599.
93. McDonald PJ, Mather LE, Story MJ. Studies on absorption of a newly developed enteric-coated erythromycin base. *J Clin Pharmacol*. 1977;17:601–606.
94. Yakatan GJ, Rasmussen CE, Feis PJ, et al. Bioinequivalence of erythromycin ethylsuccinate and enteric-coated erythromycin pellets following multiple oral doses. *J Clin Pharmacol*. 1985;25:36–42.
95. DiSanto AR, Chodos DJ. Influence of study design in assessing food effects on absorption of erythromycin base and erythromycin stearate. *Antimicrob Agents Chemother*. 1981;20:190–196.
96. Janicki RS, Garnham JC, Worland MC, et al. Comparison of erythromycin ethyl succinate, stearate and estolate treatments of group A streptococcal infections of the upper respiratory tract. *Clin Pediatr (Phila)*. 1975;14:1098–1107.
97. Osono T, Umezawa H. Pharmacokinetics of macrolides, lincosamides and streptogramins. *J Antimicrob Chemother*. 1985;16(supplA):151–166.
98. Bass JW, Steele RW, Wiebe RA, et al. Erythromycin concentrations in middle ear exudates. *Pediatrics*. 1971;48:417–422.
99. Howard JE, Nelson JD, Clahsen J, et al. Otitis media of infancy and early childhood: a double-blind study of four treatment regimens. *Am J Dis Child*. 1976;130: 965–970.
100. Hand WL, Corwin RW, Steinberg TH, et al. Uptake of antibiotics by human alveolar macrophages. *Am Rev Respir Dis*. 1984;129:933–937.
101. Miller MF, Martin JR, Johnson P, et al. Erythromycin uptake and accumulation by human polymorphonuclear leukocytes and efficacy of erythromycin in killing ingested *Legionella pneumophila*. *J Infect Dis*. 1984;149: 714–718.
102. Griffith RS, Black HR. Erythromycin. *Med Clin North Am*. 1970;54:1199–1215.
103. Romansky M, Nasou JP, Davis DS, et al. The treatment of 171 patients with erythromycin, including 132 with bacterial pneumonia. *Antibiot Annu*. 1955-1956;3:48–62.
104. Philipson A, Sabath LD, Charles D. Transplacental passage of erythromycin and clindamycin. *N Engl J Med*. 1973;288:1219–1221.
105. Atkinson HC, Begg EJ, Darlow BA. Drugs in human milk. Clinical pharmacokinetic considerations. *Clin Pharmacokinet*. 1988;14:217–240.
106. Hammond J, Griffith RS. Factors affecting the absorption and biliary excretion of erythromycin and two of its derivatives in humans. *Clin Pharmacol Ther*. 1961;2: 308–312.
107. Mao J-H, Tardrew PL. Demethylation of erythromycin by rabbit tissues in vitro. *Biochem Pharmacol*. 1965;14: 1049–1058.
108. Kunin CM. A guide to use of antibiotics in patients with renal disease: a table of recommended doses and factors governing serum levels. *Ann Intern Med*. 1967;67:151–158.
109. Handbook of Antimicrobial Therapy. New Rochelle, NY: The Medical Letter on Drugs and Therapeutics; 2011.
110. Ellsworth AJ, Christensen DB, Volpone-McMahon MT. Prospective comparison of patient tolerance to enteric-coated vs nonenteric-coated erythromycin. *J Fam Pract*. 1990;31:265–270.
111. Gantz NM, Zawacki JK, Dickerson WJ, et al. Pseudomembranous colitis associated with erythromycin. *Ann Intern Med*. 1979;91:866–867.
112. Owens R, Donskey CJ, Gaynes RP, et al. Antimicrobial-associated risk factors for *Clostridium difficile* infection. *Clin Infect Dis*. 2008;46:S19–S31.
113. Sullivan S, Harger B, Cleary JD. Stevens-Johnson syndrome secondary to erythromycin. *Ann Pharmacother*. 1999;33:1369.
114. Inman WH, Rawson NS. Erythromycin estolate and jaundice. *Br Med J (Clin Res Ed)*. 1983;286:1954–1955.
115. Braun P. Hepatotoxicity of erythromycin. *J Infect Dis*. 1969;119:300–306.
116. Pessayre D, Larrey D, Funck-Brentano C, et al. Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother*. 1985;16(supplA):181–194.
117. Carson JL, Strom BL, Duff A, et al. Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. *Ann Intern Med*. 1993;119:576–583.
118. Karmody CS, Weinstein L. Reversible sensorineural hearing loss with intravenous erythromycin lactobionate. *Ann Otol Rhinol Laryngol*. 1977;86:9–11.
119. Eckman MR, Johnson T, Riess R. Letter: partial deafness after erythromycin. *N Engl J Med*. 1975;292:649.
120. Taylor R, Schofield IS, Ramos JM, et al. Ototoxicity of erythromycin in peritoneal dialysis patients. *Lancet*. 1981;2:935–936.
121. Haydon RC, Thelin JW, Davis WE. Erythromycin ototoxicity: analysis and conclusions based on 22 case reports. *Otolaryngol Head Neck Surg*. 1984;92:678–684.
122. Agusti C, Ferran F, Gea J, et al. Ototoxic reaction to erythromycin. *Arch Intern Med*. 1991;151:380.
123. Duewelhenke N, Krut O, Eysel P. Influence on mitochondria and cytotoxicity of different antibiotics administered in high concentrations on primary human osteoblasts and cell lines. *Antimicrob Agents Chemother*. 2007;51:54–63.
124. Salimi A, Eybagi S, Seydi E, et al. Toxicity of macrolide antibiotics on isolated heart mitochondria: a justification for their cardiotoxic adverse effect. *Xenobiotica*. 2016;46:82–93.
125. Katapadi K, Kostandy G, Katapadi M, et al. A review of erythromycin-induced malignant tachyarrhythmia—torsades de pointes: a case report. *Angiology*. 1997;48:821–826.
126. Schoenenberger RA, Haefeli WE, Weiss P, et al. Association of intravenous erythromycin and potentially fatal ventricular tachycardia with Q-T prolongation (torsades de pointes). *BMJ*. 1990;300:1375–1376.
127. Ray WA, Murray KT, Meredith S. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med*. 2004;351:1089–1096.
128. Daleau P, Lessard E, Groleau MF, et al. Erythromycin blocks the rapid component of the delayed rectifier potassium current and lengthens repolarization of guinea pig ventricular myocytes. *Circulation*. 1995;91:3010–3016.
129. SanFilippo J. Infantile hypertrophic pyloric stenosis related to ingestion of erythromycin estolate: a report of five cases. *J Pediatr Surg*. 1976;11:177–180.
130. Cooper WO, Griffin MR, Arbogast P, et al. Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med*. 2002;156:647–650.
131. Cooper WO, Ray WA, Griffin MR. Prenatal prescription of macrolide antibiotics and infantile hypertrophic pyloric stenosis. *Obstet Gynecol*. 2002;100:101–106.
132. Ludden TM. Pharmacokinetic interactions of the macrolide antibiotics. *Clin Pharmacokinet*. 1985;10:63–79.
133. Amsden GW. Macrolides versus azalides: a drug interaction update. *Ann Pharmacother*. 1995;29:906–917.
134. Kim R. The Medical Letter Handbook of Adverse Drug Interactions. New Rochelle, NY: The Medical Letter on Drugs and Therapeutics; 2003.
135. Bass JW, Freitas BC, Freitas AD, et al. Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch disease. *Pediatr Infect Dis J*. 1998;17:447–452.
136. Ohl ME, Spach DH. *Bartonella quintana* and urban trench fever. *Clin Infect Dis*. 2000;31:131–135.
137. Aoyama T, Sunakawa K, Iwata S, et al. Efficacy of short-term treatment of pertussis with clarithromycin and azithromycin. *J Pediatr*. 1996;129:761–764.
138. Kuschner RA, Trofa AF, Thomas RJ, et al. Use of azithromycin for the treatment of *Campylobacter enteritis* in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. *Clin Infect Dis*. 1995;21:536–541.
139. Bailey RL, Arullendran P, Whittle HC, et al. Randomised controlled trial of single-dose azithromycin in treatment of trachoma. *Lancet*. 1993;342:453–456.
140. Stout JE, Yu VL. Legionellosis. *N Engl J Med*. 1997;337:682–687.
141. Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. The Azithromycin for Chlamydial Infections Study Group. *N Engl J Med*. 1992;327:921–925.
142. Girgis NI, Butler T, Frenck RW, et al. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. *Antimicrob Agents Chemother*. 1999;43:1441–1444.
143. Khan WA, Seas C, Dhar U, et al. Treatment of shigellosis: V. Comparison of azithromycin and ciprofloxacin. A double-blind, randomized, controlled trial. *Ann Intern Med*. 1997;126:697–703.
144. Mabey D, Peeling RW. Lymphogranuloma venereum. *Sex Transm Infect*. 2002;78:90–92.
145. Steere AC. Lyme disease. *N Engl J Med*. 2001;345:115–125.
146. Krause PJ, Lepore T, Sikand VK, et al. Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med*. 2000;343:1454–1458.
147. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of

community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44:S27–S72.

148. Rasch J, Mogabgab WJ. Therapeutic effect of erythromycin on *Mycoplasma pneumoniae* pneumonia. *Antimicrob Agents Chemother*. 1965;5:399.
149. Shames JM, George RB, Holliday WB, et al. Comparison of antibiotics in the treatment of mycoplasmal pneumonia. *Arch Intern Med*. 1970;125: 680–684.
150. Edelstein PH, Meyer RD. Susceptibility of *Legionella pneumophila* to twenty antimicrobial agents. *Antimicrob Agents Chemother*. 1980;18:403–408.
151. Kuzman I, Soldo I, Schonwald S, et al. Azithromycin for treatment of community acquired pneumonia caused by *Legionella pneumophila:* a retrospective study. *Scand J Infect Dis*. 1995;27:503–505.
152. Fields BS, Benson RF, Besser RE. *Legionella* and Legionnaires' disease: 25 years of investigation. *Clin Microbiol Rev*. 2002;15:506–526.
153. Sprauer MA, Cochi SL, Zell ER, et al. Prevention of secondary transmission of pertussis in households with early use of erythromycin. *Am J Dis Child*. 1992;146:177–181.
154. Centers for Disease Control and Prevention. Guidelines for the Control of Pertussis Outbreaks. Atlanta: Centers for Disease Control and Prevention; 2000.
155. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2006. *MMWR Morb Mortal Wkly Rep*. 2006;51(RR–11):1–100.
156. Anders BJ, Lauer BA, Paisley JW, et al. Double-blind placebo controlled trial of erythromycin for treatment of *Campylobacter enteritis*. *Lancet*. 1982;1:131–132.
157. Salazar-Lindo E, Sack RB, Chea-Woo E, et al. Early treatment with erythromycin of *Campylobacter jejuni*-associated dysentery in children. *J Pediatr*. 1986;109:355–360.
158. Taylor DN, Blaser MJ, Echeverria P, et al. Erythromycin-resistant *Campylobacter* infections in Thailand. *Antimicrob Agents Chemother*. 1987;31:438–442.
159. Clarke JS, Condon RE, Bartlett JG, et al. Preoperative oral antibiotics reduce septic complications of colon operations: results of prospective, randomized, double-blind clinical study. *Ann Surg*. 1977;186:251–259.
160. Stellato TA, Danziger LH, Gordon N, et al. Antibiotics in elective colon surgery. A randomized trial of oral, systemic, and oral/systemic antibiotics for prophylaxis. *Am Surg*. 1990;56:251–254.
161. Gasquet S, Maurin M, Brouqui P, et al. Bacillary angiomatosis in immunocompromised patients. *AIDS*. 1998;12:1793–1803.
162. Angelakis E, Raoult D. Pathogenicity and treatment of Bartonella infections. *Int J Antimicrob Agents*. 2014;44:16–25.
163. Koehler JE, Tappero JW. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1993;17:612–624.
164. Kabir I, Khan WA, Haider R, et al. Erythromycin and trimethoprim-sulphamethoxazole in the treatment of cholera in children. *J Diarrhoeal Dis Res*. 1996;14:243–247.
165. Prunier AL, Malbruny B, Tande D, et al. Clinical isolates of *Staphylococcus aureus* with ribosomal mutations conferring resistance to macrolides. *Antimicrob Agents Chemother*. 2002;46:3054–3056.
166. Zinner SH, Sabath LD, Casey JI, et al. Erythromycin and alkalinisation of urine in the treatment of urinary-tract infections due to gram-negative bacilli. *Lancet*. 1971;1:1267–1268.
167. Catnach SM, Fairclough PD. Erythromycin and the gut. *Gut*. 1992;33:397–401.
168. Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. *N Engl J Med*. 1990;322:1028–1031.
169. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. *Am J Gastroenterol*. 1993;88:203–207.
170. Kendall BJ, Chakravarti A, Kendall E, et al. The effect of intravenous erythromycin on solid meal gastric emptying in patients with chronic symptomatic post-vagotomy-antrectomy gastroparesis. *Aliment Pharmacol Ther*. 1997;11:381–385.
171. Dive A, Miesse C, Galanti L, et al. Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients: a double-blind, randomized, placebo-controlled study. *Crit Care Med*. 1995;23:1356–1362.
172. Nogami K, Nishikubo T, Minowa H, et al. Intravenous low-dose erythromycin administration for infants with feeding intolerance. *Pediatr Int*. 2001;43:605–610.
173. Kudoh S, Azuma A, Yamamoto M, et al. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med*. 1998;157:1829–1832.
174. Keicho N, Kudoh S. Diffuse panbronchiolitis: the role of macrolides in therapy. *Am J Respir Med*. 2002;1: 119–131.
175. Abdelghaffar H, Vazifeh D, Labro MT. Erythromycin A-derived macrolides modify the functional activities of human neutrophils by altering the phospholipase D-phosphatidate phosphohydrolase transduction pathway: L-cladinose is involved both in alterations of neutrophil functions and modulation of this transductional pathway. *J Immunol*. 1997;159:3995–4005.
176. Ianaro A, Ialenti A, Maffia P, et al. Anti-inflammatory activity of macrolide antibiotics. *J Pharmacol Exp Ther*. 2000;292:156–163.
177. Aoki Y, Kao PN. Erythromycin inhibits transcriptional activation of NF-kappaB, but not NFAT, through calcineurin-independent signaling in T cells. *Antimicrob Agents Chemother*. 1999;43:2678–2684.
178. Desaki M, Takizawa H, Ohtoshi T, et al. Erythromycin suppresses nuclear factor-kappaB and activator protein-1 activation in human bronchial epithelial cells. *Biochem Biophys Res Commun*. 2000;267:124–128.
179. Yamamoto T, Kajikawa O, Martin TR, et al. The role of leukocyte emigration and IL-8 on the development of lipopolysaccharide-induced lung injury in rabbits. *J Immunol*. 1998;161:5704–5709.
180. Mikasa K, Kita E, Sawaki M, et al. The anti-inflammatory effect of erythromycin in zymosan-induced peritonitis of mice. *J Antimicrob Chemother*. 1992;30:339–348.
181. Li Y, Azuma A, Takahashi S, et al. Fourteen-membered ring macrolides inhibit vascular cell adhesion molecule 1 messenger RNA induction and leukocyte migration: role in preventing lung injury and fibrosis in bleomycin-challenged mice. *Chest*. 2002;122:2137–2145.
182. Shryock TR, Mortensen JE, Baumholtz M. The effects of macrolides on the expression of bacterial virulence mechanisms. *J Antimicrob Chemother*. 1998;41:505–512.
183. Bahal N, Nahata MC. The new macrolide antibiotics: azithromycin, clarithromycin, dirithromycin, and roxithromycin. *Ann Pharmacother*. 1992;26:46–55.
184. Piscitelli S, Danziger LH, Rodvold KA. Clarithromycin and azithromycin: new macrolide antibiotics. *Clin Pharm*. 1992;11:137–152.
185. Neu HC. Clinical microbiology of azithromycin. *Am J Med*. 1991;91:12S–18S.
186. Versalovic J, Shortridge D, Kibler K, et al. Mutations in 23S rRNA are associated with clarithromycin resistance in *Helicobacter pylori*. *Antimicrob Agents Chemother*. 1996;40:477–480.
187. Koletzko S, Richy F, Bontems P, et al. Prospective multicentre study on antibiotic resistance of *Helicobacter pylori* strains obtained from children living in Europe. *Gut*. 2006;55:1711–1716.
188. Taylor DE, Ge Z, Purych D, et al. Cloning and sequence analysis of two copies of a 23S rRNA gene from *Helicobacter pylori* and association of clarithromycin resistance with 23S rRNA mutations. *Antimicrob Agents Chemother*. 1997;41:2621–2628.
189. Nash KA, Inderlied CB. Genetic basis of macrolide resistance in *Mycobacterium avium* isolated from patients with disseminated disease. *Antimicrob Agents Chemother*. 1995;39:2625–2630.
190. Hicks LA, Chien YW, Taylor TH Jr, et al; Active Bacterial Core Surveillance (ABCs) Team. Outpatient antibiotic prescribing and nonsusceptible Streptococcus pneumoniae in the United States, 1996-2003. *Clin Infect Dis*. 2011;53:631–639.
191. Hardy DJ, Guay DR, Jones RN. Clarithromycin, a unique macrolide: a pharmacokinetic, microbiological, and clinical overview. *Diagn Microbiol Infect Dis*. 1992;15:39–53.
192. Credito KL, Lin G, Pankuch GA, et al. Susceptibilities of *Haemophilus influenzae* and *Moraxella catarrhalis* to ABT-773 compared to their susceptibilities to 11 other agents. *Antimicrob Agents Chemother*. 2001;45:67–72.
193. Farmer S, Li ZS, Hancock RE. Influence of outer membrane mutations on susceptibility of *Escherichia coli* to the dibasic macrolide azithromycin. *J Antimicrob Chemother*. 1992;29:27–33.
194. Tateda K, Ishii Y, Matsumoto T, et al. Potential of macrolide antibiotics to inhibit protein synthesis of *Pseudomonas aeruginosa:* suppression of virulence factors and stress response. *J Infect Chemother*. 2000;6:1–7.
195. Skindersoe ME, Alhede M, Phipps R, et al. Effects of antibiotics on quorum sensing in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2008;52:3648–3663.
196. Kirkcaldy RD, Harvey A, Papp JR, et al. *Neisseria gonorrhoeae* antimicrobial susceptibility surveillance - the gonococcal isolate surveillance project, 27 sites, United States, 2014. *MMWR Surveill Summ*. 2016;65:1–19.
197. Cole MJ, Spiteri G, Jacobsson S, et al. Overall low extended-spectrum cephalosporin resistance but high azithromycin resistance in *Neisseria gonorrhoeae* in 24 European countries, 2015. *BMC Infect Dis*. 2017;17:617.
198. Bohte R, van't Wout JW, Lobatto S, et al. Efficacy and safety of azithromycin versus benzylpenicillin or erythromycin in community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis*. 1995;14:182–187.
199. Derouin F, Chastang C. Activity in vitro against *Toxoplasma gondii* of azithromycin and clarithromycin alone and with pyrimethamine. *J Antimicrob Chemother*. 1990;25:708–711.
200. Yew WW, Piddock LJ, Li MS, et al. In-vitro activity of quinolones and macrolides against mycobacteria. *J Antimicrob Chemother*. 1994;34:343–351.
201. Steele-Moore L, Stark K, Holloway WJ. In vitro activities of clarithromycin and azithromycin against clinical isolates of *Mycobacterium avium-M. intracellulare*. *Antimicrob Agents Chemother*. 1999;43:1530.
202. Perronne C, Gikas A, Truffot-Pernot C, et al. Activities of sparfloxacin, azithromycin, temafloxacin, and rifapentine compared with that of clarithromycin against multiplication of *Mycobacterium avium* complex within human macrophages. *Antimicrob Agents Chemother*. 1991;35:1356–1359.
203. Bastian S, Veziris N, Roux AL, et al. Assessment of clarithromycin susceptibility in strains belonging to the Mycobacterium abscessus group by erm(41) and rrl sequencing. *Antimicrob Agents Chemother*. 2011;55:775–781.
204. Choi GE, Shin SJ, Won CJ, et al. Macrolide treatment for Mycobacterium abscessus and Mycobacterium massiliense infection and inducible resistance. *Am J Respir Crit Care Med*. 2012;186:917–925.
205. Mougari F, Bouziane F, Crockett F, et al. Selection of Resistance to Clarithromycin in Mycobacterium abscessus Subspecies. *Antimicrob Agents Chemother*. 2016;61:e00943–16.
206. Schentag JJ, Ballow CH. Tissue-directed pharmacokinetics. *Am J Med*. 1991;91:5S–11S.
207. Foulds G, Luke DR, Teng R, et al. The absence of an effect of food on the bioavailability of azithromycin administered as tablets, sachet or suspension. *J Antimicrob Chemother*. 1996;37(supplC):37–44.
208. Foulds G, Hilligoss DM, Henry EB, et al. The effects of an antacid or cimetidine on the serum concentrations of azithromycin. *J Clin Pharmacol*. 1991;31:164–167.
209. Drehobl MA, De Salvo MC, Lewis DE, et al. Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. *Chest*. 2005;128:2230–2237.
210. Ballow CH, Amsden GW. Azithromycin: the first azalide antibiotic. *Ann Pharmacother*. 1992;26:1253–1261.
211. Jaruratanasirikul S, Hortiwakul R, Tantisarasart T, et al. Distribution of azithromycin into brain tissue, cerebrospinal fluid, and aqueous humor of the eye. *Antimicrob Agents Chemother*. 1996;40: 825–826.
212. Gan VN, McCarty JM, Chu SY, et al. Penetration of clarithromycin into middle ear fluid of children with acute otitis media. *Pediatr Infect Dis J*. 1997;16: 39–43.
213. Sanche S, Williams K, Stein K. Cerebrospinal fluid penetration of clarithromycin and 14-hydroxyclarithromycin (abstract 728). Thirty-third Interscience Conference on Antimicrobial Agents and Chemotherapy. New Orleans, October 1993.
214. Anderson R, Joone G, van Rensburg CE. An in-vitro evaluation of the cellular uptake and intraphagocytic bioactivity of clarithromycin (A-56268, TE-031), a new macrolide antimicrobial agent. *J Antimicrob Chemother*. 1988;22:923–933.
215. Hopkins S. Clinical toleration and safety of azithromycin. *Am J Med*. 1991;91:40S–45S.
216. Abeles SR, Jones MB, Santiago-Rodriguez TM, et al. Microbial diversity in individuals and their household contacts following typical antibiotic courses. *Microbiome*. 2016;4:39.
217. Nobel YR, Cox LM, Kirigin FF, et al. Metabolic and metagenomic outcomes from early-life pulsed antibiotic treatment. *Nat Commun*. 2015;6:7486.
218. Ruiz VE, Battaglia T, Kurtz ZD, et al. A single early-in-life macrolide course has lasting effects on murine microbial network topology and immunity. *Nat Commun*. 2017;8:518.
219. Korpela K, Salonen A, Virta LJ, et al. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nat Commun*. 2016;7:10410.
220. Chandrupatla S, Demetris AJ, Rabinovitz M. Azithromycin-induced intrahepatic cholestasis. *Dig Dis Sci*. 2002;47:2186–2188.

221. Wallace RJ Jr, Brown BA, Griffith DE. Drug intolerance to high-dose clarithromycin among elderly patients. *Diagn Microbiol Infect Dis*. 1993;16:215–221.
222. Kolkman W, Groeneveld JH, Baur HJ, et al. Ototoxicity induced by clarithromycin. *Ned Tijdschr Geneeskd*. 2002;146:1743–1745.
223. Shaffer D, Singer S, Korvick J, et al. Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. *Clin Infect Dis*. 2002;35:197–200.
224. Yang Z, Prinsen JK, Bersell KR, et al. Azithromycin causes a novel proarrhythmic syndrome. *Circ Arrhythm Electrophysiol*. 2017;10.
225. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med*. 2012;366:1881–1890.
226. Wong AY, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ*. 2016;352:h6926.
227. Jespersen CM, Als-Nielsen B, Damgaard M, et al; CLARICOR Trial Group. Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. *BMJ*. 2006;332:22–27.
228. Trac MH, McArthur E, Jandoc R, et al. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. *CMAJ*. 2016;188:E120–E129.
229. In brief: FDA azithromycin warning. *Med Lett Drugs Ther*. 2013;55:28.
230. FDA Drug Safety Communication: azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms. www.fda.gov/drugs/drugsafety/ucm341822.htm. March 14, 2013.
231. Harris S, Hilligoss DM, Colangelo PM, et al. Azithromycin and terfenadine: lack of drug interaction. *Clin Pharmacol Ther*. 1995;58:310–315.
232. Periti P, Mazzei T, Mini E, et al. Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet*. 1992;23:106–131.
233. Polis MA, Piscitelli SC, Vogel S, et al. Clarithromycin lowers plasma zidovudine levels in persons with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. 1997;41:1709–1714.
234. Vance E, Watson-Bitar M, Gustavson L, et al. Pharmacokinetics of clarithromycin and zidovudine in patients with AIDS. *Antimicrob Agents Chemother*. 1995;39:1355–1360.
235. Nawarskas JJ, McCarthy DM, Spinler SA. Digoxin toxicity secondary to clarithromycin therapy. *Ann Pharmacother*. 1997;31:864–866.
236. Hammerschlag MR, Roblin PM, Bebear CM. Activity of telithromycin, a new ketolide antibacterial, against atypical and intracellular respiratory tract pathogens. *J Antimicrob Chemother*. 2001;48(supplT1):25–31.
237. Bisno AL, Gerber MA, Gwaltney JM Jr, et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America. *Clin Infect Dis*. 2002;35:113–125.
238. Still JG, Hubbard WC, Poole JM, et al. Comparison of clarithromycin and penicillin VK suspensions in the treatment of children with streptococcal pharyngitis and review of currently available alternative antibiotic therapies. *Pediatr Infect Dis J*. 1993;12:S134–S141.
239. Hooton TM. A comparison of azithromycin and penicillin V for the treatment of streptococcal pharyngitis. *Am J Med*. 1991;91:23S–26S.
240. Schaad UB, Kellerhals P, Altwegg M. Azithromycin versus penicillin V for treatment of acute group A streptococcal pharyngitis. *Pediatr Infect Dis J*. 2002;21:304–308.
241. Kaplan EL, Gooch WM, Notario GF, et al. Macrolide therapy of group A streptococcal pharyngitis: 10 days of macrolide therapy (clarithromycin) is more effective in streptococcal eradication than 5 days (azithromycin). *Clin Infect Dis*. 2001;32:1798–1802.
242. Hamill J. Multicentre evaluation of azithromycin and penicillin V in the treatment of acute streptococcal pharyngitis and tonsillitis in children. *J Antimicrob Chemother*. 1993;31(supplE):89–94.
243. Casey JR, Pichichero ME. Higher dosages of azithromycin are more effective in treatment of Group A streptococcal tonsillopharyngitis. *Clin Infect Dis*. 2005;40:1748–1755.
244. Ghirga G, Palazzi C, Ghirga P, et al. Inefficacy of a 3-day course of azithromycin in preventing acute rheumatic fever after group A streptococcal infection (scarlet fever) in an 8-year-old child. *J Pediatr*. 1999;134:123–124.
245. Aronovitz G. A multicenter, open label trial of azithromycin vs. amoxicillin/clavulanate for the management of acute otitis media in children. *Pediatr Infect Dis J*. 1996;15:S15–S19.
246. Arguedas A, Loaiza C, Rodriguez F, et al. Comparative trial of 3 days of azithromycin versus 10 days of clarithromycin in the treatment of children with acute otitis media with effusion. *J Chemother*. 1997;9:44–50.
247. Bochud PY, Calandra T, Moreillon P, et al. Breakthrough *Streptococcus pneumoniae* meningitis during clarithromycin therapy for acute otitis media. *Eur J Clin Microbiol Infect Dis*. 2001;20:136–137.
248. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis*. 2003;36:389–395.
249. Gikas A, Kofteridis DP, Manios A, et al. Newer macrolides as empiric treatment for acute Q fever infection. *Antimicrob Agents Chemother*. 2001;45:3644–3646.
250. Principi N, Esposito S, Blasi F, et al. Role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in children with community-acquired lower respiratory tract infections. *Clin Infect Dis*. 2001;32:1281–1289.
251. Socan M. Treatment of atypical pneumonia with azithromycin: comparison of a 5-day and a 3-day course. *J Chemother*. 1998;10:64–68.
252. Gleason PP, Meehan TP, Fine JM, et al. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. *Arch Intern Med*. 1999;159:2562–2572.
253. Houck PM, MacLehose RF, Niederman MS, et al. Empiric antibiotic therapy and mortality among Medicare pneumonia inpatients in 10 western states: 1993, 1995, and 1997. *Chest*. 2001;119:1420–1426.
254. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978-1997. *Am J Med*. 1999;107:34S–43S.
255. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med*. 2001;161:1837–1842.
256. Langley JM, Halperin SA, Boucher FD, et al. Azithromycin is as effective as and better tolerated than erythromycin estolate for the treatment of pertussis. *Pediatrics*. 2004;114:e96–e101.
257. Tiwari T, Murphy TV, Moran J, National Immunization Program, CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. *MMWR Recomm Rep*. 2005;54(RR–14):1–16.
258. Hoppe JE, Haug A. Treatment and prevention of pertussis by antimicrobial agents (Part II). *Infection*. 1988;16:148–152.
259. American Academy of Pediatrics. Pertussis. In: Pickering LK, ed. *Red Book: Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2000.
260. Meier A, Heifets L, Wallace RJ Jr, et al. Molecular mechanisms of clarithromycin resistance in *Mycobacterium avium:* observation of multiple 23S rRNA mutations in a clonal population. *J Infect Dis*. 1996;174:354–360.
261. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease: a randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. *Ann Intern Med*. 1994;121:905–911.
262. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. *N Engl J Med*. 1996;335:384–391.
263. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med*. 1996;335:392–398.
264. Aberg JA, Williams PL, Liu T, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated *Mycobacterium avium* complex: AIDS Clinical Trial Group 393 Study Team. *J Infect Dis*. 2003;187:1046–1052.
265. Tabbara KF, Abu-el-Asrar A, al-Omar O, et al. Single-dose azithromycin in the treatment of trachoma: a randomized, controlled study. *Ophthalmology*. 1996;103:842–846.
266. Keenan JD, Bailey RL, West SK, et al; MORDOR Study Group. Azithromycin to reduce childhood mortality in sub-Saharan Africa. *N Engl J Med*. 2018;378:1583–1592.
267. Stamm WE, Hicks CB, Martin DH, et al. Azithromycin for empirical treatment of the nongonococcal urethritis syndrome in men: a randomized double-blind study. *JAMA*. 1995;274:545–549.
268. Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhea in adults in the United States. *Clin Infect Dis*. 2007;44:S84–S101.
269. Chey WD, Leontiadis GI, Howden CW, et al. ACG Clinical Guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2017;112:212–239.
270. Marshall B. Sequential therapy for *Helicobacter pylori*: a worthwhile effort for your patients. *Ann Intern Med*. 2008;148:962–963.
271. Tompkins DS, Perkin J, Smith C. Failed treatment of *Helicobacter pylori* infection associated with resistance to clarithromycin. *Helicobacter*. 1997;2:185–187.
272. Buckley MJ, Xia HX, Hyde DM, et al. Metronidazole resistance reduces efficacy of triple therapy and leads to secondary clarithromycin resistance. *Dig Dis Sci*. 1997;42:2111–2115.
273. Hoge CW, Gambel JM, Srijan A, et al. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. *Clin Infect Dis*. 1998;26:341–345.
274. Wallace RJ Jr, Tanner D, Brennan PJ, et al. Clinical trial of clarithromycin for cutaneous (disseminated) infection due to *Mycobacterium chelonae*. *Ann Intern Med*. 1993;119:482–486.
275. Vemulapalli RK, Cantey JR, Steed LL, et al. Emergence of resistance to clarithromycin during treatment of disseminated cutaneous *Mycobacterium chelonae* infection: case report and literature review. *J Infect*. 2001;43:163–168.
276. Ji B, Jamet P, Perani EG, et al. Powerful bactericidal activities of clarithromycin and minocycline against *Mycobacterium leprae* in lepromatous leprosy. *J Infect Dis*. 1993;168:188–190.
277. Dattwyler RJ, Grunwaldt E, Luft BJ. Clarithromycin in treatment of early Lyme disease: a pilot study. *Antimicrob Agents Chemother*. 1996;40:468–469.
278. Luft BJ, Dattwyler RJ, Johnson RC, et al. Azithromycin compared with amoxicillin in the treatment of erythema migrans: a double-blind, randomized, controlled trial. *Ann Intern Med*. 1996;124:785–791.
279. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis and babeseosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43:1089–1134.
280. Andersen SL, Ager AL, McGreevy P, et al. Efficacy of azithromycin as a causal prophylactic agent against murine malaria. *Antimicrob Agents Chemother*. 1994;38:1862–1863.
281. Anderson SL, Berman J, Kuschner R, et al. Prophylaxis of *Plasmodium falciparum* malaria with azithromycin administered to volunteers. *Ann Intern Med*. 1995;123:771–773.
282. Andersen SL, Oloo AJ, Gordon DM, et al. Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in western Kenya. *Clin Infect Dis*. 1998;26:146–150.
283. Taylor WR, Richie TL, Fryauff DJ, et al. Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. *Clin Infect Dis*. 1999;28:74–81.
284. Ohrt C, Willingmyre GD, Lee P, et al. Assessment of azithromycin in combination with other antimalarial drugs against *Plasmodium falciparum* in vitro. *Antimicrob Agents Chemother*. 2002;46:2518–2524.
285. Noedl H, Krudsood S, Chalermratana K, et al. Azithromycin combination therapy with artesunate or quinine for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults: a randomized, phase 2 clinical trial in Thailand. *Clin Infect Dis*. 2006;43:1264–1271.
286. Kalilani L, Mofolo I, Chaponda M, et al. A randomized controlled pilot trial of azithromycin or artesunate added to sulfadoxine-pyramethamine as treatment for malaria in pregnant women. *PLoS ONE*. 2007;2:e1166.
287. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. *Nat Rev Immunol*. 2006;6:508–519.
288. Schneider CA, Diedrichs H, Riedel KD, et al. In vivo uptake of azithromycin in human coronary plaques. *Am J Cardiol*. 2000;86:789–791, A9.
289. Gupta S, Leatham EW, Carrington D, et al. Elevated *Chlamydia pneumoniae* antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. *Circulation*. 1997;96:404–407.
290. Cercek B, Shah PK, Noc M, et al. Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial. *Lancet*. 2003;361:809–813.
291. Muhlestein JB, Anderson JL, Carlquist JF, et al. Randomized secondary prevention trial of azithromycin in patients with coronary artery disease: primary clinical

results of the ACADEMIC study. *Circulation*. 2000;102:1755–1760.

292. O'Connor CM, Dunne MW, Pfeffer MA, et al. Azithromycin for the secondary prevention of coronary heart disease events. The WIZARD Study: a randomized controlled trial. *JAMA*. 2003;290:1459–1466.
293. Wolter J, Seeney S, Bell S, et al. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax*. 2002;57:212–216.
294. Equi A, Balfour-Lynn IM, Bush A, et al. Long term azithromycin in children with cystic fibrosis: a randomized, placebo-controlled crossover trial. *Lancet*. 2002;360:978–984.
295. Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa:* a randomized controlled trial. *JAMA*. 2003;290:1749–1756.
296. Clement A, Tamalet A, Leroux E, et al. Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax*. 2006;61:895–902.
297. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365:689–698.
298. Giamarellos-Bourboulis EJ, Pechère J-C, Routsi C, et al. Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. *Clin Infect Dis*. 2008;46:1157–1164.
299. Spyridaki A, Raftogiannis M, Antonopoulou A, et al. Effect of clarithromycin in inflammatory markers of patients with ventilator-associated pneumonia and sepsis caused by gram-negative bacteria: results from a randomized study. *Antimicrob Agents Chemother*. 2012;56:3819–3825.
300. Healy DP. Macrolide immunomodulation of chronic respiratory diseases. *Curr Infect Dis Rep*. 2007;9:7–13.
301. Renna M, Schaffner C, Brown K, et al. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. *J Clin Invest*. 2011;121:3553–3563.
302. McGehee R, Smith CB, Wilcox C, et al. Comparative studies of antibacterial activity in vitro and absorption and excretion of lincomycin and clindamycin. *Am J Med Sci*. 1968;256:279–292.
303. Schwarz S, Shen J, Kadlec K, et al. Lincosamides, streptogramins, phenicols, and pleuromutilins: mode of action and mechanisms of resistance. *Cold Spring Harb Perspect Med*. 2016;6.
304. Weisblum B. Erythromycin resistance by ribosome modification. *Antimicrob Agents Chemother*. 1995;39:577–585.
305. Siberry GK, Tekle T, Carroll K, et al. Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible clindamycin resistance in vitro. *Clin Infect Dis*. 2003;37:1257–1260.
306. Daurel C, Huet C, Dhalluin A, et al. Differences in the potential for selection of clindamycin-resistant mutants between inducible *erm*(A) and *erm*(C) *Staphylococcus aureus* genes. *J Clin Microbiol*. 2008;46:546–550.
307. LaPlante KL, Leonard SN, Andes DR, et al. Activities of clindamycin, daptomycin, doxycycline, linezolid, trimethoprim-sulfamethoxazole, and vancomycin against community-associated methicillin-resistant *Staphylococcus aureus* with inducible clindamycin resistance in murine thigh infection and in vitro pharmacodynamic models. *Antimicrob Agents Chemother*. 2008;52:2156–2162.
308. Kehrenberg C, Schwarz S, Jacobsen L, et al. A new mechanism for chloramphenicol, florfenicol and clindamycin resistance: methylation of 23S ribosomal RNA at A2503. *Mol Microbiol*. 2005;57:1064–1073.
309. Long KS, Poehlsgaard J, Kehrenberg C, et al. The Cfr rRNA methyltransferase confers resistance to Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, and Streptogramin A antibiotics. *Antimicrob Agents Chemother*. 2006;50:2500–2505.
310. Matzov D, Eyal Z, Benhamou RI, et al. Structural insights of lincosamides targeting the ribosome of *Staphylococcus aureus*. *Nucleic Acids Res*. 2017;45:10284–10292.
311. Poehlsgaard J, Pfister P, Bottger EC, et al. Molecular mechanisms by which rRNA mutations confer resistance to clindamycin. *Antimicrob Agents Chemother*. 2005;49:1553–1555.
312. Leclercq R, Brisson-Noel A, Duval J, et al. Phenotypic expression and genetic heterogeneity of lincosamide inactivation in *Staphylococcus* spp. *Antimicrob Agents Chemother*. 1987;31:1887–1891.
313. Archard A, Villers C, Pichereau V, et al. New Inu(C) gene conferring resistance to lincomycin by nucleotidylation in *Streptococcus agalactiae* UCN36. *Antimicrob Agents Chemother*. 2005;49:2716–2719.
314. Low DE, de Azavedo J, Weiss K, et al. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in Canada during 2000. *Antimicrob Agents Chemother*. 2002;46:1295–1301.
315. Aldridge KE, Ashcraft D, Cambre K, et al. Multicenter survey of the changing in vitro antimicrobial susceptibilities of clinical isolates of *Bacteroides fragilis* group, *Prevotella, Fusobacterium, Porphyromonas,* and *Peptostreptococcus* species. *Antimicrob Agents Chemother*. 2001;45:1238–1243.
316. Liu C-Y, Huang Y-T, Liao C-H, et al. Increasing trends in antimicrobial resistance among clinically important anaerobes and *Bacteroides fragilis* isolates causing nosocomial infections: emerging resistance to carbapenems. *Antimicrob Agents Chemother*. 2008;52:3161–3168.
317. Snydman DR, Jacobus NV, McDermott LA, et al. National survey on the susceptibility of *Bacteroides fragilis* group: report and analysis of trends in the United States from 1997 to 2004. *Antimicrob Agents Chemother*. 2008;51:1649–1655.
318. Snydman DR, Jacobus NV, McDermott LA, et al. Trends in antimicrobial resistance among *Bacteroides* species and *Parabacteroides* species in the United States from 2010-2012 with comparison to 2008-2009. *Anaerobe*. 2017;43:21–26.
319. Snydman DR, Jacobus NV, McDermott LA, et al. Update on resistance of *Bacteroides fragilis* group and related species with special attention to carbapenems 2006-2009. *Anaerobe*. 2011;17:147–151.
320. Schaumann R, Funke M, Janssen E, et al. *In vitro* activities of clindamycin, imipenem, metronidazole and piperacillin-tazobactam against susceptible and resistant isolates of *Bacteroides fragilis* evaluated by kill kinetics. *Antimicrob Agents Chemother*. 2012;56:3413–3416.
321. Marchand-Austin A, Rawte P, Toye B, et al. Antimicrobial susceptibility of clinical isolates of anaerobic bacteria in Ontario, 2010-2011. *Anaerobe*. 2014;28:120–125.
322. Veloo AC, van Winkelhoff AJ. Antibiotic susceptibility profiles of anaerobic pathogens in The Netherlands. *Anaerobe*. 2015;31:19–24.
323. Wang FD, Liao CH, Lin YT, et al. Trends in the susceptibility of commonly encountered clinically significant anaerobes and susceptibilities of blood isolates of anaerobes to 16 antimicrobial agents, including fidaxomicin and rifaximin, 2008-2012, northern Taiwan. *Eur J Clin Microbiol Infect Dis*. 2014;33:2041–2052.
324. Doern GV, Richter SS, Miller A, et al. Antimicrobial resistance among *Streptococcus pneumoniae* in the United States: have we begun to turn the corner on resistance to certain antimicrobial classes? *Clin Infect Dis*. 2005;41:139–148.
325. Chochua S, Metcalf BJ, Li Z, et al. Population and whole genome sequence based characterization of invasive group A streptococci recovered in the United States during 2015. *MBio*. 2017;8:e01422–17.
326. Andreoni F, Zurcher C, Tarnutzer A, et al. Clindamycin affects group a *Streptococcus* virulence factors and improves clinical outcome. *J Infect Dis*. 2017;215:269–277.
327. Linner A, Darenberg J, Sjolin J, et al. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. *Clin Infect Dis*. 2014;59:851–857.
328. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T*. 2015;40:277–283.
329. Sader HS, Mendes RE, Streit JM, et al. Antimicrobial susceptibility trends among *Staphylococcus aureus* isolates from U.S. Hospitals: results from 7 years of the ceftaroline (AWARE) surveillance program, 2010 to 2016. *Antimicrob Agents Chemother*. 2017;61.
330. Duncan IB. Development of lincomycin resistance by staphylococci. *Antimicrob Agents Chemother (Bethesda)*. 1967;7:723–729.
331. Tenover FC, McAllister S, Fosheim G, et al. Characterization of *Staphylococcus aureus* isolates from nasal cultures collected from individuals in the United States in 2001 to 2004. *J Clin Microbiol*. 2008;46:2837–2841.
332. Huang H, Flynn NM, King JH, et al. Comparisons of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) and hospital-associated MRSA infections in Sacramento, California. *J Clin Microbiol*. 2006;44:2423–2427.
333. David MZ, Glikman D, Crawford SE, et al. What is community-associated methicillin-resistant *Staphylococcus aureus*? *J Infect Dis*. 2008;197:1235–1243.
334. Sande MA, Johnson ML. Antimicrobial therapy of experimental endocarditis caused by *Staphylococcus aureus*. *J Infect Dis*. 1975;131:367–375.
335. Nastro LJ, Finegold SM. Bactericidal activity of five antimicrobial agents against *Bacteroides fragilis*. *J Infect Dis*. 1972;126:104–107.
336. Stevens D, Ma Y, Salmi DB, et al. Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*. *J Infect Dis*. 2007;195:202–211.
337. Pfefferkorn ER, Nothnagel RF. Borotz SE. Parasiticidal effect of clindamycin on *Toxoplasma gondii* grown in cultured cells and selection of a drug-resistant mutant. *Antimicrob Agents Chemother*. 1992;36:1091–1096.
338. Seaberg LS, Parquette AR, Gluzman IY, et al. Clindamycin activity against chloroquine-resistant *Plasmodium falciparum*. *J Infect Dis*. 1984;150:904–911.
339. DeHaan RM, Metzler CM, Schellenberg D, et al. Pharmacokinetic studies of clindamycin phosphate. *J Clin Pharmacol*. 1973;13:190–209.
340. Fass RJ. Saslaw S. Clindamycin: clinical and laboratory evaluation of parenteral therapy. *Am J Med Sci*. 1972;263:368–382.
341. Townsend RJ, Baker RP. Pharmacokinetic comparison of three clindamycin phosphate dosing schedules. *Drug Intell Clin Pharm*. 1987;21:279–281.
342. Panzer JD, Brown DC, Epstein WL, et al. Clindamycin levels in various body tissues and fluids. *J Clin Pharmacol New Drugs*. 1972;12:259–262.
343. Nicholas P, Meyers BR, Levy RN, et al. Concentration of clindamycin in human bone. *Antimicrob Agents Chemother*. 1975;8:220–221.
344. Prokesch RC, Hand WL. Antibiotic entry into human polymorphonuclear leukocytes. *Antimicrob Agents Chemother*. 1982;21:373–380.
345. Joiner KA, Lowe BR, Dzink JL, et al. Antibiotic levels in infected and sterile subcutaneous abscesses in mice. *J Infect Dis*. 1981;143:487–494.
346. McCall CE, Steigbigel NH, Finland M. Lincomycin: activity in vitro and absorption and excretion in normal young men. *Am J Med Sci*. 1967;254:144–155.
347. Kager L, Liljeqvist L, Malmborg AS, et al. Effect of clindamycin prophylaxis on the colonic microflora in patients undergoing colorectal surgery. *Antimicrob Agents Chemother*. 1981;20:736–740.
348. Brown RB, Martyak SN, Barza M, et al. Penetration of clindamycin phosphate into the abnormal human biliary tract. *Ann Intern Med*. 1976;84:168–170.
349. Joshi AM, Stein RM. Altered serum clearance of intravenously administered clindamycin phosphate in patients with uremia. *J Clin Pharmacol*. 1974;14:140–144.
350. Williams DN, Crossley K, Hoffman C, et al. Parenteral clindamycin phosphate: pharmacology with normal and abnormal liver function and effect on nasal staphylococci. *Antimicrob Agents Chemother*. 1975;7:153–158.
351. Shehab N, Patel PR, Srinivasin A, et al. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008;47735–47743.
352. Yang Y, Chen S, Yang F, et al. HLA-B*51:01 is strongly associated with clindamycin-related cutaneous adverse drug reactions. *Pharmacogenomics J*. 2017;17:501–505.
353. Bartlett JG. Historical perspectives on studies of *Clostridium difficile* and *C. difficile* infection. *Clin Infect Dis*. 2008;46(suppl 1):S4–S11.
354. Tedesco FJ. Clindamycin and colitis: a review. *J Infect Dis*. 1977;135(suppl):S95–S98.
355. Kelly CP, LaMont JT. *Clostridium difficile*—more difficult than ever. *N Engl J Med*. 2008;359:1932–1940.
356. Owens R, Donskey CJ, Gaynes RP, et al. Antimicrobial-associated risk factors for *Clostridium difficile* infection. *Clin Infect Dis*. 2008;46:S19–S31.
357. Dial S, Kezouh A, Dascal A, et al. Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection. *CMAJ*. 2008;179:767–772.
358. Meadowcroft AM, Diaz PR, Latham GS. *Clostridium difficile* toxin-induced colitis after use of clindamycin phosphate vaginal cream. *Ann Pharmacother*. 1998;32:309–311.
359. Elmore M, Rissing JP, Rink L, et al. Clindamycin-associated hepatotoxicity. *Am J Med*. 1974;57:627–630.
360. Brook I. Spectrum and treatment of anaerobic infections. *J Infect Chemother*. 2016;22:1–13.
361. Montravers P, Dupont H, Leone M, et al. Guidelines for management of intra-abdominal infections. *Anaesth Crit Care Pain Med*. 2015;34:117–130.
362. Sartelli M, Catena F, Abu-Zidan FM, et al. Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference. *World J Emerg Surg*. 2017;12:22.
363. Bartlett JG, Gorbach SL. Treatment of aspiration pneumonia and primary lung abscess: penicillin G vs clindamycin. *JAMA*. 1975;234:935–937.
364. Levison ME, Mangura CT, Lorber B, et al. Clindamycin compared with penicillin for the treatment of anaerobic lung abscess. *Ann Intern Med*. 1983;98:466–471.
365. Bartlett JG, Gorbach SL. Penicillin or clindamycin for primary lung abscess? *Ann Intern Med*. 1983;98:546–548.
366. Gudiol F, Manresa F, Pallares R, et al. Clindamycin vs penicillin for anaerobic lung infections. High rate of penicillin failures associated with penicillin-resistant

Bacteroides melaninogenicus. *Arch Intern Med*. 1990;150:2525–2529.
367. Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia: when should they be treated and what is optimal therapy. *Infect Dis Clin North Am*. 2013;27:149–155.
368. Stevens DL, Maier KA, Mitten JE. Effect of antibiotics on toxin production and viability of *Clostridium perfringens*. *Antimicrob Agents Chemother*. 1987;31: 213–218.
369. Stevens DL, Maier KA, Laine BM, et al. Comparison of clindamycin, rifampin, tetracycline, metronidazole, and penicillin for efficacy in prevention of experimental gas gangrene due to *Clostridium perfringens*. *J Infect Dis*. 1987;155:220–228.
370. Watanakunakorn C. Clindamycin therapy of *Staphylococcus aureus* endocarditis: clinical relapse and development of resistance to clindamycin, lincomycin and erythromycin. *Am J Med*. 1976;60:419–425.
371. Leyden JJ, Berger RS, Dunlap FE, et al. Comparison of the efficacy and safety of a combination topical gel formulation of benzoyl peroxide and clindamycin with benzoyl peroxide, clindamycin and vehicle gel in the treatments of acne vulgaris. *Am J Clin Dermatol*. 2001;2:33–39.
372. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. *Arch Dermatol*. 1986;122:583–584.
373. Schmitt C, Sobel JD, Meriwether C. Bacterial vaginosis: treatment with clindamycin cream versus oral metronidazole. *Obstet Gynecol*. 1992;79:1020–1023.
374. Haahr T, Ersboll AS, Karlsen MA, et al. Treatment of bacterial vaginosis in pregnancy in order to reduce the risk of spontaneous preterm delivery - a clinical recommendation. *Acta Obstet Gynecol Scand*. 2016;95:850–860.
375. Lamont RF, Keelan JA, Larsson PG, et al. The treatment of bacterial vaginosis in pregnancy with clindamycin to reduce the risk of infection-related preterm birth: a response to the Danish Society of Obstetrics and Gynecology guideline group's clinical recommendations. *Acta Obstet Gynecol Scand*. 2017;96:139–143.
376. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS: a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. *Ann Intern Med*. 1992;116:33–43.
377. Masur H, Brooks JT, Benson CA, et al. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: updated guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;58:1308–1311.
378. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS: a double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med*. 1996;124:792–802.
379. Benfield T, Atzori C, Miller RF, et al. Second-line salvage treatment of AIDS-associated *Pneumocystis jirovecii* pneumonia. A case series and systematic review. *J Acquir Immune Defic Syndr*. 2008;48:63–67.
380. Kremsner PG, Radloff P, Metzger W, et al. Quinine plus clindamycin improves chemotherapy of severe malaria in children. *Antimicrob Agents Chemother*. 1995;39:1603–1605.
381. Wittner M, Rowin KS, Tanowitz HB, et al. Successful chemotherapy of transfusion babesiosis. *Ann Intern Med*. 1982;96:601–604.
382. Ramharter M, Oyakhirome S, Klein Klouwenberg P, et al. Artesunate-clindamycin versus quinine-clindamycin in the treatment of *Plasmodium falciparum* malaria: a randomized controlled trial. *Clin Infect Dis*. 2005;40:1777–1784.
383. Brook I, Hirokawa R. Treatment of patients with a history of recurrent tonsillitis due to group A beta-hemolytic streptococci: a prospective randomized study comparing penicillin, erythromycin, and clindamycin. *Clin Pediatr (Phila)*. 1985;24:331–336.
384. Orrling A, Stjernquist-Desatnik A, Schalen C, et al. Clindamycin in persisting streptococcal pharyngotonsillitis after penicillin treatment. *Scand J Infect Dis*. 1994;26:535–541.
385. Smacchia C, Rebulla P, Drago F, et al. A micro colorimetric assay using cryopreserved monocytes to evaluate antibody-mediated red cell-monocyte interaction. *Haematologica*. 1997;82:526–531.
386. American Academy of Pediatrics, Committee on Infectious Diseases. Severe invasive group A streptococcal infections: a subject review. *Pediatrics*. 1998;101:136–140.
387. Stevens DL, Madaras-Kelly KJ, Richards DM. In vitro antimicrobial effects of various combinations of penicillin and clindamycin against four strains of *Streptococcus pyogenes*. *Antimicrob Agents Chemother*. 1998;42:1266–1268.
388. Hoppe JE, Bryskier A. In vitro susceptibilities of *Bordetella pertussis* and *Bordetella parapertussis* to two ketolides (HMR 3004 and HMR 3647), four macrolides (azithromycin, clarithromycin, erythromycin A, and roxithromycin), and two ansamycins (rifampin and rifapentine). *Antimicrob Agents Chemother*. 1998;42:965–966.
389. Bebear CM, Renaudin H, Bryskier A, et al. Comparative activities of telithromycin (HMR 3647), levofloxacin, and other antimicrobial agents against human mycoplasmas. *Antimicrob Agents Chemother*. 2000;44:1980–1982.
390. Roblin PM, Hammerschlag MR. In vitro activity of a new ketolide antibiotic, HMR 3647, against *Chlamydia pneumoniae*. *Antimicrob Agents Chemother*. 1998;42:1515–1516.

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

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]

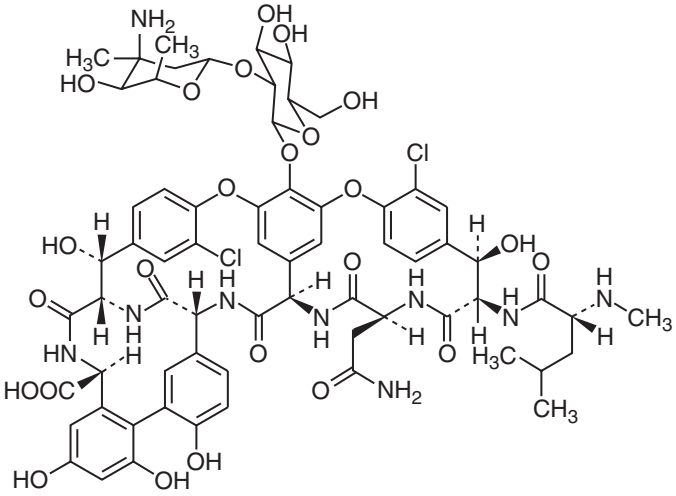

FIG. 30.1 **Chemical structure of vancomycin.**

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.

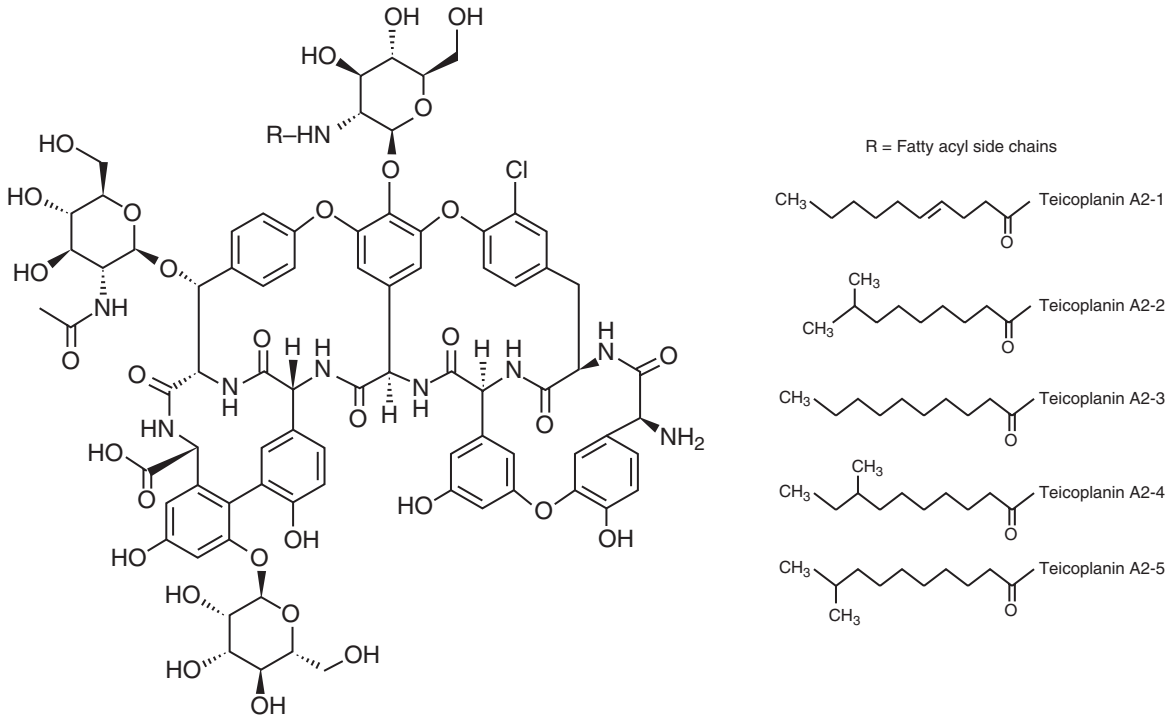

FIG. 30.2 **Chemical structure of teicoplanin.**

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

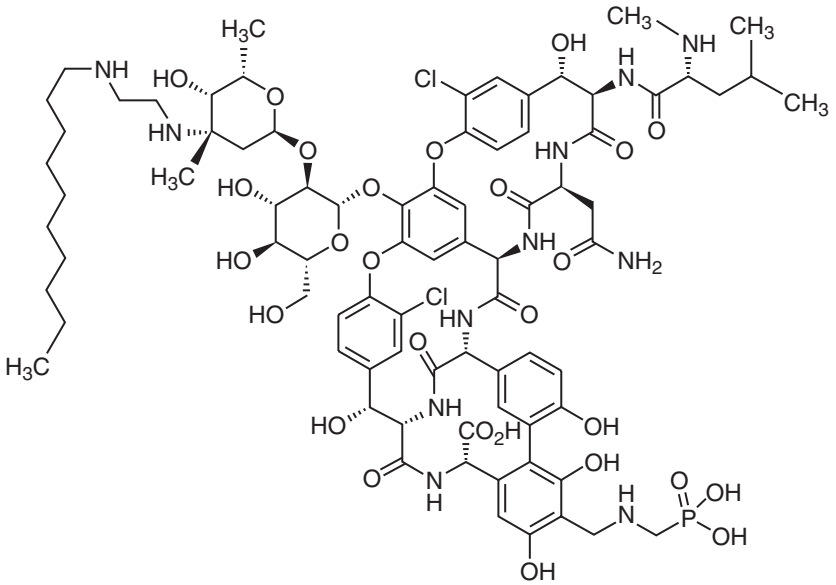

FIG. 30.3 Chemical structure of telavancin.

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.

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.

Key References

The complete reference list is available online at Expert Consult.

9. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
10. Hiramatsu K. Vancomycin-resistant *Staphylococcus aureus*: a new model of antibiotic resistance. *Lancet Infect Dis*. 2001;1:147–155.
24. Wootton M, Howe RA, Hillman R, et al. A modified population analysis profile (PAP) method to detect hetero-resistance to vancomycin in *Staphylococcus aureus* in a UK hospital. *J Antimicrob Chemother*. 2001;47:399–403.
25. Howden BP, Davies JK, Johnson PD, et al. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clin Microbiol Rev*. 2010;23:99–139.
32. Sakoulas G, Moise-Broder PA, Schentag J, et al. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol*. 2004;42:2398–2402.
34. Hidayat LK, Hsu DI, Quist R, et al. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Arch Intern Med*. 2006;166:2138–2144.
38. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis*. 2012;54:755–771.
43. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
44. Sievert DM, Rudrik JT, Patel JB, et al. Vancomycin-resistant *Staphylococcus aureus* in the United States, 2002-2006. *Clin Infect Dis*. 2008;46:668–674.
48. Perichon B, Courvalin P. VanA-type vancomycin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2009;53:4580–4587.
53. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis*. 2006;42(suppl 1):S35–S39.
55. Moise-Broder PA, Forrest A, Birmingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet*. 2004;43:925–942.
56. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82–98.
58. Kullar R, Davis SL, Levine DP, et al. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis*. 2011;52:975–981.
64. Mohr JF, Murray BE. Point: vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2007;44:1536–1542.
67. Vesga O, Agudelo M, Salazar BE, et al. Generic vancomycin products fail in vivo despite being pharmaceutical equivalents of the innovator. *Antimicrob Agents Chemother*. 2010;54:3271–3279.
92. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016;36:481–508.
95. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64:e34–e65.
100. Zelenitsky SA, Ariano RE, McCrae ML, et al. Initial vancomycin dosing protocol to achieve therapeutic serum concentrations in patients undergoing hemodialysis. *Clin Infect Dis*. 2012;55:527–533.
108. Elyasi S, Khalili H, Dashti-Khavidaki S, et al. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations: a literature review. *Eur J Clin Pharmacol*. 2012;68:1243–1255.
113. Bosso JA, Nappi J, Rudisill C, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. *Antimicrob Agents Chemother*. 2011;55:5475–5479.
114. Lodise TP, Lomaestro B, Graves J, et al. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob Agents Chemother*. 2008;52:1330–1336.
116. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis*. 2009;48:713–721.
126. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41:1373–1406.
129. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355:653–665.
132. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. *Antimicrob Agents Chemother*. 2008;52:3315–3320.
138. Murray BE. The life and times of the *Enterococcus*. *Clin Microbiol Rev*. 1990;3:46–65.
142. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.
146. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis*. 2012;54:621–629.
148. Rubinstein E, Lalani T, Corey GR, et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. *Clin Infect Dis*. 2011;52:31–40.
154. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431–455.
159. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70:195–283.
166. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
171. Wilson AP, Gruneberg RN, Neu HC. A critical review of the dosage of teicoplanin in Europe and the USA. *Int J Antimicrob Agents*. 1994;4(suppl 1):S1–S30.
182. Chang HJ, Hsu PC, Yang CC, et al. Influence of teicoplanin MICs on treatment outcomes among patients with teicoplanin-treated methicillin-resistant *Staphylococcus aureus* bacteraemia: a hospital-based retrospective study. *J Antimicrob Chemother*. 2012;67:736–741.
192. Van Bambeke F. Glycopeptides in clinical development: pharmacological profile and clinical perspectives. *Curr Opin Pharmacol*. 2004;4:471–478.
196. Higgins DL, Chang R, Debabov DV, et al. Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2005;49:1127–1134.
197. Lunde CS, Hartouni SR, Janc JW, et al. Telavancin disrupts the functional integrity of the bacterial membrane through targeted interaction with the cell wall precursor lipid II. *Antimicrob Agents Chemother*. 2009;53:3375–3383.
202. Stryjewski ME, Graham DR, Wilson SE, et al. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. *Clin Infect Dis*. 2008;46:1683–1693.
228. Jauregui LE, Babazadeh S, Seltzer E, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis*. 2005;41:1407–1415.
226. Boucher HW, Wilcox M, Talbot GH, et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. *N Engl J Med*. 2014;370:2169–2179.
231. Zhanel GG, Schweizer F, Karlowsky JA. Oritavancin: mechanism of action. *Clin Infect Dis*. 2012;54(suppl 3):S214–S219.
233. Morrissey I, Seifert H, Canton R, et al. Activity of oritavancin against methicillin-resistant staphylococci, vancomycin-resistant enterococci and β-haemolytic streptococci collected from western European countries in 2011. *J Antimicrob Chemother*. 2013;68:164–167.
234. Mendes RE, Farrell DJ, Sader HS, et al. Activity of oritavancin against gram-positive clinical isolates responsible for documented skin and soft-tissue infections in European and US hospitals (2010-13). *J Antimicrob Chemother*. 2015;70:498–504.
244. Corey GR, Kabler H, Mehra P, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. *N Engl J Med*. 2014;370:2180–2190.

References

1. Kirst HA, Thompson DG, Nicas TI. Historical yearly usage of vancomycin. *Antimicrob Agents Chemother*. 1998;42:1303–1304.
2. Gladsone BP, et al. Antimicrobial resistance rates in gram-positive bacteria do not drive glycopeptides use. *PLoS ONE*. 2017;12:e0181358.
3. Lipsky BA, Baker CA, McDonald LL, et al. Improving the appropriateness of vancomycin use by sequential interventions. *Am J Infect Control*. 1999;27:84–91.
4. Fraser TG, Stosor V, Wang Q, et al. Vancomycin and home health care. *Emerg Infect Dis*. 2005;11:1558–1564.
5. Siebert WT, Moreland N, Williams TW Jr. Synergy of vancomycin plus cefazolin or cephalothin against methicillin-resistance *Staphylococcus epidermidis*. *J Infect Dis*. 1979;139:452–457.
6. Hiramatsu K, Hanaki H, Ino T, et al. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother*. 1997;40:135–136.
7. Clinical and Laboratory Standards Institute. CLSI document M100-S22. Supplement. Wayne, PA: CLSI; 2012.
8. Galloway-Pena J, Roh JH, Latorre M, et al. Genomic and SNP analyses demonstrate a distant separation of the hospital and community-associated clades of *Enterococcus faecium*. *PLoS ONE*. 2012;7:e30187.
9. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
10. Hiramatsu K. Vancomycin-resistant *Staphylococcus aureus*: a new model of antibiotic resistance. *Lancet Infect Dis*. 2001;1:147–155.
11. Leonard SN. Synergy between vancomycin and nafcillin against *Staphylococcus aureus* in an in vitro pharmacokinetic/pharmacodynamic model. *PLoS ONE*. 2012;7:e42103.
12. Hagihara M, Wiskirchen DE, Kuti JL, et al. In vitro pharmacodynamics of vancomycin and cefazolin alone and in combination against methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2012;56:202–207.
13. Domenech A, Ribes S, Cabellos C, et al. Experimental study on the efficacy of combinations of glycopeptides and beta-lactams against *Staphylococcus aureus* with reduced susceptibility to glycopeptides. *J Antimicrob Chemother*. 2005;56:709–716.
14. Fernandez J, Abbanat D, Shang W, et al. Synergistic activity of ceftobiprole and vancomycin in a rat model of infective endocarditis caused by methicillin-resistant and glycopeptide-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2012;56:1476–1484.
15. Zhang S, Sun X, Chang W, et al. Systematic review and meta-analysis of the epidemiology of vancomycin-intermediate and heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates. *PLoS ONE*. 2015;10:e0136082.
16. Richter SS, Satola SW, Crispell EK, et al. Detection of *Staphylococcus aureus* isolates with heterogeneous intermediate-level resistance to vancomycin in the United States. *J Clin Microbiol*. 2011;49:4203–4207.
17. Cui L, Neoh HM, Shoji M, et al. Contribution of vraSR and graSR point mutations to vancomycin resistance in vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2009;53:1231–1234.
18. Shoji M, Cui L, Iizuka R, et al. walK and clpP mutations confer reduced vancomycin susceptibility in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2011;55:3870–3881.
19. Howden BP, McEvoy CR, Allen DL, et al. Evolution of multidrug resistance during *Staphylococcus aureus* infection involves mutation of the essential two component regulator WalKR. *PLoS Pathog*. 2011;7:e1002359.
20. Sakoulas G, Eliopoulos GM, Moellering RC Jr, et al. Accessory gene regulator (agr) locus in geographically diverse *Staphylococcus aureus* isolates with reduced susceptibility to vancomycin. *Antimicrob Agents Chemother*. 2002;46:1492–1502.
21. Sakoulas G, Moellering RC Jr, Eliopoulos GM. Adaptation of methicillin-resistant *Staphylococcus aureus* in the face of vancomycin therapy. *Clin Infect Dis*. 2006;42(suppl 1):S40–S50.
22. Moise-Broder PA, Sakoulas G, Eliopoulos GM, et al. Accessory gene regulator group II polymorphism in methicillin-resistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. *Clin Infect Dis*. 2004;38:1700–1705.
23. Cafiso V, Bertuccio T, Spina D, et al. Modulating activity of vancomycin and daptomycin on the expression of autolysis cell-wall turnover and membrane charge genes in hVISA and VISA strains. *PLoS ONE*. 2012;7:e29573.
24. Wootton M, Howe RA, Hillman R, et al. A modified population analysis profile (PAP) method to detect hetero-resistance to vancomycin in *Staphylococcus aureus* in a UK hospital. *J Antimicrob Chemother*. 2001;47:399–403.
25. Howden BP, Davies JK, Johnson PD, et al. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clin Microbiol Rev*. 2010;23:99–139.
26. Appelbaum PC. Reduced glycopeptide susceptibility in methicillin-resistant *Staphylococcus aureus* (MRSA). *Int J Antimicrob Agents*. 2007;30:398–408.
27. Wootton M, MacGowan AP, Walsh TR, et al. A multicenter study evaluating the current strategies for isolating *Staphylococcus aureus* strains with reduced susceptibility to glycopeptides. *J Clin Microbiol*. 2007;45:329–332.
28. Vaudaux P, Huggler E, Bernard L, et al. Underestimation of vancomycin and teicoplanin MICs by broth microdilution leads to underdetection of glycopeptide-intermediate isolates of *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2010;54:3861–3870.
29. Miller CE, Batra R, Cooper BS, et al. An association between bacterial genotype combined with a high-vancomycin minimum inhibitory concentration and risk of endocarditis in methicillin-resistant *Staphylococcus aureus* bloodstream infection. *Clin Infect Dis*. 2012;54:591–600.
30. Howden BP, Smith DJ, Mansell A, et al. Different bacterial gene expression patterns and attenuated host immune responses are associated with the evolution of low-level vancomycin resistance during persistent methicillin-resistant *Staphylococcus aureus* bacteraemia. *BMC Microbiol*. 2008;8:39.
31. Horne KC, Howden BP, Grabsch EA, et al. Prospective comparison of the clinical impacts of heterogeneous vancomycin-intermediate methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible MRSA. *Antimicrob Agents Chemother*. 2009;53:3447–3452.
32. Sakoulas G, Moise-Broder PA, Schentag J, et al. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol*. 2004;42:2398–2402.
33. Moise PA, Sakoulas G, Forrest A, et al. Vancomycin in vitro bactericidal activity and its relationship to efficacy in clearance of methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2007;51:2582–2586.
34. Hidayat LK, Hsu DI, Quist R, et al. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Arch Intern Med*. 2006;166:2138–2144.
35. Maclayton DO, Suda KJ, Coval KA, et al. Case-control study of the relationship between MRSA bacteremia with a vancomycin MIC of 2 microg/mL and risk factors, costs, and outcomes in inpatients undergoing hemodialysis. *Clin Ther*. 2006;28:1208–1216.
36. Holmes NE, Turnidge JD, Munckhof WJ, et al. Antibiotic choice may not explain poorer outcomes in patients with *Staphylococcus aureus* bacteremia and high vancomycin minimum inhibitory concentrations. *J Infect Dis*. 2011;204:340–347.
37. Wang JL, Wang JT, Sheng WH, et al. Nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in Taiwan: mortality analyses and the impact of vancomycin, MIC = 2 mg/L, by the broth microdilution method. *BMC Infect Dis*. 2010;10:159.
38. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis*. 2012;54:755–771.
39. Kalil AC, Van Schooneveld TC, Fey PD, et al. Association between vancomycin minimum inhibitory concentration and mortality among patients with *Staphylococcus aureus* bloodstream infections: a systematic review and meta-analysis. *JAMA*. 2014;312:1552–1564.
40. Honda H, Doern CD, Michael-Dunne W Jr, et al. The impact of vancomycin susceptibility on treatment outcomes among patients with methicillin resistant *Staphylococcus aureus* bacteremia. *BMC Infect Dis*. 2011;11:335.
41. Song KH, et al. Impact of vancomycin MIC on treatment outcomes in invasive *Staphylococcus aureus* infections. *Antimicrob Agents Chemother*. 2017;61:pii: e01845-16.
42. Keel RA, Sutherland CA, Aslanzadeh J, et al. Correlation between vancomycin and daptomycin MIC values for methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* by 3 testing methodologies. *Diagn Microbiol Infect Dis*. 2010;68:326–329.
43. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
44. Sievert DM, Rudrik JT, Patel JB, et al. Vancomycin-resistant *Staphylococcus aureus* in the United States, 2002-2006. *Clin Infect Dis*. 2008;46:668–674.
45. Walters MS, Eggers P, Albrecht V, et al. Vancomycin-resistant *Staphylococcus aureus*—Delaware, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64:1056.
46. Rossi F, Diaz L, Wollam A, et al. Transferable vancomycin resistance in a community-associated MRSA lineage. *N Engl J Med*. 2014;370:1524–1531.
47. Panesso D, Planet PJ, Diaz L, et al. Methicillin-susceptible, vancomycin-resistant *Staphylococcus aureus*, Brazil. *Emerg Infect Dis*. 2015;21:1844–1848.
48. Perichon B, Courvalin P. VanA-type vancomycin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2009;53:4580–4587.
49. Mashaly GE, El-Mahdy RH. Vancomycin heteroresistance in coagulase negative *Staphylococcus* blood stream infections from patients of intensive care units in Mansoura University Hospitals, Egypt. *Ann Clin Microbiol Antimicrob*. 2017;16:63.
50. Rodriguez CA, Atkinson R, Bitar W, et al. Tolerance to vancomycin in pneumococci: detection with a molecular marker and assessment of clinical impact. *J Infect Dis*. 2004;190:1481–1487.
51. Olivares A, Trejo JO, Arellano-Galindo J, et al. pep27 and lytA in vancomycin-tolerant pneumococci. *J Microbiol Biotechnol*. 2011;21:1345–1351.
52. Liu X, Li JW, Feng Z, et al. Transcriptional repressor PtvR regulates phenotypic tolerance to vancomycin in *Streptococcus pneumoniae*. *J Bacteriol*. 2017;199:e00054-17.
53. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis*. 2006;42(suppl 1):S35–S39.
54. Moise PA, Forrest A, Bhavnani SM, et al. Area under the inhibitory curve and a pneumonia scoring system for predicting outcomes of vancomycin therapy for respiratory infections by *Staphylococcus aureus*. *Am J Health Syst Pharm*. 2000;57(suppl 2):S4–S9.
55. Moise-Broder PA, Forrest A, Birmingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet*. 2004;43:925–942.
56. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82–98.
57. Neely MN, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother*. 2018;62.
58. Kullar R, Davis SL, Levine DP, et al. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis*. 2011;52:975–981.
59. Jung Y, et al. Area under the concentration-time curve to minimum inhibitory concentration ratio as a predictor of vancomycin treatment outcome in methicillin-resistant *Staphylococcus aureus* bacteraemia. *Int J Antimicrob Agents*. 2014;43:179–183.
60. Song KH, et al. Impact of area under the concentration-time curve to minimum inhibitory concentration ratio on vancomycin treatment outcomes in methicillin-resistant *Staphylococcus aureus* bacteraemia. *Int J Antimicrob Agents*. 2015;46:689–695.
61. Men P, Li HB, Zhai SD, et al. Association between the AUC0-24/MIC ratio of vancomycin and its clinical effectiveness: a systematic review and meta-analysis. *PLoS ONE*. 2016;11:e0146224.
62. Neely MN, Youn G, Jones B, et al. Are vancomycin trough concentrations adequate for optimal dosing? *Antimicrob Agents Chemother*. 2014;58:309–316.
63. Patel N, Pai MP, Rodvold KA, et al. Vancomycin: we can't get there from here. *Clin Infect Dis*. 2011;52:969–974.
64. Mohr JF, Murray BE. Point: vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2007;44:1536–1542.

65. Jumah MTB, Vasoo S, Menon SR, et al. Pharmacokinetic/pharmacodynamic determinants of vancomycin efficacy in enterococcal bacteremia. *Antimicrob Agents Chemother*. 2018;62:pii: e01602-17.
66. Britt NS, Patel N, Shireman TI, et al. Relationship between vancomycin tolerance and clinical outcomes in *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother*. 2017;72:535–542.
67. Vesga O, Agudelo M, Salazar BE, et al. Generic vancomycin products fail in vivo despite being pharmaceutical equivalents of the innovator. *Antimicrob Agents Chemother*. 2010;54:3271–3279.
68. Nambiar S, Madurawe RD, Zuk SM, et al. Product quality of parenteral vancomycin products in the United States. *Antimicrob Agents Chemother*. 2012;56:2819–2823.
69. Tattevin P, Saleh-Mghir A, Davido B, et al. Comparison of six generic vancomycin products for treatment of methicillin-resistant *Staphylococcus aureus* experimental endocarditis in rabbits. *Antimicrob Agents Chemother*. 2013;57:1157–1162.
70. Griffith RS. Vancomycin use—an historical review. *J Antimicrob Chemother*. 1984;14(supplD):1–5.
71. Moellering RC. Pharmacokinetics of vancomycin. *J Antimicrob Chemother*. 1984;14(supplD):43–52.
72. Beach JE, Perrott J, Turgeon RD, et al. Penetration of vancomycin into the cerebrospinal fluid: a systematic review. *Clin Pharmacokinet*. 2017;56:1479–1490.
73. Ricard JD, Wolff M, Lacherade JC, et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. *Clin Infect Dis*. 2007;44:250–255.
74. Albanese J, Leone M, Bruguerolle B, et al. Cerebrospinal fluid penetration and pharmacokinetics of vancomycin administered by continuous infusion to mechanically ventilated patients in an intensive care unit. *Antimicrob Agents Chemother*. 2000;44:1356–1358.
75. Daschner FD, Frank U, Kummel A, et al. Pharmacokinetics of vancomycin in serum and tissue of patients undergoing open-heart surgery. *J Antimicrob Chemother*. 1987;19:359–362.
76. Payne CJ, Thomson AH, Stearns AT, et al. Pharmacokinetics and tissue penetration of vancomycin continuous infusion as prophylaxis for vascular surgery. *J Antimicrob Chemother*. 2011;66:2624–2627.
77. Lodise TP, Drusano GL, Butterfield JM, et al. Penetration of vancomycin into epithelial lining fluid in healthy volunteers. *Antimicrob Agents Chemother*. 2011;55:5507–5511.
78. Kitzes-Cohen R, Farin D, Piva G, et al. Pharmacokinetics of vancomycin administered as prophylaxis before cardiac surgery. *Ther Drug Monit*. 2000;22:661–667.
79. Garazzino S, Aprato A, Baietto L, et al. Glycopeptide bone penetration in patients with septic pseudoarthrosis of the tibia. *Clin Pharmacokinet*. 2008;47:793–805.
80. Bue M, et al. Bone and subcutaneous adipose tissue pharmacokinetics of vancomycin in total knee replacement patients. *Acta Orthop*. 2017;1–6.
81. Hao JJ, Chen H, Zhou JX. Continuous versus intermittent infusion of vancomycin in adult patients: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2016;47:28–35.
82. Wang JT, Fang CT, Chen YC, et al. Necessity of a loading dose when using vancomycin in critically ill patients. *J Antimicrob Chemother*. 2001;47:246.
83. Truong J, Levkovich BJ, Padiglione AA. Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels. *Intern Med J*. 2012;42:23–29.
84. Grace E. Altered vancomycin pharmacokinetics in obese and morbidly obese patients: what we have learned over the past 30 years. *J Antimicrob Chemother*. 2012;67:1305–1310.
85. Kaplan EL. Vancomycin in infants and children: a review of pharmacology and indications for therapy and prophylaxis. *J Antimicrob Chemother*. 1984;14(supplD):59–66.
86. Frymoyer A, Guglielmo BJ, Wilson SD, et al. Impact of a hospitalwide increase in empiric pediatric vancomycin dosing on initial trough concentrations. *Pharmacotherapy*. 2011;31:871–876.
87. Buckel WR. Risk factors for non-therapeutic initial steady-state vancomycin trough concentrations in children and adolescents receiving high empiric doses of intravenous vancomycin. *Paediatr Drugs*. 2017;19:43–51.
88. Anderson BJ, Allegaert K, Van den Anker JN, et al. Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. *Br J Clin Pharmacol*. 2007;63:75–84.
89. Badran EF, Shamayleh A, Irshaid YM. Pharmacokinetics of vancomycin in neonates admitted to the neonatology unit at the Jordan University Hospital. *Int J Clin Pharmacol Ther*. 2011;49:252–257.
90. Ringenberg T, Robinson C, Meyers R, et al. Achievement of therapeutic vancomycin trough serum concentrations with empiric dosing in neonatal intensive care unit patients. *Pediatr Infect Dis J*. 2015;34:742–747.
91. Morse GD, Farolino DF, Apicella MA, et al. Comparative study of intraperitoneal and intravenous vancomycin pharmacokinetics during continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother*. 1987;31:173–177.
92. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016;36:481–508.
93. The management of neurosurgical patients with postoperative bacterial or aseptic meningitis or external ventricular drain-associated ventriculitis. Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy. *Br J Neurosurg*. 2000;14:7–12.
94. Ng K, Mabasa VH, Chow I, et al. Systematic review of efficacy, pharmacokinetics, and administration of intraventricular vancomycin in adults. *Neurocrit Care*. 2014;20:158–171.
95. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis*. 2017;64:e34–e65.
96. Vandecasteele SJ, De Vriese AS. Recent changes in vancomycin use in renal failure. *Kidney Int*. 2010;77:760–764.
97. Vandecasteele SJ, De Vriese AS. Vancomycin dosing in patients on intermittent hemodialysis. *Semin Dial*. 2011;24:50–55.
98. Barth RH, DeVincenzo N. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. *Kidney Int*. 1996;50:929–936.
99. Taylor ME, Allon M. Practical vancomycin dosing in hemodialysis patients in the era of emerging vancomycin resistance: a single-center experience. *Am J Kidney Dis*. 2010;55:1163–1165.
100. Zelenitsky SA, Ariano RE, McCrae ML, et al. Initial vancomycin dosing protocol to achieve therapeutic serum concentrations in patients undergoing hemodialysis. *Clin Infect Dis*. 2012;55:527–533.
101. Stamatakis MK, Schreiber JM, Slain D, et al. Vancomycin administration during dialysis with low-flux polysulfone membranes: traditional versus a supplemental dosage regimen. *Am J Health Syst Pharm*. 2003;60:1564–1568.
102. van de Vijsel LM, Walker SA, Walker SE, et al. Initial vancomycin dosing recommendations for critically ill patients undergoing continuous venovenous hemodialysis. *Can J Hosp Pharm*. 2010;63:196–206.
103. Wilson FP, Berns JS. Vancomycin levels are frequently subtherapeutic during continuous venovenous hemodialysis (CVVHD). *Clin Nephrol*. 2012;77:329–331.
104. Chaijamorn W, Jitsurong A, Wiwattanawongsa K, et al. Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients. *Int J Antimicrob Agents*. 2011;38:152–156.
105. Sin JH, Newman K, Elshaboury RH, et al. Prospective evaluation of a continuous infusion vancomycin dosing nomogram in critically ill patients undergoing continuous venovenous haemofiltration. *J Antimicrob Chemother*. 2018;73:199–203.
106. Geraci JE, Heilman FR, Nichols DR, et al. Antibiotic therapy of bacterial endocarditis, VII. Vancomycin for acute micrococcal endocarditis. *Proc Staff Meet Mayo Clin*. 1958;33:172–181.
107. Forouzesh A, Moise PA, Sakoulas G. Vancomycin ototoxicity: a reevaluation in an era of increasing doses. *Antimicrob Agents Chemother*. 2009;53:483–486.
108. Elyasi S, Khalili H, Dashti-Khavidaki S, et al. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations: a literature review. *Eur J Clin Pharmacol*. 2012;68:1243–1255.
109. Sakamoto Y, et al. Vancomycin induces reactive oxygen species- dependent apoptosis via mitochondrial cardiolipin peroxidation in renal tubular epithelial cells. *Eur J Pharmacol*. 2017;800:48–56.
110. Jeffres MN, Isakow W, Doherty JA, et al. Predictors of mortality for methicillin-resistant *Staphylococcus aureus* health-care-associated pneumonia: specific evaluation of vancomycin pharmacokinetic indices. *Chest*. 2006;130:947–955.
111. Van Hal S, Paterson D, Lodise T. Systematic review and meta- analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother*. 2013;57:734–744.
112. Jeffres MN. The whole price of vancomycin: toxicities, troughs, and time. *Drugs*. 2017;77:1143–1154.
113. Bosso JA, Nappi J, Rudisill C, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. *Antimicrob Agents Chemother*. 2011;55:5475–5479.
114. Lodise TP, Lomaestro B, Graves J, et al. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob Agents Chemother*. 2008;52:1330–1336.
115. Cano EL, Haque NZ, Welch VL, et al. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP database. *Clin Ther*. 2012;34:149–157.
116. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis*. 2009;48:713–721.
117. Hammond DA, Smith MN, Li C, et al. Systematic review and meta-analysis of acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam. *Clin Infect Dis*. 2017;64:666–674.
118. Luther MK, Timbrook TT, Caffrey AR, et al. Vancomycin plus piperacillin-tazobactam and acute kidney injury in adults: a systematic review and meta-analysis. *Crit Care Med*. 2018;46:12–20.
119. McKamy S, Hernandez E, Jahng M, et al. Incidence and risk factors influencing the development of vancomycin nephrotoxicity in children. *J Pediatr*. 2011;158:422–426.
120. Hanrahan T, Whitehouse T, Lipman J, et al. Vancomycin-associated nephrotoxicity: a meta-analysis of administration by continuous versus intermittent infusion. *Int J Antimicrob Agents*. 2015;46:249–253.
121. Filippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. *Clin Pharmacol Ther*. 2017;102:459–469.
122. Myers AL, Gaedigk A, Dai H, et al. Defining risk factors for red man syndrome in children and adults. *Pediatr Infect Dis J*. 2012;31:464–468.
123. Von Drygalski A, Curtis BR, Bougie DW, et al. Vancomycin-induced immune thrombocytopenia. *N Engl J Med*. 2007;356:904–910.
124. Minhas JS, Wickner PG, Long AA, et al. Immune-mediated reactions to vancomycin: a systematic case review and analysis. *Ann Allergy Asthma Immunol*. 2016;116:544–553.
125. Chen Y, Yang XY, Zeckel M, et al. Risk of hepatic events in patients treated with vancomycin in clinical studies: a systematic review and meta-analysis. *Drug Saf*. 2011;34:73–82.
126. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41:1373–1406.
127. Deresinski S. Counterpoint: vancomycin and *Staphylococcus aureus*—an antibiotic enters obsolescence. *Clin Infect Dis*. 2007;44:1543–1548.
128. Baddour LM, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.
129. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355:653–665.
130. Bayer AS, Murray BE. Initial low-dose aminoglycosides in *Staphylococcus aureus* bacteremia: good science, urban legend or just plain toxic? *Clin Infect Dis*. 2009;48:722–724.
131. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391:668–678.
132. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. *Antimicrob Agents Chemother*. 2008;52:3315–3320.
133. Truong J, Veillette JJ, Forland SC, et al. Outcomes of vancomycin plus a β-lactam versus vancomycin only for the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2018;62:pii: e01554-17.
134. Casapao AM, et al. Early administration of adjuvant β-lactam therapy in combination with vancomycin among patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection: a retrospective, multicenter analysis. *Pharmacotherapy*. 2017;37:1347–1356.
135. Davis JS, Sud A, O'Sullivan MV, et al. Combination of vancomycin and β-lactam therapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a pilot multicenter randomized controlled trial. *Clin Infect Dis*. 2016;62:173–180.
136. Smith T, Pearson ML, Wilcox KR, et al. Emergence of vancomycin resistance in *Staphylococcus aureus:* epidemiology and clinical significance. *N Engl J Med*. 1999;340:493–501.

137. Pericàs JM. Influence of vancomycin minimum inhibitory concentration on the outcome of methicillin-susceptible *Staphylococcus aureus* left-sided infective endocarditis treated with antistaphylococcal β-lactam antibiotics: a prospective cohort study by the International Collaboration on Endocarditis. *Clin Microbiol Infect*. 2017;23:544–549.
138. Murray BE. The life and times of the *Enterococcus*. *Clin Microbiol Rev*. 1990;3:46–65.
139. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075–3128.
140. Kaplan SL. Management of pneumococcal meningitis. *Pediatr Infect Dis J*. 2002;21:589–591, discussion 613–614.
141. Fitch MT, Abrahamian FM, Moran GJ, et al. Emergency department management of meningitis and encephalitis. *Infect Dis Clin North Am*. 2008;22:33–52, v–vi.
142. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.
143. Aguilar J, Urday-Cornejo V, Donabedian S, et al. *Staphylococcus aureus* meningitis: case series and literature review. *Medicine (Baltimore)*. 2010;89:117–125.
144. Rubinstein E, Cammarata S, Oliphant T, et al. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32:402–412.
145. Wunderink RG, Cammarata SK, Oliphant TH, et al. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25:980–992.
146. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis*. 2012;54:621–629.
147. Jung YJ, Koh Y, Hong SB, et al. Effect of vancomycin plus rifampicin in the treatment of nosocomial methicillin-resistant *Staphylococcus aureus* pneumonia. *Crit Care Med*. 2010;38:175–180.
148. Rubinstein E, Lalani T, Corey GR, et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. *Clin Infect Dis*. 2011;52:31–40.
149. Eliakim-Raz N, et al. Trimethoprim/sulfamethoxazole versus vancomycin in the treatment of healthcare/ventilator-associated MRSA pneumonia: a case-control study. *J Antimicrob Chemother*. 2017;72:882–887.
150. Dombrowski JC, Winston LG. Clinical failures of appropriately-treated methicillin-resistant *Staphylococcus aureus* infections. *J Infect*. 2008;57:110–115.
151. Daver NG, Shelburne SA, Atmar RL, et al. Oral step-down therapy is comparable to intravenous therapy for *Staphylococcus aureus* osteomyelitis. *J Infect*. 2007;54:539–544.
152. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. *N Engl J Med*. 2002;346:334–339.
153. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*–associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45:302–307.
154. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431–455.
155. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364:422–431.
156. Manthey CF, Eckmann L, Fuhrmann V. Therapy for *Clostridium difficile* infection—any news beyond metronidazole and vancomycin? *Expert Rev Clin Pharmacol*. 2017;10:1239–1250.
157. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56–e93.
158. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736–1754.
159. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70:195–283.
160. Sewick A, Makani A, Wu C, et al. Does dual antibiotic prophylaxis better prevent surgical site infections in total joint arthroplasty? *Clin Orthop Relat Res*. 2012;470:2702–2707.
161. Courtney PM, Melnic CM, Zimmer Z, et al. Addition of vancomycin to cefazolin prophylaxis is associated with acute kidney injury after primary joint arthroplasty. *Clin Orthop Relat Res*. 2015;473:2197–2203.
162. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR–10):1–36.
163. Bakhsheshian J, Dahdaleh NS, Lam SK, et al. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. *World Neurosurg*. 2015;83:816–823.
164. Adogwa O, et al. Prophylactic use of intraoperative vancomycin powder and postoperative infection: an analysis of microbiological patterns in 1200 consecutive surgical cases. *J Neurosurg Spine*. 2017;27:328–334.
165. Goldschmidt E, et al. The effect of vancomycin powder on human dural fibroblast culture and its implications for dural repair during spine surgery. *J Neurosurg Spine*. 2016;25:665–670.
166. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
167. van de Wetering MD, van Woensel JB, Lawrie TA. Prophylactic antibiotics for preventing gram positive infections associated with long-term central venous catheters in oncology patients. *Cochrane Database Syst Rev*. 2013;(11):CD003295.
168. Hope R, Livermore DM, Brick G, et al. Non-susceptibility trends among staphylococci from bacteraemias in the UK and Ireland, 2001-06. *J Antimicrob Chemother*. 2008;62(suppl 2):ii65–ii74.
169. Decousser JW, Desroches M, Bourgeois-Nicolaos N, et al. Susceptibility trends including emergence of linezolid resistance among coagulase-negative staphylococci and methicillin-resistant *Staphylococcus aureus* from invasive infections. *Int J Antimicrob Agents*. 2015;46:622–630.
170. Kristof K, Kocsis E, Szabo D, et al. Significance of methicillin-teicoplanin resistant *Staphylococcus haemolyticus* in bloodstream infections in patients of the Semmelweis University hospitals in Hungary. *Eur J Clin Microbiol Infect Dis*. 2011;30:691–699.
171. Wilson AP, Gruneberg RN, Neu HC. A critical review of the dosage of teicoplanin in Europe and the USA. *Int J Antimicrob Agents*. 1994;4(suppl 1):S1–S30.
172. Wilson AP. Clinical pharmacokinetics of teicoplanin. *Clin Pharmacokinet*. 2000;39:167–183.
173. Mimoz O, Rolland D, Adoun M, et al. Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia. *Intensive Care Med*. 2006;32:775–779.
174. Ueda T, Takesue Y, Nakajima K, et al. High-dose regimen to achieve novel target trough concentration in teicoplanin. *J Infect Chemother*. 2014;20:43–47.
175. Nakamura A, et al. Development of a teicoplanin loading regimen that rapidly achieves target serum concentrations in critically ill patients with severe infections. *J Infect Chemother*. 2015;21:449–455.
176. Takechi K, Yanagawa H, Zamami Y, et al. Evaluation of factors associated with the achievement of an optimal teicoplanin trough concentration. *Int J Clin Pharmacol Ther*. 2017;55:672–677.
177. Ueda T, et al. Enhanced loading regimen of teicoplanin is necessary to achieve therapeutic pharmacokinetics levels for the improvement of clinical outcomes in patients with renal dysfunction. *Eur J Clin Microbiol Infect Dis*. 2016;35:1501–1509.
178. Targocid package insert. https://www.medicines.org.uk/emc/medicine/27321.
179. Papaioannou MG, Marinaki S, Pappas M, et al. Pharmacokinetics of teicoplanin in patients undergoing chronic haemodialysis. *Int J Antimicrob Agents*. 2002;19:233–236.
180. Pea F, Viale P, Pavan F, et al. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. *Clin Pharmacokinet*. 2007;46:997–1038.
181. Bellmann R, Falkensammer G, Seger C, et al. Teicoplanin pharmacokinetics in critically ill patients on continuous veno-venous hemofiltration. *Int J Clin Pharmacol Ther*. 2010;48:243–249.
182. Chang HJ, Hsu PC, Yang CC, et al. Influence of teicoplanin MICs on treatment outcomes among patients with teicoplanin-treated methicillin-resistant *Staphylococcus aureus* bacteraemia: a hospital-based retrospective study. *J Antimicrob Chemother*. 2012;67:736–741.
183. Wang JT, Wu HS, Weng CM, et al. Prognosis of patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection treated with teicoplanin: a retrospective cohort study investigating effect of teicoplanin minimum inhibitory concentrations. *BMC Infect Dis*. 2013;13:182.
184. Lai C, et al. Combination of cephalosporins with vancomycin or teicoplanin enhances antibacterial effect of glycopeptides against heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) and VISA. *Sci Rep*. 2017;7:41758.
185. Davey PG, Williams AH. A review of the safety profile of teicoplanin. *J Antimicrob Chemother*. 1991;27 Suppl B:69–73.
186. Wilson AP. Comparative safety of teicoplanin and vancomycin. *Int J Antimicrob Agents*. 1998;10:143–152.
187. Hung YP, Lee NY, Chang CM, et al. Tolerability of teicoplanin in 117 hospitalized adults with previous vancomycin-induced fever, rash, or neutropenia: a retrospective chart review. *Clin Ther*. 2009;31:1977–1986.
188. Svetitsky S, Leibovici L, Paul M. Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis. *Antimicrob Agents Chemother*. 2009;53:4069–4079.
189. Yoon YK, et al. Multicenter prospective observational study of the comparative efficacy and safety of vancomycin versus teicoplanin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2014;58:317–324.
190. Popovic N, Korac M, Nesic Z, et al. Oral teicoplanin versus oral vancomycin for the treatment of severe *Clostridium difficile* infection: a prospective observational study. *Eur J Clin Microbiol Infect Dis*. 2018;37:745–754.
191. Tornero E, et al. Prophylaxis with teicoplanin and cefuroxime reduces the rate of prosthetic joint infection after primary arthroplasty. *Antimicrob Agents Chemother*. 2015;59:831–837.
192. Van Bambeke F. Glycopeptides in clinical development: pharmacological profile and clinical perspectives. *Curr Opin Pharmacol*. 2004;4:471–478.
193. Guskey MT, Tsuji BT. A comparative review of the lipoglycopeptides: oritavancin, dalbavancin, and telavancin. *Pharmacotherapy*. 2010;30:80–94.
194. Swartz TH, Huprikar S, Labombardi V, et al. Heart transplantation in a patient with heteroresistant vancomycin-intermediate *Staphylococcus aureus* ventricular assist device mediastinitis and bacteremia. *Transpl Infect Dis*. 2013;15:E177–E181.
195. Werth BJ, Jain R, Hahn A, et al. Emergence of dalbavancin non-susceptible, vancomycin-intermediate *Staphylococcus aureus* (VISA) after treatment of MRSA central line-associated bloodstream infection with a dalbavancin- and vancomycin-containing regimen. *Clin Microbiol Infect*. 2018;24:429.e1–429.e5.
196. Higgins DL, Chang R, Debabov DV, et al. Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2005;49:1127–1134.
196a. Hegde SS, Skinner R, Lewis SR, et al. Activity of telavancin against heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) in vitro and in an in vivo mouse model of bacteraemia. *J Antimicrob Chemother*. 2010;65:725–728.
196b. Leuthner KD, Cheung CM, Rybak MJ. Comparative activity of the new lipoglycopeptide telavancin in the presence and absence of serum against 50 glycopeptide non-susceptible staphylococci and three vancomycin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother*. 2006;58:338–343.
196c. Barcia-Macay M, Lemaire S, Mingeot-Leclercq MP, et al. Evaluation of the extracellular and intracellular activities (human THP-1 macrophages) of telavancin versus vancomycin against methicillin-susceptible, methicillin-resistant, vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother*. 2006;58:1177–1184.
197. Lunde CS, Hartouni SR, Janc JW, et al. Telavancin disrupts the functional integrity of the bacterial membrane through targeted interaction with the cell wall precursor lipid II. *Antimicrob Agents Chemother*. 2009;53:3375–3383.
198. Karlowsky JA, Nichol K, Zhanel GG. Telavancin: mechanisms of action, in vitro activity, and mechanisms of resistance. *Clin Infect Dis*. 2015;61(S2):S58–S68.

198a. Barcia-Macay M, Lemaire S, Mingeot-Leclercq MP, et al. Evaluation of the extracellular and intracellular activities (human THP-1 macrophages) of telavancin versus vancomycin against methicillin-susceptible, methicillin-resistant, vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother*. 2006;58:1177–1184.

198b. Steed ME, Vidaillac C, Rybak MJ. Evaluation of telavancin activity versus daptomycin and vancomycin against daptomycin-nonsusceptible *Staphylococcus aureus* in an in vitro pharmacokinetic/pharmacodynamic model. *Antimicrob Agents Chemother*. 2012;56:955–959.

199. Duncan LR, Sader HS, Smart JI, et al. Telavancin activity in vitro tested against a worldwide collection of gram-positive clinical isolates (2014). *J Glob Antimicrob Resist*. 2017;10:271–276.

200. Goldstein EJ, Citron DM, Merriam CV, et al. In vitro activities of the new semisynthetic glycopeptide telavancin (TD-6424), vancomycin, daptomycin, linezolid, and four comparator agents against anaerobic gram-positive species and *Corynebacterium* spp. *Antimicrob Agents Chemother*. 2004;48:2149–2152.

200a. Vibativ package insert. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001240/WC500115364.pdf. Accessed January 3, 2018.

200b. Hegde SS, Reyes N, Wiens T, et al. Pharmacodynamics of telavancin (TD-6424), a novel bactericidal agent, against gram-positive bacteria. *Antimicrob Agents Chemother*. 2004;48:3043–3050.

200c. Sun HK, Duchin K, Nightingale CH, et al. Tissue penetration of telavancin after intravenous administration in healthy subjects. *Antimicrob Agents Chemother*. 2006;50:788–790.

200d. Gotfried MH, Shaw JP, Benton BM, et al. Intrapulmonary distribution of intravenous telavancin in healthy subjects and effect of pulmonary surfactant on in vitro activities of telavancin and other antibiotics. *Antimicrob Agents Chemother*. 2008;52:92–97.

200e. Lodise TP Jr, Gotfried M, Barriere S, et al. Telavancin penetration into human epithelial lining fluid determined by population pharmacokinetic modeling and Monte Carlo simulation. *Antimicrob Agents Chemother*. 2008;52:2300–2304.

200f. Samara E, Shaw JP, Barriere SL, et al. Population pharmacokinetics of telavancin in healthy subjects and patients with infections. *Antimicrob Agents Chemother*. 2012;56:2067–2073.

200g. Lodise TP, Butterfield JM, Hegde SS, et al. Telavancin pharmacokinetics and pharmacodynamics in patients with complicated skin and skin structure infections and various degrees of renal function. *Antimicrob Agents Chemother*. 2012;56:2062–2066.

201. Vibativ package insert. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001240/WC500115364.pdf. Accessed January 3, 2018.

201a. Madrigal AG, Basuino L, Chambers HF. Efficacy of telavancin in a rabbit model of aortic valve endocarditis due to methicillin-resistant *Staphylococcus aureus* or vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2005;49:3163–3165.

201b. Miro JM, Garcia-de-la-Maria C, Armero Y, et al. Efficacy of telavancin in the treatment of experimental endocarditis due to glycopeptide-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2007;51:2373–2377.

201c. Crandon JL, Kuti JL, Nicolau DP. Comparative efficacies of human simulated exposures of telavancin and vancomycin against methicillin-resistant *Staphylococcus aureus* with a range of vancomycin MICs in a murine pneumonia model. *Antimicrob Agents Chemother*. 2010;54:5115–5119.

201d. Polyzos KA, Mavros MN, Vardakas KZ, et al. Efficacy and safety of telavancin in clinical trials: a systematic review and meta-analysis. *PLoS ONE*. 2012;7:e41870.

202. Stryjewski ME, Graham DR, Wilson SE, et al. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. *Clin Infect Dis*. 2008;46:1683–1693.

202a. Marcos LA, Camins BC, Ritchie DJ, et al. Acute renal insufficiency during telavancin therapy in clinical practice. *J Antimicrob Chemother*. 2012;67:723–726.

203. Chuan J, Zhang Y, He X, et al. Systematic review and meta-analysis of the efficacy and safety of telavancin for treatment of infectious disease: are we clearer? *Front Pharmacol*. 2016;7:330.

204. Corey GR, Kollef MH, Shorr AF, et al. Telavancin for hospital-acquired pneumonia: clinical response and 28-day survival. *Antimicrob Agents Chemother*. 2014;58:2030–2037.

204a. Stryjewski ME, O'Riordan WD, Lau WK, et al. Telavancin versus standard therapy for treatment of complicated skin and soft-tissue infections due to gram-positive bacteria. *Clin Infect Dis*. 2005;40:1601–1607.

204b. Stryjewski ME, Chu VH, O'Riordan WD, et al. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. *Antimicrob Agents Chemother*. 2006;50:862–867.

205. Lacy MK, Stryjewski ME, Wang W, et al. Telavancin hospital-acquired pneumonia trials: impact of gram-negative infections and inadequate gram-negative coverage on clinical efficacy and all-cause mortality. *Clin Infect Dis*. 2015;61(S2):S87–S93.

206. Stryjewski ME, Lentnek A, O'Riordan W, et al. A randomized Phase 2 trial of telavancin versus standard therapy in patients with uncomplicated *Staphylococcus aureus* bacteremia: the ASSURE study. *BMC Infect Dis*. 2014;14:289.

207. Ruggero MA, Peaper DR, Topal JE. Telavancin for refractory methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis. *Infect Dis (Lond)*. 2015;47:379–384.

208. Marcos LA, Camins BC. Successful treatment of vancomycin-intermediate *Staphylococcus aureus* pacemaker lead infective endocarditis with telavancin. *Antimicrob Agents Chemother*. 2010;54:5376–5378.

209. Twilla JD, Gelfand MS, Cleveland KO, et al. Telavancin for the treatment of methicillin- resistant *Staphylococcus aureus* osteomyelitis. *J Antimicrob Chemother*. 2011;66:2675–2677.

210. Harting J, et al. Telavancin for the treatment of methicillin-resistant *Staphylococcus aureus* bone and joint infections. *Diagn Microbiol Infect Dis*. 2017;89:294–299.

211. Van Bambeke F. Lipoglycopeptide antibacterial agents in gram-positive infections: a comparative review. *Drugs*. 2015;75:2073–2095.

212. Cheng M, Ziora ZM, Hansford KA, et al. Anti-cooperative ligand binding and dimerisation in the glycopeptide antibiotic dalbavancin. *Org Biomol Chem*. 2014;12:2568–2575.

213. Goldstein BP, Draghi DC, Sheehan DJ, et al. Bactericidal activity and resistance development profiling of dalbavancin. *Antimicrob Agents Chemother*. 2007;51:1150–1154.

214. Belley A, Lalonde Seguin D, Arhin F, et al. Comparative in vitro activities of oritavancin, dalbavancin, and vancomycin against methicillin-resistant *Staphylococcus aureus* isolates in a nondividing state. *Antimicrob Agents Chemother*. 2016;60:4342–4345.

215. Streit JM, Sader HS, Fritsche T, et al. Dalbavancin activity against selected populations of antimicrobial-resistant gram-positive pathogens. *Diagn Microbiol Infect Dis*. 2005;53:307–310.

216. McCurdy SP, Jones RN, Mendes RE, et al. In vitro activity of dalbavancin against drug-resistant *Staphylococcus aureus* isolates from a global surveillance program. *Antimicrob Agents Chemother*. 2015;59:5007–5009.

217. Pfaller MA, Mendes RE, Sader HS, et al. Activity of dalbavancin tested against gram-positive clinical isolates causing skin and skin-structure infections in paediatric patients from US hospitals (2014-2015). *J Glob Antimicrob Resist*. 2017;11:4–7.

218. Goldstein EJ, Citron DM, Merriam CV, et al. In vitro activities of dalbavancin and nine comparator agents against anaerobic gram-positive species and corynebacteria. *Antimicrob Agents Chemother*. 2003;47:1968–1971.

219. Nicolau DP, Sun HK, Seltzer E, et al. Pharmacokinetics of dalbavancin in plasma and skin blister fluid. *J Antimicrob Chemother*. 2007;60:681–684.

220. Dunne MW, Puttagunta S, Sprenger CR, et al. Extended-duration dosing and distribution of dalbavancin into bone and articular tissue. *Antimicrob Agents Chemother*. 2015;59:1849–1855.

221. Gonzalez D, et al. Dalbavancin pharmacokinetics and safety in children 3 months to 11 years of age. *Pediatr Infect Dis J*. 2017;36:645–653.

222. Bradley JS, Puttagunta S, Rubino CM. Pharmacokinetics, safety and tolerability of single dose dalbavancin in children 12–17 years of age. *Pediatr Infect Dis J*. 2015;34:748–752.

223. Andes D, Craig WA. In vivo pharmacodynamic activity of the glycopeptide dalbavancin. *Antimicrob Agents Chemother*. 2007;51:1633–1642.

224. Marbury T, Dowell JA, Seltzer E, et al. Pharmacokinetics of dalbavancin in patients with renal or hepatic impairment. *J Clin Pharmacol*. 2009;49:465–476.

225. Dalvance (dalbavancin) [full prescribing information]; Durata Therapeutics U.S. Limited. https://www.allergan.com/assets/pdf/dalvance_pi. Accessed November 19, 2017.

226. Boucher HW, Wilcox M, Talbot GH, et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. *N Engl J Med*. 2014;370:2169–2179.

227. Dunne MW, Zhou M, Darpo B. A thorough QT study with dalbavancin: a novel lipoglycopeptide antibiotic for the treatment of acute bacterial skin and skin-structure infections. *Int J Antimicrob Agents*. 2015;45:393–398.

228. Jauregui LE, Babazadeh S, Seltzer E, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis*. 2005;41:1407–1415.

229. Dunne MW, Puttagunta S, Giordano P, et al. A randomized clinical trial of single-dose versus weekly dalbavancin for treatment of acute bacterial skin and skin structure infection. *Clin Infect Dis*. 2016;62:545–551.

229a. Rappo R, Puttagunta S, Shevchenko V, et al. Dalbavancin for the Treatment of Osteomyelitis in Adult Patients: A Randomized Clinical Trial of Efficacy and Safety. *Open Forum Infect Dis*. 2018;6:ofy331.

230. Steele JM, Seabury RW, Hale CM, et al. Unsuccessful treatment of methicillin-resistant *Staphylococcus aureus* endocarditis with dalbavancin. *J Clin Pharm Ther*. 2018;43:101–103.

231. Zhanel GG, Schweizer F, Karlowsky JA. Oritavancin: mechanism of action. *Clin Infect Dis*. 2012;54(suppl 3):S214–S219.

232. Munch D, Engels I, Muller A, et al. Structural variations of the cell wall precursor lipid II - influence on binding and activity of the lipoglycopeptide antibiotic oritavancin. *Antimicrob Agents Chemother*. 2015;59:772–781.

233. Morrissey I, Seifert H, Canton R, et al. Activity of oritavancin against methicillin-resistant staphylococci, vancomycin-resistant enterococci and β-haemolytic streptococci collected from western European countries in 2011. *J Antimicrob Chemother*. 2013;68:164–167.

234. Mendes RE, Farrell DJ, Sader HS, et al. Activity of oritavancin against gram-positive clinical isolates responsible for documented skin and soft-tissue infections in European and US hospitals (2010-13). *J Antimicrob Chemother*. 2015;70:498–504.

235. Mendes RE, et al. Longitudinal (2001-14) analysis of enterococci and VRE causing invasive infections in European and US hospitals, including a contemporary (2010-13) analysis of oritavancin in vitro potency. *J Antimicrob Chemother*. 2016;71:3453–3458.

236. Schwalbe RS, McIntosh AC, Qaiyumi S, et al. In vitro activity of LY333328, an investigational glycopeptide antibiotic, against enterococci and staphylococci. *Antimicrob Agents Chemother*. 1996;40:2416–2419.

237. Sweeney D, Stoneburner A, Shinabarger DL, et al. Comparative in vitro activity of oritavancin and other agents against vancomycin-susceptible and -resistant enterococci. *J Antimicrob Chemother*. 2017;72:622–624.

238. Duncan LR, Sader HS, Flamm RK, et al. Oritavancin in vitro activity against contemporary *Staphylococcus aureus* isolates responsible for invasive community- and healthcare-associated infections among patients in the United States (2013-2014). *Diagn Microbiol Infect Dis*. 2016;86:303–306.

239. Smith JR, Yim J, Raut A, et al. Oritavancin combinations with β-lactams against multidrug-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. *Antimicrob Agents Chemother*. 2016;60:2352–2358.

240. Rubino CM, Bhavnani SM, Moeck G, et al. Population pharmacokinetic analysis for a single 1,200-milligram dose of oritavancin using data from two pivotal phase 3 clinical trials. *Antimicrob Agents Chemother*. 2015;59:3365–3372.

241. Fetterly GJ, Ong CM, Bhavnani SM, et al. Pharmacokinetics of oritavancin in plasma and skin blister fluid following administration of a 200-milligram dose for 3 days or a single 800-milligram dose. *Antimicrob Agents Chemother*. 2005;49:148–152.

242. Boylan CJ, Campanale K, Iversen PW, et al. Pharmacodynamics of oritavancin (LY333328) in a neutropenic-mouse thigh model of *Staphylococcus aureus* infection. *Antimicrob Agents Chemother*. 2003;47:1700–1706.

243. Belley A, Neesham-Grenon E, McKay G, et al. Oritavancin kills stationary-phase and biofilm *Staphylococcus aureus* cells in vitro. *Antimicrob Agents Chemother*. 2009;53:918–925.

244. Corey GR, Kabler H, Mehra P, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. *N Engl J Med*. 2014;370:2180–2190.

245. Corey GR, et al. Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. *Clin Infect Dis*. 2015;60:254–262.

246. Orbactiv package insert. http://www.orbactiv.com/pdfs/orbactiv-prescribing-information.pdf. Accessed January 6, 2018.

247. Belley A, et al. Effects of oritavancin on coagulation tests in the clinical laboratory. *Antimicrob Agents Chemother*. 2017;61:e01968–16.

248. Dunbar LM, Milata J, McClure T, et al. Comparison of the efficacy and safety of oritavancin front-loaded dosing regimens to daily dosing: an analysis of the SIMPLIFI Trial. *Antimicrob Agents Chemother*. 2011;55:3476–3484.

249. Bhavnani SM, Passarell JA, Owen JS, et al. Pharmacokinetic-pharmacodynamic relationships describing the efficacy of oritavancin in patients with Staphylococcus aureus bacteremia. *Antimicrob Agents Chemother*. 2006;50:994–1000.

31 Daptomycin and Quinupristin-Dalfopristin

Jose M. Munita, Barbara E. Murray, and Cesar A. Arias

SHORT VIEW SUMMARY

DAPTOMYCIN

- Daptomycin (Cubicin) is a high-molecular-weight cyclic lipopeptide antibiotic that targets the cell membrane of gram-positive bacteria in a calcium-dependent manner.
- The antimicrobial activity closely overlaps that of glycopeptides. Daptomycin retains activity against most organisms with decreased susceptibility to glycopeptides, although high minimal inhibitory concentration (MICs) of daptomycin have been observed in some vancomycin-intermediate *Staphylococcus aureus* (VISA) isolates.
- Currently, daptomycin is approved by the US Food and Drug Administration (FDA) for treatment of acute bacterial skin and skin structure infection (ABSSSI) caused by gram-positive cocci and for *S. aureus* bacteremia, including right-sided endocarditis.
- Daptomycin is administered intravenously, once daily; the approved doses are 4 and 6 mg/kg/day for ABSSSI and for *S. aureus* bacteremia and right-sided endocarditis, respectively. However, some experts recommend higher doses (8–12 mg/kg/day) for serious infections, particularly those caused by vancomycin-resistant enterococci (VRE). Dosage adjustment is required if the creatinine clearance is less than 30 mL/min.
- Reversible muscle toxicity is the main adverse event. Less frequent adverse events are paresthesias, peripheral neuropathies, and eosinophilic pneumonia.
- Because of the high risk for development of resistance and the "seesaw effect" (increased susceptibility to β-lactams when organisms become nonsusceptible to daptomycin), combinations of daptomycin and β-lactams are potential options for recalcitrant infections.

QUINUPRISTIN-DALFOPRISTIN

- Quinupristin-dalfopristin (Synercid) contains a streptogramin B (quinupristin) and a streptogramin A (dalfopristin) component in a 30:70 ratio. Streptogramins act synergistically within the 50S ribosomal subunit of the 70S unit in the elongation stage of protein synthesis.
- This combination is active against most gram-positive organisms (except *Enterococcus faecalis*) and a few gram-negative organisms.
- Variable rates of resistance among *Enterococcus faecium* isolates have been reported. *Staphylococcus* spp. strains with high MICs of quinupristin-dalfopristin have been rare.
- The intravenous dose is 7.5 mg/kg every 12 hours for ABSSSI caused by *S. aureus* and *Streptococcus pyogenes*. Dosage adjustment is not required in renal failure, but a lower dose may be considered with hepatic disease. Quinupristin-dalfopristin may increase the levels of drug metabolized through the cytochrome P-450 3A4 isoenzyme system.
- Irritation at the venous site is common when the drug is administered through peripheral veins. Arthralgias and myalgias may lead to drug discontinuation.
- The FDA approval of quinupristin-dalfopristin for VRE was withdrawn after the initial trials failed to prove clinical benefit; however, anecdotal cases of success, usually in combination with other agent(s), for serious VRE infections suggest that it still may have a role in selected patients.
- Because of its potential adverse events, the need for a central venous catheter for administration, and issues with efficacy and resistance, it is not often used in clinical practice.

DAPTOMYCIN

Daptomycin is a high-molecular-weight (1620.67 Da) cyclic 13-member lipopeptide antibiotic produced by *Streptomyces roseosporus* that was discovered in the early 1980s (Fig. 31.1). In 1991, despite clinical trials that showed some efficacy, skeletal muscle toxicity was observed with twice-daily doses in phase II trials, which led to discontinuation of clinical studies. The drug was subsequently "resurrected" in the form of once-daily dosing, which reduced the muscle toxicity. Daptomycin was approved for use in 2003 in the United States and in 2006 in Europe.

Mechanism of Action

The exact mechanism for the antimicrobial activity of daptomycin is not fully understood. This agent targets the cell membrane of gram-positive organisms in a calcium-dependent manner, becoming a de facto cationic antimicrobial peptide.[1] Insights into the mechanism of action of daptomycin suggest that the antibiotic binds to the cell membrane preferentially at the level of the division septum.[2] The interaction of the antibiotic with the bacterial cell membrane produces important distortions in the architecture of the membrane that likely result in displacement of inner membrane proteins essential for cell wall synthesis and cell division.[3] Moreover, an important step in the mechanism of daptomycin-mediated disruption of the cell membrane is the oligomerization of antibiotic molecules within the cell membrane, a step that seems to depend on the presence of the phospholipid phosphatidylglycerol, a negatively charged phospholipid.[4] As a final result, daptomycin produces irreversible alteration of the cell envelope structure and physiology, leading to loss of ions such as potassium that eventually results in cell death by mechanisms that have yet to be fully elucidated.[1] Interesting to note, staphylococci and enterococci that develop nonsusceptibility to daptomycin are able to withstand the antibiotic-mediated alteration of the cell membrane physiology, supporting the fact that the membrane is the primary target. In addition, daptomycin exerts its bactericidal effect against *Staphylococcus aureus* without significant cell lysis, which may explain the decreased release of proinflammatory mediators from infected macrophages compared with oxacillin and vancomycin.

Antimicrobial Activity

The spectrum of antimicrobial activity of daptomycin closely overlaps that of glycopeptides. Because the in vitro activity of this drug is dependent on the presence of calcium in the medium, testing for susceptibility to daptomycin needs to be performed with dilution methods using calcium-adjusted Mueller-Hinton broth medium (calcium concentration of 50 μg/mL); the use of the Kirby-Bauer disk diffusion method is inaccurate and is not recommended. Calcium-supplemented gradient diffusion strips (Etest [bioMérieux, Marcy l'Etoile, France]) for use on agar are reliable, although discrepancies with broth macrodilution occur and, most important, poor interlaboratory reproducibility

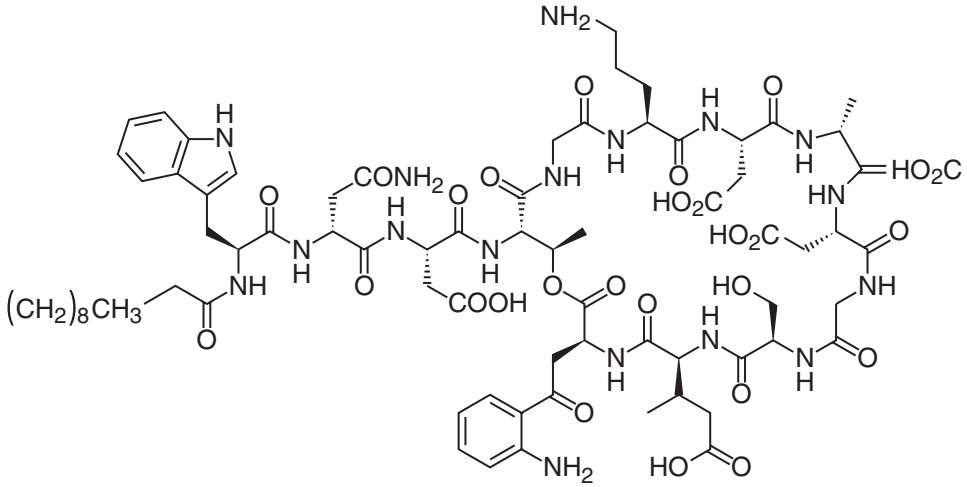

FIG. 31.1 **Chemical structure of daptomycin.**

is common. Automated and semiautomated systems for susceptibility have been developed and are also available.[5]

The US Food and Drug Administration (FDA)–, Clinical and Laboratory Standards Institute (CLSI)–, and European Committee on Antimicrobial Susceptibility Testing (EUCAST)–approved breakpoints for daptomycin with use of calcium-supplemented Mueller-Hinton broth are less than or equal to 1 μg/mL (susceptible) for staphylococci and streptococci. In the case of *Enterococcus* spp., data are less clear and, therefore, wider interagency variation exists. The FDA established a susceptibility breakpoint only for *Enterococcus faecalis* (≤4 μg/mL). CLSI has recently changed the breakpoints for enterococci. Indeed, daptomycin-susceptible enterococci are now considered to have an MIC ≤1 μg/mL. A susceptible dose-dependent category (doses of 8–12 mg/kg of daptomycin) was introduced for isolates with MICs of 2 to 4 μg/mL. Finally, an MIC ≥8 μg/mL is now considered fully resistant. It is important to note that the breakpoints were established using broth microdilution as the preferred testing method and not Etest. EUCAST has not established breakpoints for daptomycin.

Important to note, daptomycin shows rapid, concentration-dependent bactericidal activity in vitro against staphylococci, pneumococci, *E. faecalis,* and *Enterococcus faecium,*[6] including methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant enterococci (VRE) isolates.[6,7] Daptomycin also shows good in vitro activity against gram-positive anaerobes such as *Peptostreptococcus* spp. (MIC_{90}, 1 μg/mL), *Clostridium perfringens* (MIC_{90}, 0.5 μg/mL), and *Clostridioides difficile* (formerly *Clostridium difficile*) (MIC_{90}, 1 μg/mL); some other clostridial species require higher concentrations for inhibition. It should be noted, however, that there are no established breakpoints for daptomycin susceptibility for anaerobes. The activity of daptomycin against different species of *Actinomyces* is variable (MIC_{90}s, 4–32 μg/mL), and some *Lactobacillus* spp. appear to be less susceptible to daptomycin, whereas most *Propionibacterium* spp. and the vancomycin-resistant species *Leuconostoc* and *Pediococcus* are inhibited by higher concentrations of 2 μg/mL.

A correlation between increased vancomycin MICs and daptomycin nonsusceptibility has been observed in *S. aureus,* with a high proportion of VISA strains (80% of isolates with vancomycin MIC of 4 μg/mL) reported as nonsusceptible to daptomycin (MIC >1 μg/mL)[8]; this observation has not been confirmed in other studies.[9] Unlike many other antibacterial agents, daptomycin at high concentrations maintains its bactericidal activity against *S. aureus* even in stationary phase cultures,[10] a phenomenon that could be related to its effect on the cell membrane. Daptomycin appears to maintain its activity against *Staphylococcus epidermidis* and *S. aureus* strains embedded in biofilm, perhaps explaining its reported efficacy against these structures and as antibiotic lock therapy in an animal model of staphylococcal central venous catheter infection.

Resistance

Development of resistance to daptomycin in vitro is uncommon, although strains with decreased susceptibility were obtained after serial passage.[11] Only 0.7% and 0.04% of 10,000 clinical *S. aureus* strains in one large survey had an MIC ≥1 μg/mL and ≥2 μg/mL, respectively.[9] These results were later confirmed in a more recent study evaluating more than 36,000 isolates from Europe and the United States.[12] Nevertheless, increased daptomycin MICs of 2 μg/mL or greater were observed in 6% of patients participating in a large *S. aureus* bacteremia and an endocarditis clinical trial.[13] The majority of these strains were associated with microbiologic failure and, in most cases, patients had an undrained focus of infection.[13] A much higher rate of development of nonsusceptibility to daptomycin was described among 10 patients with persistent *S. aureus* bacteremia who were switched from vancomycin to an approved dose of daptomycin (4–6 mg/kg/day).[14] *S. aureus* strains with higher daptomycin MICs displayed several phenotypic changes at the level of the cell membrane, including enhanced membrane fluidity, increased net positive surface charge, resistance to depolarization and/or permeabilization, a reduced amount of phosphatidylglycerol, increased pigment production, and decreased daptomycin surface binding. All of the aforementioned features correlated with reduction of daptomycin-induced depolarization.[15]

Mutations in several genes have been implicated in the development of daptomycin nonsusceptibility in *S. aureus.* Among the most studied are mutations in (1) *mprF,* a gene that encodes a lysyl-phosphatidylglycerol (LPG) synthase with flippase activity that contributes to increased cell membrane positive charge by adding more LPG (a positively charged phospholipid) to the outer leaflet of the cell membrane[16]; (2) genes encoding two-component regulatory systems, specifically *yycFG (walKR)* and *vraSR,* which appear to participate in the regulation of cell envelope homeostasis and stress response[17]; (3) the *dlt* cluster, which encodes the enzymatic machinery necessary for the D-alanylation of cell wall teichoic acids, contributing to increased cell surface charge[18]; (4) *rpoB* and *rpoC,* encoding the subunits of RNA polymerase; and (5) *pgsA* and *cls,* which encode enzymes involved in cell membrane phospholipid metabolism (phosphatidylglycerol synthase and cardiolipin synthase, respectively), that modify cell membrane composition preventing daptomycin binding.[19] In addition, development of daptomycin nonsusceptibility has also been associated with cross-resistance to endogenous antimicrobial peptides, including thrombin-induced platelet microbicidal proteins and human neutrophil-derived defensin 1.[20] Finally, evidence suggests that some *S. aureus* strains have the ability to inactivate daptomycin by releasing membrane phospholipids (particularly phosphatidylglycerol) that bind and inactivate daptomycin; however, the clinical relevance of this phenomenon remains to be elucidated.[21]

Although the majority of enterococci remain apparently "susceptible" to daptomycin in vitro, the emergence of daptomycin nonsusceptibility seems to be more frequent in these organisms than in staphylococci. Indeed, several case reports have documented development of resistance to daptomycin (MICs ranging from 6 to >32 μg/mL) during treatment of enterococcal infections caused by *E. faecalis* and *E. faecium*. Moreover, the presence of daptomycin resistance in the absence of exposure to the antibiotic has also been described.[22] Insights into the mechanism of daptomycin resistance have been provided.[23–25] Although some phenotypic changes in the cell envelope and cell membrane appear to be similar to those described in staphylococci, the genetic pathways seem to be different. The initial crucial event in the development of daptomycin resistance in enterococci involves changes in the LiaFSR system (a homologue of VraTSR of *S. aureus*), a three-component regulatory system that is predicted to orchestrate the cell envelope response to antibiotics and antimicrobial peptides. Indeed, deletion of *liaR,* the putative transcriptional regulator of the system, was able to completely restore daptomycin susceptibility in *E. faecium* and *E. faecalis*, independent of the genetic background.[26,27] Moreover, a mutation in the first gene of the system, *liaF,* encoding a putative transmembrane protein, was sufficient to decrease daptomycin susceptibility (although not above the clinical breakpoint) and abolish the in vitro bactericidal activity of the antibiotic.[25] An increase in daptomycin MICs above the breakpoint is usually associated with additional mutations in genes encoding enzymes involved in cell membrane phospholipid metabolism (e.g., *gdpD* and *cls*) that affect cell membrane homeostasis.[25] Of note, a marked decrease in cell membrane phosphatidylglycerol content, important for daptomycin oligomerization within the cell membrane (see earlier discussion), has been documented in daptomycin-resistant *E. faecalis* and *E. faecium* recovered from patients during therapy with daptomycin[28] and in other daptomycin-resistant gram positive organisms.[29]

The events leading to increased daptomycin nonsusceptibility in both staphylococci and enterococci can result in increased susceptibility to certain β-lactams (the "seesaw effect").[30] Indeed, daptomycin plus oxacillin significantly decreased colony-forming units per gram of vegetation when compared with daptomycin alone in experimental endocarditis caused by *S. aureus* with daptomycin-nonsusceptible strains (MICs of 2 and 4 μg/mL).[30] The combination of daptomycin with other β-lactams (nafcillin, imipenem, amoxicillin-clavulanate, cefotaxime, ceftriaxone, ertapenem, and ceftaroline) has been associated with increased in vitro and in vivo activity against daptomycin-nonsusceptible MRSA strains. Although the mechanisms underlying this synergy are not fully understood, it has been postulated that β-lactams decrease the net cell membrane positive charge in daptomycin-nonsusceptible strains, favoring daptomycin binding to the cell membrane.[31] In addition, recent evidence in *S. aureus* suggests that daptomycin nonsusceptibility is associated with mislocalization of penicillin-binding proteins (PBPs) and changes in proteins involved in the maturation of important PBPs (e.g., PBP2A), providing a mechanistic link for the hypersusceptibility to β-lactams observed in these strains.[32] Moreover, in vitro and in vivo studies have shown that the addition of β-lactams to daptomycin prevents or delays the emergence of daptomycin nonsusceptibility against *E. faecalis, E. faecium, Streptococcus mitis,* and *Streptococcus oralis* isolates.[33,34]

Some streptococci (e.g. *S. mitis*) are capable of developing rapid and sustainable daptomycin resistance on exposure to the drug, both in vivo and in vitro.[35,36] The mechanism has been attributed to loss of function mutations in *cds* encoding a phosphatidate cytidylyltransferase, an enzyme that is required for the synthesis of phosphatidylglycerol and cardiolipin in cell membranes.[37] Similarly, there are several reports of daptomycin resistance arising in vivo and in vitro in *Corynebacterium* spp., most of them related to patients developing endovascular or device-related infections due to *Corynebacterium striatum*.[38,39,40]

Clinical Pharmacokinetics and Pharmacodynamics

Distribution and Elimination

The pharmacokinetics of once-daily intravenous daptomycin are linear up to doses of 12 mg/kg with minor accumulation.[41] The mean daptomycin peak serum concentrations in healthy volunteers are approximately 55, 86, 116, 130, and 165 μg/mL after a single intravenous dose (infused over 30 minutes) of 4, 6, 8, 10, and 12 mg/kg, respectively.[41,42] The daptomycin area under the concentration-time curve (AUC_{0-24h}) at steady state is in the range of 500 and 750 μg•h/mL for once-daily doses of 4 and 6 mg/kg, respectively, and 850 μg•h/mL for a dose of 8 mg/kg/day.[41,42] Daptomycin exhibits a long terminal half-life (7.3–9.6 hours) and small volume of distribution (92–117 mL/kg), suggesting distribution mainly into plasma and interstitial fluid.[41,42]

Daptomycin has significant affinity for plasma proteins in humans (90%–93% protein bound)[41,42] but lower affinity for tissue proteins and is eliminated primarily through renal excretion, largely as unchanged drug. Little daptomycin crosses the uninflamed blood-brain barrier (about 2%), although it was effective for the treatment of *Streptococcus pneumoniae* in a rabbit meningitis model of central nervous system (CNS) infection (penetration rate of approximately 6%).[43] A similar percentage of CNS penetration (5%) was reported in a clinical case of methicillin-susceptible *S. aureus* (MSSA) meningitis treated with daptomycin.[44] Mean daptomycin concentrations in inflammatory skin blisters of 68% of those in plasma have been observed in healthy volunteers after a dose of 4 mg/kg/day.[45] In an experimental endocarditis model, daptomycin achieved concentrations in cardiac vegetations that were about half those in serum and with homogeneous distribution within the vegetations. Important to note, the antimicrobial activity of daptomycin is abolished by the interaction with pulmonary surfactant, resulting in failure to reduce bacterial burden in a mouse model of bronchoalveolar pneumonia caused by *S. pneumoniae*. On the other hand, daptomycin was effective in an animal model of *S. aureus* hematogenous pneumonia and inhalation anthrax. Poor penetration of daptomycin into uninfected and infected bone has been shown in a rabbit model of osteomyelitis. However, bone maximal concentration (C_{max}) of daptomycin in metatarsal bones of a group of patients with diabetic foot infection was 4.7 μg/mL.[46]

Pharmacodynamics

The in vivo parameters that best correlated with efficacy in an animal model of infection with *S. aureus* and *S. pneumoniae* were the peak/MIC and the 24-hour AUC/MIC ratios.[47] In the same model of infection, daptomycin unbound (free drug) peak concentrations of 2.5 to 7 and 7 to 25 times the MIC were required to produce a bacteriostatic and bactericidal effect, respectively.[47] Clinical studies have not been able to confirm a specific AUC/MIC cutoff value to predict clinical efficacy. Daptomycin was shown to produce an in vitro postantibiotic effect with a mean of 2.5 and 1.7 hours against staphylococci and pneumococci, respectively.[48] The in vivo postantibiotic effect in a neutropenic murine thigh infection model was 5 hours against *S. aureus* and 10.8 hours against *S. pneumoniae*.[47] Against *E. faecalis,* daptomycin exerted a dose-dependent postantibiotic effect that was longer than that noted with vancomycin (0.6–6.7 hours and 0.5–1.0 hours, respectively).[49]

Drug Dosage and Administration

Daptomycin is administered intravenously, diluted in 0.9% sodium chloride, once daily (by injection over a 2-minute period or infused in 30 minutes); the drug is not compatible with dextrose-containing solutions. The approved doses are 4 and 6 mg/kg/day for acute bacterial skin and skin structure infection (ABSSSI) and *S. aureus* bacteremia and right-sided endocarditis, respectively, although some experts recommend a higher dose of 8 to 12 mg/kg/day (Table 31.1). In patients on hemodialysis, the dose should be given after the completion of the hemodialysis. Dosage adjustment is required in subjects with a creatinine clearance of less than 30 mL/min, including patients on hemodialysis and on peritoneal dialysis. In these patients, according to the underlying infection, the dose prescribed should be given every 48 hours. This proposed regimen yielded adequate serum levels even in 3-day interdialysis periods in one study[50] but not in another.[51] In patients under extended intermittent dialysis (starting 8 hours after daptomycin infusion), a daily dose of 6 mg/kg appears to be needed.[52] There is still no uniform recommendation as to how to administer daptomycin to patients on continuous renal replacement therapy (CRRT). In a small number of critically ill patients undergoing continuous venovenous hemodialysis (CVVHD), daptomycin 8 mg/kg administered every 48

TABLE 31.1 Route of Administration, Recommended Dosages, and Infusions of Daptomycin and Quinupristin-Dalfopristin

DRUG	ROUTE OF ADMINISTRATION	RECOMMENDED DOSAGE (ADULTS)	INFUSION	COMMENTS
Daptomycin	Intravenous	4 mg/kg/day for ABSSSI; 6 mg/kg/day for bacteremia and right-sided endocarditis (FDA approved)	2-min injection or 30-min infusion	*For severe infections:* higher doses (8–12 mg/kg/day) are recommended by some experts
Quinupristin-dalfopristin	Intravenous (frequent need for a central venous access)	7.5 mg/kg q12h for ABSSSI	1-h infusion	Infrequently used owing to side effects

ABSSSI, Acute bacterial skin and skin structure infection.

hours resulted in higher peak and lower trough concentrations than the regimen of 4 mg/kg every 24 hours.[53] Patients treated with continuous venovenous hemodiafiltration (CVVHDF) appear to have higher clearance of daptomycin than those undergoing CVVHD.[54] Because daptomycin given as 6 mg/kg/day led to drug accumulation in a small series of patients undergoing CVVHDF, a regimen of 8 mg/kg every 48 hours has been suggested in this setting, although, owing to high variability in serum levels and to data suggesting that administration every 48 hours could result in less-than-optimal drug exposure, performing drug monitoring would be useful if feasible.[55,56] Daptomycin-related muscle toxicity should be monitored more frequently than once weekly in patients with renal insufficiency.

Daptomycin dosage does not require adjustment in patients with moderate hepatic impairment (Child-Pugh class B). Subjects with obesity have higher C_{max} and AUC concentration than nonobese patients but still within the safety range, indicating that dosage adjustment is not required for this population. Even though daptomycin has not been approved for use in children, a favorable outcome with no attributable adverse events was accomplished in most of 15 children (median age, 6.5 years) with invasive staphylococcal infection, the majority of whom had persistent community-acquired MRSA bacteremia.[57] A multicenter randomized trial was recruiting pediatric patients (2–17 years old) with complicated skin and soft tissue infections to receive daptomycin given at 5, 7, and 9 mg/kg/day for ages 12 to 17 years, 7 to 11 years, and 2 to 6 years, respectively (see NCT 00711802 at ClinicalTrials.gov), although it is was on hold at the time of this writing. Animal studies have failed to detect abnormalities or harm to the fetus, but there are insufficient clinical data to support the use of daptomycin during pregnancy in humans (teratogenic effect: pregnancy category B). Because it is unknown if this drug is excreted in human milk, daptomycin should be administered in these circumstances only when the potential benefits outweigh risks.

Adverse Reactions and Drug Interactions

Daptomycin has been generally well tolerated in preclinical and clinical studies; the proportion of patients who discontinued the drug because of an adverse event has been similar in the daptomycin arm to that in study participants receiving the comparator antibiotic. Of initial concern was the description of daptomycin-related skeletal muscle toxicity in early trials when the drug was administered at 4 mg/kg every 12 hours. Subsequent animal studies showed that this reversible toxicity was related more to the frequency than to the total daily dose of the drug. Analysis of daptomycin-related muscular toxicity disclosed a microscopic degenerative-regenerative process of the myofibers associated with increased serum creatine phosphokinase (CPK) levels with no muscle cell lysis or fibrosis and no electrophysiologic changes. Of note, cardiac muscle cells do not appear to be affected by daptomycin. The mechanism of skeletal muscle damage has not been delineated yet, although it has been associated with direct cell membrane toxicity to the muscle cell. Moreover, a good correlation with the daptomycin minimal concentration (C_{min}) in serum and time of exposure appears to exist. In clinical trials using the 4 mg/kg/day dose, no significant differences were observed in the level of serum CPK during treatment between those patients receiving daptomycin and those receiving standard of care (2.1% vs. 1.4%, respectively).[58] When daptomycin was administered at 6 mg/kg/day in an *S. aureus* bacteremia and endocarditis phase III clinical trial,[13] a higher rate of CPK elevation was observed in the group of patients receiving daptomycin than those in the standard-of-care group receiving other antibiotics (6.7% vs. 0.9%, respectively); however, daptomycin was discontinued owing to CPK elevation in only 2.5% of the patients, and CPK serum level returned to normal range during or after daptomycin therapy in the majority of the patients in whom this adverse event occurred.[13] After analysis of data from this trial, a significantly higher number of patients (50%) with C_{min} values of greater than or equal to 24.3 mg/L developed CPK elevation than those with levels below this value (2.9%).[59] A retrospective case series study of 61 patients receiving daptomycin for various indications at a mean dose of 8 mg/kg/day for 25 days reported a rate of symptomatic CPK elevation of 4.9%.[60] Overall, symptoms associated with muscle toxicity typically appear after at least 7 days of therapy and resolve about 3 days after daptomycin is discontinued. Daptomycin should be discontinued in patients with unexplained signs and symptoms of myopathy together with increased CPK serum level to more than 1000 units/L and in those without muscle pain but with CPK levels above 2000 units/L (10 times the normal upper limit).

In clinical trials using daptomycin at 6 mg/kg/day, the frequency of gastrointestinal symptoms was not different from that observed in the comparative arm; however, at this dosage, symptoms related to the peripheral nervous system such as paresthesias, dysesthesias, and peripheral neuropathies were significantly more common in participants in the daptomycin arm of the study than in those on standard therapy (9% vs. 2%, respectively); these events were mild to moderate in severity, and most resolved during treatment.[13] Daptomycin use was associated in a single patient with acute renal failure and hepatotoxicity without CPK increase or rhabdomyolysis.

Daptomycin did not affect the QTc interval in human studies and, in the bacteremia trial, the rate of nephrotoxicity was lower in those on daptomycin than in those in the comparator arm of the study, which included gentamicin for the first few days.[13] Interesting to note, daptomycin has been reported to exert a protective role on the aminoglycoside-induced renal toxicity by counteracting the inhibition of the phospholipase activity induced by these drugs, especially gentamicin.

Confirmed cases of acute eosinophilic pneumonia associated with the use of daptomycin have been described.[61] This potentially serious event of unclear mechanism is rare, usually occurs after 10 days of therapy, tends to affect older patients, and is associated with fever, diffuse pulmonary infiltrates, hypoxemia, and a high percentage of eosinophils in bronchoalveolar lavage (eosinophilia might be absent) or eosinophilic pneumonia at lung biopsy. A high degree of clinical suspicion is essential because discontinuation of daptomycin is followed by resolution of the clinical picture. Corticosteroids have been used for treatment of this condition in some cases, and chronic corticosteroid dependence has been reported.

Because daptomycin is not metabolized through the cytochrome P-450 system, no interactions are expected with drugs metabolized in this system. CPK levels should be monitored more frequently when daptomycin is coadministered with other drugs carrying potential muscle toxicity, such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, although retrospective studies found no increase in rates of muscular toxicity when patients received daptomycin plus these drugs. Daptomycin may cause a false increase in the prothrombin time depending on the reagents and assay used to measure it; if this

occurs, blood should be drawn at the lowest serum daptomycin concentration for prothrombin time assessment.

Clinical Uses

Skin and Soft Tissue Infections

Two randomized phase III, evaluator-blinded trials for the treatment of ABSSSI at a dose of 4 mg/kg every 24 hours showed efficacy comparable to that of conventional therapy (vancomycin or antistaphylococcal semisynthetic penicillins), leading to FDA approval for use in the treatment of infections caused by the following susceptible gram-positive cocci: *E. faecalis* (vancomycin-susceptible isolates only), *S. aureus* (including methicillin-resistant isolates), *Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis,* and *Streptococcus pyogenes.* A subset analysis of patients with infected diabetic foot ulcers enrolled in the two phase III studies of ABSSSI showed comparable results in terms of clinical and microbiologic outcome in the two study arms.[62] Daptomycin could be considered an option in patients with ABSSSIs with prior failure or intolerance to glycopeptides and in ABSSSIs caused by MRSA with higher vancomycin MICs.

Staphylococcus aureus Bacteremia and Right-Sided Endocarditis

Daptomycin has also been granted FDA approval for *S. aureus* bloodstream infection, including right-sided endocarditis, based on a multicenter, open-label, randomized trial comparing daptomycin at 6 mg/kg/day with standard of care (penicillinase-resistant penicillins or vancomycin, each with gentamicin 1 mg/kg every 8 hours for the first 4 days).[13] About half of the patients had complicated bacteremia (defined by positive blood cultures for at least 2 days up to study day 5, evidence of spread of infection, or infected prosthesis material not removed within 4 days), and less than 10% had left-sided endocarditis; MRSA accounted for 38% of the isolated strains. Daptomycin was not inferior to standard therapy, with similar success rates across all final diagnoses; and no significant differences were observed when patients with MSSA and MRSA infection were analyzed separately. The median time to clear the MSSA or MRSA bacteremia was similar in both treatment groups: 4 and 8 days for daptomycin and 3 and 9 days for standard therapy, respectively. Persisting or relapsing *S. aureus* infection occurred in 16% (19 of 120) of patients receiving daptomycin and in 10% of those in the standard therapy group (11 of 115, with 9 receiving vancomycin and 2 patients on an antistaphylococcal penicillin); most of these patients did not receive adequate surgical drainage for a deep-seated infection.[13] Among those patients with microbiologic failure, strains with increased MICs to greater than or equal to 2 μg/mL were found in 6 of 19 patients receiving daptomycin and in 4 of 9 receiving vancomycin.[13] Low success rates in both arms of the study were found in the few patients with left-sided infective endocarditis, owing, at least in part, to the very rigorous definition of cure. Similar outcomes in subgroups of patients with different degrees of renal impairment (excluded from the *S. aureus* bacteremia-endocarditis trial) were observed in a retrospective postmarketing study evaluating daptomycin for the treatment of bacteremia caused by gram-positive organisms (mainly MRSA, VRE, and coagulase-negative staphylococci). A clinical cure rate of 83% among 92 patients with *S. aureus* endocarditis was noted in a retrospective report on the European postmarketing use of daptomycin. Most of these patients were treated with a dose of 6 mg/kg, but in only 36% as monotherapy.[63] Similar cure rates were found for patients with endocarditis caused by coagulase-negative staphylococci.

In a large retrospective study comparing the use of a standard dose (6 mg/kg/day; $n = 233$) versus higher doses (≥7 mg/kg/day; $n = 138$) of daptomycin in patients with MRSA bloodstream infections, patients receiving higher doses were found to have a significantly lower propensity score-matched 30-day mortality (8.6% vs. 18.6%, respectively; hazard ratio, 0.31; 95% confidence interval [CI], 0.1–0.94). Of note, further analyses suggested that the benefit of higher daptomycin doses was particularly relevant in patients with higher predicted probabilities of 30-day mortality.[64] Similar results regarding the benefit of higher daptomycin doses (≥8 mg/kg/day) were reported in another retrospective study that included 250 patients with a variety of invasive infections caused by MRSA and VRE, in which daptomycin was associated with a good clinical response rate (84%), a low frequency of adverse events (1.2%), and a 5.2% rate of development of nonsusceptible strains (mainly in patients with prior extensive exposure to vancomycin).[65]

Several retrospective studies have compared the use of daptomycin versus vancomycin for the treatment of MRSA bacteremia caused by strains with vancomycin MICs greater than 1 μg/mL. Overall, these retrospective data suggest that patients receiving daptomycin tend to have better clinical outcomes; however, despite reported apparent benefits associated with daptomycin use, prospective data are needed before a universal recommendation of early treatment with high-dose daptomycin is made for infections caused by such strains.[66–68]

The combination of daptomycin with other agents against staphylococci has been explored in in vitro and in vivo models. The bactericidal activity of daptomycin against *S. aureus* was enhanced by the addition of gentamicin in various in vitro models. The interaction between daptomycin and rifampin in vitro has been strain dependent, and neither synergism nor antagonism has been reported consistently. However, when this combination was evaluated in an experimental MRSA endocarditis model, antagonism between these two antibiotics was reported.[69] High-dose daptomycin (10 mg/kg/day) and combination with gentamicin or rifampin prevented the development of daptomycin-nonsusceptible isolates that appeared when daptomycin at 6 mg/kg/day was used in the simulated vegetations model using *S. aureus* strains. Another approach includes the coadministration of a β-lactam plus daptomycin to take advantage of the previously mentioned seesaw effect. In vivo studies have also shown that this strategy prevented the emergence of isolates with high daptomycin MICs as compared with daptomycin monotherapy.[70] Six patients with persistent non–catheter-related MRSA bacteremia were successfully treated with daptomycin (8–10 mg/kg/day) plus nafcillin (or oxacillin in one case) after the failure of multiple regimens including vancomycin and daptomycin (6–8 mg/kg/day) monotherapy.[31] In addition, there are reports of patients with infective endocarditis due to daptomycin-nonsusceptible MRSA (one case of which was also ceftaroline resistant and vancomycin intermediate) and persistent bacteremia that were successfully treated with the addition of ceftaroline to daptomycin[71,72]; this combination also restored in vitro activity of daptomycin against this strain.[71]

Therefore, based on the concentration-dependent activity of daptomycin and the reported risk of development of resistance during treatment of deep-seated staphylococcal infections, clinicians often use high-dose daptomycin (e.g., 8–10 mg/kg/day), especially in patients in whom vancomycin therapy has previously failed. Other approaches considered by some experts consist of combination therapy with high-dose daptomycin with β-lactams (including ceftaroline) or gentamicin (if the infecting strain is susceptible) or trimethoprim-sulfamethoxazole, which demonstrated a significant increase in the in vitro activity of daptomycin against *S. aureus.* Any of these novel approaches deserves further clinical evaluation.

Osteoarticular Infections Caused by Staphylococci

Daptomycin displayed efficacy similar to that of vancomycin in animal models of chronic MRSA osteomyelitis. Daptomycin has not been approved for this indication, but many studies addressing its efficacy have been published. In humans, a retrospective analysis of daptomycin for chronic osteomyelitis caused by gram-positive bacteria, mostly MRSA, showed an overall success rate of 82% (cure, 63%; improvement, 19%) at a median follow-up of 76 days (range, 1–547 days).[73] About half of the patients had received another antibiotic, and, important, a significantly higher success rate was observed in those patients who received an initial dose higher than 4 mg/kg/day.[73] Post hoc analysis of 32 patients from the *S. aureus* bacteremia-endocarditis study who also had osteoarticular infections (mostly septic arthritis and vertebral osteomyelitis) showed similar success rates to those in the comparator arm of the study.[74] Daptomycin at 6 and 8 mg/kg/day was compared with standard of care (vancomycin, teicoplanin, or semisynthetic penicillin) in a phase II randomized trial including 49 patients with prosthetic joint infections caused by *S. aureus* who underwent two-stage revision arthroplasty. Although higher clinical success rates were observed in the daptomycin arm of the trial (58% and 61% for the 6 and 8 mg/kg/day dosage groups,

respectively) compared with the pooled comparator arm (38%), the results did not reach statistical significance.[75] Because daptomycin does not reach high levels in bone tissue and resistance might emerge during therapy, high-dose daptomycin (i.e., 8–10 mg/kg/day) and the administration of other agents with good bone penetration are suggested by some investigators. In this regard, the addition of rifampin to daptomycin in an experimental model of MRSA osteomyelitis in rabbits was associated with increased efficacy and reduced incidence of development of nonsusceptibility to either drug.[76] Daptomycin also appeared to be efficacious for the treatment of septic arthritis caused by *S. aureus,* as shown in a retrospective study[77] in which 41% and 50% of the treated patients were considered cured or improved, respectively. The median dose of daptomycin in this study was 5 mg/kg/day (range, 3–6.3 mg/kg/day), the drug was administered for a median of 22 days (range, 3–52 days), and in two-thirds of the patients another antibiotic (most commonly rifampin) was concomitantly given.[77]

Enterococcal Infections

Daptomycin and comparator agents showed similar efficacy for the treatment of ABSSSI in which vancomycin-susceptible *E. faecalis* was isolated in the randomized clinical trials mentioned earlier.[58] Infections caused by VRE were excluded in this study because vancomycin was used in the comparator arm and there were insufficient vancomycin-resistant *E. faecium* isolates to assess efficacy. Daptomycin and comparator agents (vancomycin, teicoplanin, and amoxicillin) displayed similar activity for a variety of enterococcal strains in an experimental endocarditis model. Daptomycin (low dose) activity appeared to be enhanced by the addition of gentamicin against enterococci, both in vitro and in animal models. In humans, the use of daptomycin for the treatment of VRE infections has been reported, mainly in retrospective analysis, and with variable success rates. Around 45% of patients with VRE *(E. faecium)* bacteremia in neutropenic or nonneutropenic patients were considered to have achieved clinical cure, as were about 90% of those with catheter- and non–catheter-related bacteremia in a postmarketing study.[78] Two retrospective studies including patients with VRE bacteremia reported no difference in microbiologic and clinical cure and in mortality rates between daptomycin- and linezolid-treated patients.[79,80] In one of these studies, those receiving daptomycin experienced a higher rate of recurrence, but significantly more patients in this group had hematologic malignancies or were liver transplant recipients. A retrospective study from a national cohort of Veterans Affairs (VA) patients with VRE bacteremia found that treatment with linezolid was associated with higher 30-day all-cause mortality and microbiologic failure rates than daptomycin.[80] A larger subsequent retrospective study including 2630 patients found similar results, with better 30-day survival, in patients receiving daptomycin compared with linezolid. Of note, subgroup analyses suggested that this association was mainly driven by patients with infective endocarditis.[81]

Despite these data, several reports have shown daptomycin failure in the treatment of VRE infections, mainly in cases of bacteremia and endocarditis, with emergence of resistant strains during daptomycin therapy. Important to note, data are accumulating supporting the use of higher daptomycin doses, the potential relevance of the daptomycin MICs displayed by the infecting enterococcal isolates, and the advantage provided by the association with a β-lactam (see previous discussion). Indeed, a retrospective study comparing different dosage strategies in patients with vancomycin-resistant enterococcal bacteremia treated with daptomycin (three groups: standard, medium, and high doses [6, 8, and 10 mg/kg/day, respectively]) found improved overall survival, 30-day mortality, and microbiologic clearance with medium and high doses; no increase in adverse events was observed.[82] Moreover, Chuang and colleagues performed a prospective observational study and found that patients receiving doses of 9 mg/kg/day or higher had the lowest 14-day mortality, with adjusted odds ratios of 10.57 (P = .003) and 5.01 (P = .03) as compared with doses of <7 and 7 to 9 mg/kg/day, respectively.[83]

Three retrospective studies have evaluated the potential impact of the daptomycin MIC in the outcomes of patients treated with daptomycin for severe vancomycin-resistant enterococcal infections. The first study found that subjects infected with isolates that displayed an MIC close to the established breakpoint (3–4 μg/mL) had a higher risk of microbiologic failure than isolates whose MIC was ≤2 μg/mL.[84] The second study included 262 patients and found similar results in terms of efficacy of daptomycin when MICs were considered, but, interesting to note, the daptomycin efficacy was similar (88% vs. 79% for MIC ≤2 and 3–4 μg/mL, respectively; P = .41) when investigators stratified for the use of concomitant β-lactam therapy.[85] In contrast, a third study, a small single-center report of 42 patients with hematologic malignancies and stem cell transplant recipients, did not find any statistically significant differences when stratifying by daptomycin MIC of the initial infecting isolate.[86] Therefore, owing to the high protein binding of daptomycin, the relative decreased susceptibility displayed by enterococci compared with staphylococci (reflected in the recent change of breakpoints), and the possibility of development of resistance during therapy, a high-dose regimen of daptomycin (e.g., 10–12 mg/kg/day) in combination with another active agent might be considered for severe enterococcal infections.[22] High-dose daptomycin has been successfully used with concomitant administration of rifampin and gentamicin, gentamicin and ampicillin, fosfomycin, and tigecycline for selected cases of VRE endocarditis. This approach may enhance daptomycin activity and/or avoid the emergence of mutant strains with decreased susceptibility to this agent. More recently, high-dose daptomycin plus ampicillin appeared to be beneficial in a patient with ampicillin-resistant VRE *(E. faecium)* native aortic valve endocarditis refractory to 7 days of daptomycin (standard dose) and linezolid.[87] In vitro analysis of this strain revealed increased bactericidal activity of daptomycin in the presence of ampicillin; interesting to note, the activity of some innate cationic antimicrobial peptides was also augmented by ampicillin. The use of the combination of ampicillin and daptomycin (despite ampicillin resistance) for enterococcal infections deserves further clinical study. Other combinations that have been shown to be efficacious in vitro in selected strains include daptomycin plus ceftaroline or ertapenem, although clinical data to support these combinations are still lacking.

Other Clinical Uses

Even though daptomycin has been successfully used in some cases of staphylococcal meningitis, including postsurgical meningitis and ventriculitis, daptomycin has been administered with another active agent in most of these reports.[88] The poor CNS penetration of daptomycin (about 5% with inflamed meninges)[44] and a reported daptomycin failure in a neutropenic patient with MRSA meningitis precludes the use of this antibiotic for CNS infections as monotherapy. Intraventricular administration of daptomycin has been communicated in a few reports of patients with ventriculitis due to *E. faecium, E. faecalis,* and methicillin-resistant coagulase-negative staphylococci, all of them with an intravenous drug used concomitantly.[89,90] A suggested potential benefit of the use of daptomycin in pneumococcal meningitis might be derived from the lower propensity of daptomycin to induce inflammatory changes compared with ceftriaxone in an experimental model.[91] Because of the inhibitory interaction between daptomycin and pulmonary surfactant described earlier, daptomycin (4 mg/kg/day) was inferior against the comparator drug (ceftriaxone, 2 g/day) in a clinical trial of community-acquired pneumonia.[92] Therefore, daptomycin should not be administered for the treatment of pulmonary infections unless the lung process is secondary to hematogenous spread of infection (mainly *S. aureus*).[92]

STREPTOGRAMINS

Quinupristin-Dalfopristin

The group of antibiotics named "streptogramins" is composed of different compounds, including mikamycin, virginiamycin, pristinamycin, and quinupristin-dalfopristin (Fig. 31.2). Each of these streptogramin antibiotics contains two macrocyclic lactone peptolide components referred to as streptogramin A and streptogramin B. The former are polyunsaturated cyclic peptolides, and the latter are cyclic hexadepsipeptides. Virginiamycin, a secreted product from *Streptomyces virginiae,* includes virginiamycin M (a streptogramin A) and virginiamycin S (a streptogramin B) and has been used mainly in animals as a growth promoter. Pristinamycin, a naturally occurring mixture produced by *Streptomyces pristinaespiralis,* also contains a streptogramin A (pristinamycin II_A) and

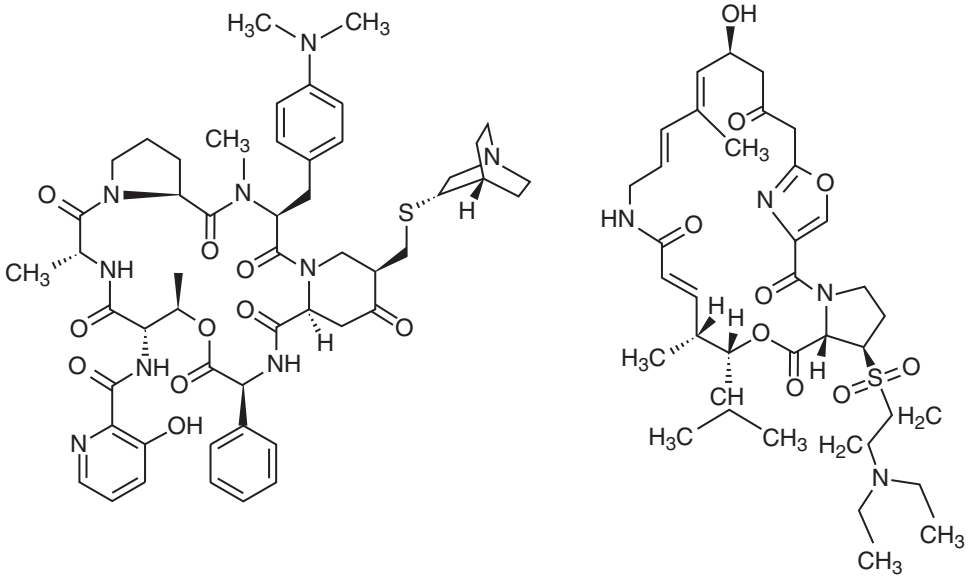

FIG. 31.2 **Chemical structures of quinupristin and dalfopristin.**

a streptogramin B (pristinamycin I_A) component, and has been used orally in some European countries, mainly France, for the treatment of skin and soft tissue infections caused by streptococci and staphylococci. Quinupristin-dalfopristin (Synercid, formerly RP 59500) is a water-soluble combination in a 30:70 ratio suitable for intravenous administration. Quinupristin, a derivative of pristinamycin I_A, is the streptogramin B constituent, and dalfopristin, a derivative of pristinamycin II_B, is the streptogramin A component.

Mechanism of Action

Streptogramins exert their action within the 50S ribosomal subunit of the 70S unit in the second phase, or elongation stage, of protein synthesis. Type A streptogramins (e.g., dalfopristin) appear to bind to the free arms of the peptidyl transferase site in the 50S ribosomal subunit, blocking the addition of new amino acids from the aminoacyl-tRNA molecule to the growing peptide chain, and thus inhibiting the earliest process of elongation. Quinupristin (a streptogramin B compound), like macrolides, works at a later phase of protein synthesis, preventing further peptide elongation and causing release of incomplete peptide chains. In the absence of specific resistance mechanisms, the affinity of quinupristin for the 50S ribosomal subunit is considerably enhanced by a conformational change produced within it by the binding of dalfopristin, explaining the synergistic antimicrobial activity observed between the two streptogramin components. The irreversibility of the complex formed results in bactericidal activity against most susceptible organisms. The blockage of different steps of the protein synthesis pathway may also help explain this synergistic activity.

Antimicrobial Activity

Quinupristin-dalfopristin is active against most gram-positive organisms (with the notable exception of *E. faecalis*) and some gram-negative organisms. In vitro, each compound separately displays bacteriostatic activity, and the bactericidal activity that can be observed with the combination may be diminished if resistance to one or both components is present. Against *E. faecium* isolates, quinupristin-dalfopristin generally displays MICs of less than or equal to 1 μg/mL, including against vancomycin- and erythromycin-resistant isolates, but is generally bacteriostatic in the presence of erythromycin resistance—for example, *ermB. E. faecalis* strains are inherently resistant to quinupristin-dalfopristin,[93] although some exceptions exist. The in vitro activity of quinupristin-dalfopristin against other enterococcal species is variable.

The MIC_{90} of quinupristin-dalfopristin against *S. aureus* and *S. epidermidis* is less than or equal to 1 μg/mL, regardless of the methicillin, vancomycin, erythromycin, or clindamycin resistance pattern. The MIC_{90} of *S. pyogenes, S. agalactiae,* group C and group G streptococci, *S. pneumoniae,* and viridans-group streptococci is less than or equal to 1 μg/mL. *Corynebacterium* spp., including *Corynebacterium jeikeium,* and *Listeria monocytogenes* are also susceptible, as are *Bacillus* spp., *Leuconostoc* spp., *Lactobacillus* spp., *Pediococcus* spp., and *Erysipelothrix rhusiopathiae.* Low MICs of quinupristin-dalfopristin against a variety of gram-positive anaerobes and some gram-negative organisms (e.g., *Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae,* and *Neisseria meningitidis*) have been reported, but in vivo studies have not been performed. Quinupristin-dalfopristin displays no activity against Enterobacteriaceae, *Pseudomonas aeruginosa,* or *Acinetobacter* spp.

Resistance

Because quinupristin and dalfopristin are chemically distinct compounds and their specific target sites within the 50S ribosomal subunit are different, the mechanism(s) leading to resistance to these components are specific for each one. The three general types of resistance to these compounds are (1) conformational changes in the target site decreasing the binding affinity of the drug (quinupristin), (2) enzymatic inactivation (quinupristin and dalfopristin), and (3) active transport of the compound(s) out of the cell (quinupristin and dalfopristin).

The species *E. faecalis* is naturally resistant to quinupristin-dalfopristin owing to the presence of an apparently intrinsic gene, named *lsa,* which encodes a homologue of an adenosine triphosphate (ATP)–binding protein that mediates resistance to lincosamides and type A streptogramins. *E. faecium* human clinical isolates with a quinupristin-dalfopristin MIC greater than or equal to 4 μg/mL have been infrequently reported. However, among VRE *(E. faecium)* strains, resistance to quinupristin-dalfopristin appears more common, especially in Europe. Indeed, in 2003, resistance to quinupristin-dalfopristin was found in 0.6% of these isolates from the United States and in 10% of those from Europe.[94] More recently, 30% of 60 clinical VRE *E. faecium* (VanA or VanB) strains from France isolated between 2006 and 2008 were resistant to quinupristin-dalfopristin (MIC_{90} of 4 μg/mL).[95] Higher rates of resistance are found among *E. faecium* strains isolated from animals in some European countries, probably related to the use of virginiamycin in animal feeds. *Staphylococcus* spp. and *S. pyogenes* strains with high MICs of quinupristin-dalfopristin have been rare.

The most common mechanism of resistance to streptogramin B in gram-positive cocci is through modification of the ribosomal target site, known as MLS_B (conferring resistance to *m*acrolides, *l*incosamides, and *s*treptogramin *B*), which does not affect dalfopristin; this phenotype is

encoded by various *erm* (erythromycin ribosomal methylation) genes. The *erm* genes encode methylases that add one or two methyl groups to a specific adenine residue (A2058) in the 23S ribosomal RNA within the 50S ribosomal subunit, resulting in reduced binding affinity of MLS_B antibiotics for their specific target. The *erm* genes are often located on transposons and can reside on the chromosome or on plasmids. These genes can be constitutively expressed or inducible and are found in many species, including staphylococci, streptococci, enterococci, *Clostridium* spp., and *Bacillus* spp., among others. In staphylococci, the ribosomal binding of 14-membered (e.g., erythromycin and clarithromycin) and 15-membered (e.g., azithromycin) ring macrolides causes a conformational change in the mRNA upstream of the specific *erm* gene (e.g., *ermC*), which then unblocks Erm translation and results in synthesis of the Erm methylase at an increased efficiency.[96] The genes conferring MLS_B resistance typically found in staphylococci are *ermA, ermB, ermC,* and *ermY.* Staphylococcal strains with inducible MLS_B ($iMLS_B$) resistance are resistant to inducer macrolides (e.g., erythromycin) and susceptible to noninducer macrolides, lincosamides (clindamycin), and streptogramin B (quinupristin). However, deletions, duplications, and multiple- or single-point mutations in the *erm* regulatory region can lead to constitutive expression—that is, constant synthesis of the Erm methylase, and resistance to all the MLS_B antibiotics, including clindamycin and quinupristin. Constitutive mutants can be selected from $iMLS_B$ strains in vitro, and clinical failures with clindamycin have been reported during treatment of such staphylococcal strains.[97] Among nosocomial MRSA isolates, constitutive expression of MLS_B ($cMLS_B$) resistance is much more common than $iMLS_B$ type, which on the other hand is more frequent in MSSA isolates and also among recent isolates from community-onset MRSA infections. Despite causing resistance to quinupristin, the presence of the $cMLS_B$ phenotype alone has no effect on the MICs of quinupristin-dalfopristin against staphylococci but decreases the bactericidal activity in vitro and in animal models. Increased MICs of quinupristin or of clindamycin appear to be a useful tool for screening for the decreased bactericidal activity of quinupristin-dalfopristin.

In enterococci, MLS_B resistance is most frequently related to the presence of *ermB* and is often $iMLS_B$ type. However, unlike staphylococci, all the MLS_B antibiotics can act as inducers of the MLS_B resistance system; therefore, resistance is expected to all MLS_B antibiotics whether MLS_B resistance is inducible or constitutively expressed. In the experimental endocarditis model, quinupristin-dalfopristin was less efficacious when the infecting *E. faecium* strain had the $iMLS_B$ resistance phenotype (vs. an MLS_B-lacking strain), although different degrees of diffusion of the two streptogramins into the vegetation may partially explain these results. The MICs of quinupristin-dalfopristin against *S. pneumoniae, S. pyogenes, S. agalactiae,* and viridans-group streptococci appear not to be affected by the presence of MLS_B resistance. The *cfr* gene, typically associated with linezolid resistance through ribosome methylation in staphylococci and enterococci, has also been shown to decrease the susceptibility to streptogramin A.

Hydrolysis of streptogramin B compounds is another mechanism of resistance to these agents. The *vgb* genes encoding a streptogramin-inactivating enzyme (lyase) have been identified in staphylococci and, rarely, in *E. faecium.* Efflux systems coding for ATP-binding transporters such as *msrA* and *msrB* in staphylococci and *msrC* in *E. faecium* can pump macrolides and streptogramin B compounds out of the cell. Streptogramin A compounds can be inactivated by acetyltransferases, which are encoded by the genes *vatA, vatB,* and *vatC* in staphylococci and by *vatD* and *vatE* in *E. faecium,* and are subjected to the action of efflux pumps encoded by the *vgaA* and *vgaB* genes in staphylococci. High MICs of quinupristin-dalfopristin generally require the presence of more than one gene conferring resistance to the individual components. Organisms with decreased susceptibility (*E. faecium* more so than *S. aureus* isolates) have been recovered from subjects in whom therapy has failed, most likely owing to a mutational mechanism.

Clinical Pharmacodynamics and Pharmacokinetics

Quinupristin-dalfopristin displays a postantibiotic effect against many gram-positive organisms with a mean of 2.8 hours for pneumococci and 4.7 hours for staphylococci, although it is shorter for isolates with $cMLS_B$ expression. For *E. faecium* isolates, the postantibiotic effect averages 2.6 and 8.5 hours for vancomycin-resistant and vancomycin-susceptible strains, respectively. The AUC/MIC ratio appears to be the pharmacodynamic parameter that best predicts response to quinupristin-dalfopristin.

Distribution and Elimination

The mean peak concentrations of quinupristin and dalfopristin after a single intravenous infusion of 7.5 mg/kg in healthy volunteers were 2.3 μg/mL and 6.1 μg/mL, respectively.[98] The terminal half-lives of both compounds are relatively short, ranging from 0.7 to 1.2 hours. The volume of distribution at steady state was reported as 460 to 540 mL/kg and 240 to 300 mL/kg of quinupristin and dalfopristin, respectively. Quinupristin displayed protein binding of 55% to 78%, and dalfopristin, 11% to 26%.[98] Quinupristin-dalfopristin is excreted mainly in the feces and only partially in the urine; it does not reach therapeutic levels in cerebrospinal fluid (CSF) and appears not to cross the placenta. Excretion into breast milk was detected in lactating rats, although no data exist in women. Both streptogramins are metabolized in the liver, resulting in metabolites with antimicrobial activity. Studies in monkeys found high levels of drug in bile and in gallbladder, liver, and kidney tissues after infusion of radiolabeled quinupristin-dalfopristin. Quinupristin diffuses homogeneously within infected vegetation, whereas dalfopristin concentrates only in the periphery, which may hinder clinical efficacy. Quinupristin-dalfopristin penetrates poorly into the peritoneal fluid of patients undergoing continuous ambulatory peritoneal dialysis (CAPD).

Administration and Dosing

The recommended intravenous dosing for quinupristin-dalfopristin is 7.5 mg/kg every 12 hours for ABSSSI, respectively (see Table 31.1). The same doses have been safely used in pediatric patients. Reconstituted drug should be diluted in 5% dextrose (not in saline) to a concentration of about 2 mg/mL and then infused over 60 minutes. If significant venous irritation is noted, which it often is, the solution can be further diluted or the drug administered through a central line, the preferred route. Dosage adjustment appears not to be necessary in patients with renal failure whether or not they are receiving hemodialysis or are undergoing CAPD. The lack of data in subjects undergoing CRRT precludes making dosage recommendations in this setting. A lower dose of quinupristin-dalfopristin may be considered in patients with hepatic disease, although further studies are needed.

Adverse Events and Drug Interactions

More than 30% of patients experience irritation at the venous site when quinupristin-dalfopristin is administered through peripheral veins.[99,100] Arthralgias (9.1%) and myalgias (6.6%), sometimes severe and typically with normal CPK levels, are the side effects that most commonly lead to drug discontinuation; these can be severe, resolving after cessation of therapy.[99,101] Risk factors associated with the development of these side effects are having chronic liver disease, having elevated bilirubin concentrations at baseline, being a liver transplant recipient, and concomitantly using cyclosporine or mycophenolate. Less common adverse events associated with quinupristin-dalfopristin are nausea, vomiting, diarrhea, rash, pruritus, headache, and asthenia[99,102]; laboratory abnormalities are mostly increased liver enzymes and total and conjugated bilirubin levels, which appear to be secondary to competition for excretion between bilirubin and this agent.[99,102] These laboratory abnormalities are rarely severe enough to cause discontinuation of this drug. Quinupristin-dalfopristin has not been associated with significant teratogenic abnormalities in animal studies, but there are no data on the use of this antibiotic in pregnant women (pregnancy category B) or in nursing woman, for whom this drug should be used only in situations in which there are no other therapeutic alternatives.

Quinupristin-dalfopristin produces significant inhibition of the cytochrome P-450 3A4 isoenzyme system, resulting in increased levels of drugs that are metabolized through it; a few examples include diazepam, verapamil, HMG-CoA reductase inhibitors, most of the human immunodeficiency virus type 1 protease inhibitors, vinca

alkaloids, cyclosporine, tacrolimus, methylprednisolone, quinidine, lidocaine, and disopyramide.[102] Drugs that are metabolized through the cytochrome P-450 3A4 isoenzyme system that can produce prolongation of the QTc interval should not be coadministered with quinupristin-dalfopristin.

Clinical Uses

Quinupristin-dalfopristin is currently approved in the United States for the treatment of skin and skin structure infections caused by MSSA or *S. pyogenes,* although this combination is seldom used. Quinupristin-dalfopristin was the first compound approved by the FDA for the treatment of VRE *(E. faecium)* infections; however, lack of consistent clinical benefit in adequately designed comparative trials led to withdrawal of this indication from its label. In open-label trials, quinupristin-dalfopristin showed a response rate of 75% to 86% in individuals with urinary tract infections, catheter-related bacteremia, and bone and joint infections caused by vancomycin-resistant *E. faecium* isolates.[99,100] Slightly lower response rates were attained in individuals with skin and skin structure infections, intraabdominal infections, and bacteremia of unknown origin; only about 25% of patients with endocarditis had a successful outcome.[99,100] In another study including mostly liver transplant recipients with vancomycin-resistant *E. faecium* infections at diverse sites, an initial favorable response was seen in approximately 80% of the patients, although 4 of 23 patients later experienced bacteriologic and clinical relapse.[103] In a prospective randomized study in cancer patients with vancomycin-resistant *E. faecium* infections, a clinical response rate of 43% was seen with quinupristin-dalfopristin, which was comparable to that of linezolid. A few cases of vancomycin-resistant *E. faecium* endocarditis have been successfully treated with quinupristin-dalfopristin in combination with rifampin and doxycycline or with high-dose ampicillin. Some patients with shunt-related meningitis caused by vancomycin-resistant *E. faecium* have been successfully treated with the addition of intraventricular quinupristin-dalfopristin[104]; based on pharmacokinetics of quinupristin-dalfopristin in the CSF, a dose of 2 mg or greater appears to be the appropriate intraventricular daily dose.[104] Intravenous plus intraperitoneal quinupristin-dalfopristin (25 mg/L in alternate dialysate bags) has been effective in a few cases of vancomycin-resistant *E. faecium* CAPD-related peritonitis.

Clinical success rates of about 70% were observed for skin and skin structure infections and bone and joint infections when quinupristin-dalfopristin was evaluated for the treatment of patients with MRSA infections who were intolerant of or were not responding to other therapies.[101] Lower response rates (about 50%) were seen in patients with endocarditis, and neither of two bacteriologically evaluable patients responded favorably.[101] A randomized trial including patients with nosocomially acquired pneumonia (aztreonam was given for empiric gram-negative therapy) in which *S. aureus* was the most common isolated organism found a clinical success rate of 56% for quinupristin-dalfopristin and 58% for vancomycin,[105] suggesting that quinupristin-dalfopristin may be an alternative for the treatment of staphylococcal nosocomial pneumonia, although it is rarely used for this indication.

Key References

The complete reference list is available online at Expert Consult.

3. Müller A, Wenzel M, Strahl H, et al. Daptomycin inhibits cell envelope synthesis by interfering with fluid membrane microdomains. *Proc Natl Acad Sci USA*. 2016;113:E7077–E7086.
5. Weber RE, Layer F, Klare I, et al. Comparative evaluation of VITEK® 2 and three commercial gradient strip assays for daptomycin susceptibility testing of *Staphylococcus aureus*. *J Antimicrob Chemother*. 2017;72:3059–3062.
12. Sader HS, Farrell DJ, Flamm RK, et al. Analysis of 5-year trends in daptomycin activity tested against *Staphylococcus aureus* and enterococci from European and US hospitals (2009-2013). *J Glob Antimicrob Resist*. 2015;3:161–165.
21. Pader V, Hakim S, Painter KL, et al. *Staphylococcus aureus* inactivates daptomycin by releasing membrane phospholipids. *Nat Microbiol*. 2016;2:16194.
26. Panesso D, Reyes J, Gaston EP, et al. Deletion of liaR reverses daptomycin resistance in *Enterococcus faecium* independent of the genetic background. *Antimicrob Agents Chemother*. 2015;59:7327–7334.
27. Reyes J, Panesso D, Tran TT, et al. A liaR deletion restores susceptibility to daptomycin and antimicrobial peptides in multidrug-resistant *Enterococcus faecalis*. *J Infect Dis*. 2015;211:1317–1325.
29. Hines KM, Waalkes A, Penewit K, et al. Characterization of the mechanisms of daptomycin resistance among Gram-positive bacterial pathogens by multidimensional lipidomics. *mSphere*. 2017;2.
32. Renzoni A, Kelley WL, Rosato RR, et al. Molecular bases determining daptomycin resistance-mediated resensitization to β-lactams (seesaw effect) in Methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2016;61.
34. Hindler JA, Wong-Beringer A, Charlton CL, et al. In vitro activity of daptomycin in combination with β-lactams, gentamicin, rifampin, and tigecycline against daptomycin-nonsusceptible enterococci. *Antimicrob Agents Chemother*. 2015;59:4279–4288.
35. Akins RL, Katz BD, Monahan C, et al. Characterization of high-level daptomycin resistance in viridans group streptococci developed upon in vitro exposure to daptomycin. *Antimicrob Agents Chemother*. 2015;59:2102–2112.
37. Mishra NN, Tran TT, Seepersaud R, et al. Perturbations of phosphatidate cytidylyltransferase (CdsA) mediate daptomycin resistance in *Streptococcus mitis/oralis* by a novel mechanism. *Antimicrob Agents Chemother*. 2017;61.
39. Werth BJ, Hahn WO, Butler-Wu SM, et al. Emergence of high-level daptomycin resistance in *Corynebacterium striatum* in two patients with left ventricular assist device infections. *Microb Drug Resist*. 2016;22:233–237.
56. Xu X, Khadzhynov D, Peters H, et al. Population pharmacokinetics of daptomycin in adult patients undergoing continuous renal replacement therapy. *Br J Clin Pharmacol*. 2017;83:498–509.
64. Timbrook TT, Caffrey AR, Luther MK, et al. Association of higher daptomycin dose (7 mg/kg or greater) with improved survival in patients with Methicillin-resistant *Staphylococcus aureus* bacteremia. *Pharmacotherapy*. 2018;38:189–196.
72. Nigo M, Diaz L, Carvajal LP, et al. Ceftaroline-resistant, Daptomycin-tolerant, and heterogeneous Vancomycin-intermediate Methicillin-resistant *Staphylococcus aureus* causing infective endocarditis. *Antimicrob Agents Chemother*. 2017;61.
81. Britt NS, Potter EM, Patel N, et al. Effect of continuous and sequential therapy among veterans receiving daptomycin or linezolid for Vancomycin-resistant *Enterococcus faecium* bacteremia. *Antimicrob Agents Chemother*. 2017;61.
82. Britt NS, Potter EM, Patel N, et al. Comparative effectiveness and safety of standard-, medium-, and high-dose daptomycin strategies for the treatment of Vancomycin-resistant enterococcal bacteremia among veterans affairs patients. *Clin Infect Dis*. 2017;64: 605–613.
83. Chuang YC, Lin HY, Chen PY, et al. Effect of daptomycin dose on the outcome of Vancomycin-resistant, daptomycin-susceptible *Enterococcus faecium* bacteremia. *Clin Infect Dis*. 2017;64:1026–1034.
84. Shukla BS, Shelburne S, Reyes K, et al. Influence of minimum inhibitory concentration in clinical outcomes of *Enterococcus faecium* bacteremia treated with daptomycin: is it time to change the breakpoint? *Clin Infect Dis*. 2016;62:1514–1520.
85. Moise PA, Sakoulas G, McKinnell JA, et al. Clinical outcomes of daptomycin for Vancomycin-resistant *Enterococcus* bacteremia. *Clin Ther*. 2015;37: 1443–1453.e2.
86. Chong PP, van Duin D, Bangdiwala A, et al. Vancomycin-resistant enterococcal bloodstream infections in hematopoietic stem cell transplant recipients and patients with hematologic malignancies: impact of daptomycin MICs of 3 to 4 mg/L. *Clin Ther*. 2016;38:2468–2476.

References

1. Hobbs JK, Miller K, O'Neill AJ, et al. Consequences of daptomycin-mediated membrane damage in *Staphylococcus aureus*. *J Antimicrob Chemother*. 2008;62:1003–1008.
2. Pogliano J, Pogliano N, Silverman JA. Daptomycin mediated reorganization of membrane architecture causes mislocalization of essential cell division proteins. *J Bacteriol*. 2012;194:4494–4504.
3. Müller A, Wenzel M, Strahl H, et al. Daptomycin inhibits cell envelope synthesis by interfering with fluid membrane microdomains. *Proc Natl Acad Sci USA*. 2016;113:E7077–E7086.
4. Muraih JK, Pearson A, Silverman J, et al. Oligomerization of daptomycin on membranes. *Biochim Biophys Acta*. 2011;1808:1154–1160.
5. Weber RE, Layer F, Klare I, et al. Comparative evaluation of VITEK® 2 and three commercial gradient strip assays for daptomycin susceptibility testing of staphylococcus aureus. *J Antimicrob Chemother*. 2017;72:3059–3062.
6. Akins RL, Rybak MJ. Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptide intermediate-resistant *Staphylococcus aureus*, vancomycin resistant *Enterococcus faecium*, and methicillin-resistant *Staphylococcus aureus* isolates in an in vitro pharmacodynamic model with simulated endocardial vegetations. *Antimicrob Agents Chemother*. 2001;45:454–459.
7. Vouillamoz J, Moreillon P, Giddey M, et al. Efficacy of daptomycin in the treatment of experimental endocarditis due to susceptible and multidrug-resistant enterococci. *J Antimicrob Chemother*. 2006;58:1208–1214.
8. Patel JB, Jevitt LA, Hageman J, et al. An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in *Staphylococcus aureus*. *Clin Infect Dis*. 2006;42:1652–1653.
9. Sader HS, Jones RN. The activity of daptomycin against wild-type *Staphylococcus aureus* and strains with reduced susceptibility to vancomycin. *Clin Infect Dis*. 2006;43:798–799, author reply 799–800.
10. Mascio CT, Alder JD, Silverman JA. Bactericidal action of daptomycin against stationary-phase and nondividing *Staphylococcus aureus* cells. *Antimicrob Agents Chemother*. 2007;51:4255–4260.
11. Silverman JA, Oliver N, Andrew T, et al. Resistance studies with daptomycin. *Antimicrob Agents Chemother*. 2001;45:1799–1802.
12. Sader HS, Farrell DJ, Flamm RK, et al. Analysis of 5-year trends in daptomycin activity tested against *Staphylococcus aureus* and enterococci from European and US hospitals (2009-2013). *J Glob Antimicrob Resist*. 2015;3:161–165.
13. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355:653–665.
14. Sharma M, Riederer K, Chase P, et al. High rate of decreasing daptomycin susceptibility during the treatment of persistent *Staphylococcus aureus* bacteremia. *Eur J Clin Microbiol Infect Dis*. 2008;27:433–437.
15. Jones T, Yeaman MR, Sakoulas G, et al. Failures in clinical treatment of *Staphylococcus aureus* infection with daptomycin are associated with alterations in surface charge, membrane phospholipid asymmetry, and drug binding. *Antimicrob Agents Chemother*. 2008;52:269–278.
16. Ernst CM, Staubitz P, Mishra NN, et al. The bacterial defensin resistance protein MprF consists of separable domains for lipid lysinylation and antimicrobial peptide repulsion. *PLoS Pathog*. 2009;5:e1000660.
17. Mehta S, Cuirolo AX, Plata KB, et al. VraSR two-component regulatory system contributes to mprF-mediated decreased susceptibility to daptomycin in in vivo-selected clinical strains of methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2012;56:92–102.
18. Cafiso V, Bertuccio T, Spina D, et al. Modulating activity of vancomycin and daptomycin on the expression of autolysis cell-wall turnover and membrane charge genes in hvisa and VISA strains. *PLoS ONE*. 2012;7:e29573.
19. Bertsche U, Weidenmaier C, Kuehner D, et al. Correlation of daptomycin resistance in a clinical *Staphylococcus aureus* strain with increased cell wall teichoic acid production and d-alanylation. *Antimicrob Agents Chemother*. 2011;55:3922–3928.
20. Mishra NN, McKinnell J, Yeaman MR, et al. In vitro cross-resistance to daptomycin and host defense cationic antimicrobial peptides in clinical methicillin-resistant *Staphylococcus aureus* isolates. *Antimicrob Agents Chemother*. 2011;55:4012–4018.
21. Pader V, Hakim S, Painter KL, et al. *Staphylococcus aureus* inactivates daptomycin by releasing membrane phospholipids. *Nat Microbiol*. 2016;2:16194.
22. Arias CA, Murray BE. Emergence and management of drug-resistant enterococcal infections. *Expert Rev Anti Infect Ther*. 2008;6:637–655.
23. Arias CA, Panesso D, McGrath DM, et al. Genetic basis for in vivo daptomycin resistance in enterococci. *N Engl J Med*. 2011;365:892–900.
24. Tran TT, Panesso D, Gao H, et al. Whole-genome analysis of a daptomycin-susceptible *Enterococcus faecium* strain and its daptomycin-resistant variant arising during therapy. *Antimicrob Agents Chemother*. 2013;57:261–268.
25. Munita JM, Tran TT, Diaz L, et al. A liaF codon deletion abolishes daptomycin bactericidal activity against vancomycin-resistant *Enterococcus faecalis*. *Antimicrob Agents Chemother*. 2013;57:2831–2833.
26. Panesso D, Reyes J, Gaston EP, et al. Deletion of liaR reverses daptomycin resistance in *Enterococcus faecium* independent of the genetic background. *Antimicrob Agents Chemother*. 2015;59:7327–7334.
27. Reyes J, Panesso D, Tran TT, et al. A liaR deletion restores susceptibility to daptomycin and antimicrobial peptides in multidrug-resistant *Enterococcus faecalis*. *J Infect Dis*. 2015;211:1317–1325.
28. Mishra NN, Bayer AS, Tran TT, et al. Daptomycin resistance in enterococci is associated with distinct alterations of cell membrane phospholipid content. *PLoS ONE*. 2012;7:e43958.
29. Hines KM, Waalkes A, Penewit K, et al. Characterization of the mechanisms of daptomycin resistance among Gram-positive bacterial pathogens by multidimensional lipidomics. *mSphere*. 2017;2.
30. Yang SJ, Xiong YQ, Boyle-Vavra S, et al. Daptomycin oxacillin combinations in treatment of experimental endocarditis caused by daptomycin-nonsusceptible strains of methicillin-resistant *Staphylococcus aureus* with evolving oxacillin susceptibility (the "seesaw effect"). *Antimicrob Agents Chemother*. 2010;54:3161–3169.
31. Dhand A, Bayer AS, Pogliano J, et al. Use of antistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin resistant *Staphylococcus aureus*: role of enhanced daptomycin binding. *Clin Infect Dis*. 2011;53:158–163.
32. Renzoni A, Kelley WL, Rosato RR, et al. Molecular bases determining daptomycin resistance-mediated resensitization to β-lactams (seesaw effect) in Methicillin-resistant staphylococcus aureus. *Antimicrob Agents Chemother*. 2016;61.
33. Entenza JM, Giddey M, Vouillamoz J, et al. In vitro prevention of the emergence of daptomycin resistance in *Staphylococcus aureus* and enterococci following combination with amoxicillin/clavulanic acid or ampicillin. *Int J Antimicrob Agents*. 2010;35:451–456.
34. Hindler JA, Wong-Beringer A, Charlton CL, et al. In vitro activity of daptomycin in combination with β-lactams, gentamicin, rifampin, and tigecycline against daptomycin-nonsusceptible enterococci. *Antimicrob Agents Chemother*. 2015;59:4279–4288.
35. Akins RL, Katz BD, Monahan C, et al. Characterization of high-level daptomycin resistance in viridans group streptococci developed upon in vitro exposure to daptomycin. *Antimicrob Agents Chemother*. 2015;59:2102–2112.
36. García-de-la-Mària C, Pericas JM, Del Río A, et al. Hospital clinic experimental endocarditis study group. Early in vitro and in vivo development of high-level daptomycin resistance is common in mitis group streptococci after exposure to daptomycin. *Antimicrob Agents Chemother*. 2013;57:2319–2325.
37. Mishra NN, Tran TT, Seepersaud R, et al. Perturbations of phosphatidate cytidylyltransferase (CdsA) mediate daptomycin resistance in *Streptococcus mitis/oralis* by a novel mechanism. *Antimicrob Agents Chemother*. 2017;61.
38. Tran TT, Jaijakul S, Lewis CT, et al. Native valve endocarditis caused by corynebacterium striatum with heterogeneous high-level daptomycin resistance: collateral damage from daptomycin therapy? *Antimicrob Agents Chemother*. 2012;56:3461–3464.
39. Werth BJ, Hahn WO, Butler-Wu SM, et al. Emergence of high-level daptomycin resistance in corynebacterium striatum in two patients with left ventricular assist device infections. *Microb Drug Resist*. 2016;22:233–237.
40. McElvania TeKippe E, Thomas BS, Ewald GA, et al. Rapid emergence of daptomycin resistance in clinical isolates of corynebacterium striatum… a cautionary tale. *Eur J Clin Microbiol Infect Dis*. 2014;33:2199–2205.
41. Benvenuto M, Benziger DP, Yankelev S, et al. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. *Antimicrob Agents Chemother*. 2006;50:3245–3249.
42. Dvorchik BH, Brazier D, DeBruin MF, et al. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. *Antimicrob Agents Chemother*. 2003;47:1318–1323.
43. Cottagnoud P, Pfister M, Acosta F, et al. Daptomycin is highly efficacious against penicillin-resistant and penicillin-and quinolone-resistant pneumococci in experimental meningitis. *Antimicrob Agents Chemother*. 2004;48:3928–3933.
44. Riser MS, Bland CM, Rudisill CN, et al. Cerebrospinal fluid penetration of high-dose daptomycin in suspected *Staphylococcus aureus* meningitis. *Ann Pharmacother*. 2010;44:1832–1835.
45. Wise R, Gee T, Andrews JM, et al. Pharmacokinetics and inflammatory fluid penetration of intravenous daptomycin in volunteers. *Antimicrob Agents Chemother*. 2002;46:31–33.
46. Traunmuller F, Schintler MV, Metzler J, et al. Soft tissue and bone penetration abilities of daptomycin in diabetic patients with bacterial foot infections. *J Antimicrob Chemother*. 2010;65:1252–1257.
47. Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother*. 2004;48:63–68.
48. Pankuch GA, Jacobs MR, Appelbaum PC. Bactericidal activity of daptomycin against *Streptococcus pneumoniae* compared with eight other antimicrobials. *J Antimicrob Chemother*. 2003;51:443–446.
49. Hanberger H, Nilsson LE, Maller R, et al. Pharmacodynamics of daptomycin and vancomycin on *Enterococcus faecalis* and *Staphylococcus aureus* demonstrated by studies of initial killing and postantibiotic effect and influence of ca2+ and albumin on these drugs. *Antimicrob Agents Chemother*. 1991;35:1710–1716.
50. Salama NN, Segal JH, Churchwell MD, et al. Single-dose daptomycin pharmacokinetics in chronic haemodialysis patients. *Nephrol Dial Transplant*. 2010;25:1279–1284.
51. Patel N, Cardone K, Grabe DW, et al. Use of pharmacokinetic and pharmacodynamic principles to determine optimal administration of daptomycin in patients receiving standardized thrice-weekly hemodialysis. *Antimicrob Agents Chemother*. 2011;55:1677–1683.
52. Kielstein JT, Eugbers C, Bode-Boeger SM, et al. Dosing of daptomycin in intensive care unit patients with acute kidney injury undergoing extended dialysis—a pharmacokinetic study. *Nephrol Dial Transplant*. 2010;25:1537–1541.
53. Vilay AM, Grio M, Depestel DD, et al. Daptomycin pharmacokinetics in critically ill patients receiving continuous venovenous hemodialysis. *Crit Care Med*. 2011;39:19–25.
54. Falcone M, Russo A, Cassetta MI, et al. Daptomycin serum levels in critical patients undergoing continuous renal replacement. *J Chemother*. 2012;24:253–256.
55. Wenisch JM, Meyer B, Fuhrmann V, et al. Multiple-dose pharmacokinetics of daptomycin during continuous venovenous haemodiafiltration. *J Antimicrob Chemother*. 2012;67:977–983.
56. Xu X, Khadzhynov D, Peters H, et al. Population pharmacokinetics of daptomycin in adult patients undergoing continuous renal replacement therapy. *Br J Clin Pharmacol*. 2017;83:498–509.
57. Ardura MI, Mejias A, Katz KS, et al. Daptomycin therapy for invasive gram-positive bacterial infections in children. *Pediatr Infect Dis J*. 2007;26:1128–1132.
58. Arbeit RD, Maki D, Tally FP, et al. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis*. 2004;38:1673–1681.
59. Bhavnani SM, Rubino CM, Ambrose PG, et al. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*. 2010;50:1568–1574.
60. Figueroa DA, Mangini E, Amodio-Groton M, et al. Safety of high-dose intravenous daptomycin treatment: three year cumulative experience in a clinical program. *Clin Infect Dis*. 2009;49:177–180.
61. Miller BA, Gray A, Leblanc TW, et al. Acute eosinophilic pneumonia secondary to daptomycin: a report of three cases. *Clin Infect Dis*. 2010;50:e63–e68.
62. Lipsky BA, Stoutenburgh U. Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. *J Antimicrob Chemother*. 2005;55:240–245.
63. Dohmen PM, Guleri A, Capone A, et al. Daptomycin for the treatment of infective endocarditis: results from a European registry. *J Antimicrob Chemother*. 2013;68:936–942.
64. Timbrook TT, Caffrey AR, Luther MK, et al. Association of higher daptomycin dose (7 mg/kg or greater) with

improved survival in patients with Methicillin-resistant staphylococcus aureus bacteremia. *Pharmacotherapy*. 2018;38:189–196.

65. Kullar R, Davis SL, Levine DP, et al. High-dose daptomycin for treatment of complicated gram-positive infections: a large, multicenter, retrospective study. *Pharmacotherapy*. 2011;31:527–536.
66. Moore CL, Osaki-Kiyan P, Haque NZ, et al. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case control study. *Clin Infect Dis*. 2012;54:51–58.
67. Murray KP, Zhao JJ, Davis SL, et al. Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. *Clin Infect Dis*. 2013;56:1562–1569.
68. Weston A, Boucher HW. Early high-dose daptomycin for methicillin-resistant *Staphylococcus aureus* bloodstream infections with elevated vancomycin minimum inhibitory concentrations: ready for prime time? *Clin Infect Dis*. 2013;56:1570–1572.
69. Miro JM, Garcia-de-la-Maria C, Armero Y, et al. Addition of gentamicin or rifampin does not enhance the effectiveness of daptomycin in treatment of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2009;53: 4172–4177.
70. Mehta S, Singh C, Plata KB, et al. β-lactams increase the antibacterial activity of daptomycin against clinical methicillin-resistant *Staphylococcus aureus* strains and prevent selection of daptomycin-resistant derivatives. *Antimicrob Agents Chemother*. 2012;56:6192–6200.
71. Rose WE, Schulz LT, Andes D, et al. Addition of ceftaroline to daptomycin after emergence of daptomycinnonsusceptible *Staphylococcus aureus* during therapy improves antibacterial activity. *Antimicrob Agents Chemother*. 2012;56:5296–5302.
72. Nigo M, Diaz L, Carvajal LP, et al. Ceftaroline-resistant, Daptomycin-tolerant, and heterogeneous Vancomycin-intermediate Methicillin-resistant staphylococcus aureus causing infective endocarditis. *Antimicrob Agents Chemother*. 2017;61.
73. Lamp KC, Friedrich LV, Mendez-Vigo L, et al. Clinical experience with daptomycin for the treatment of patients with osteomyelitis. *Am J Med*. 2007;120:S13–S20.
74. Lalani T, Boucher HW, Cosgrove SE, et al. Outcomes with daptomycin versus standard therapy for osteoarticular infections associated with *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother*. 2008;61:177–182.
75. Byren I, Rege S, Campanaro E, et al. Randomized controlled trial of the safety and efficacy of daptomycin versus standard-of-care therapy for management of patients with osteomyelitis associated with prosthetic devices undergoing two-stage revision arthroplasty. *Antimicrob Agents Chemother*. 2012;56:5626–5632.
76. Lefebvre M, Jacqueline C, Amador G, et al. Efficacy of daptomycin combined with rifampicin for the treatment of experimental meticillin-resistant *Staphylococcus aureus* (MRSA) acute osteomyelitis. *Int J Antimicrob Agents*. 2010;36:542–544.
77. Forrest GN, Donovan BJ, Lamp KC, et al. Clinical experience with daptomycin for the treatment of patients with documented gram-positive septic arthritis. *Ann Pharmacother*. 2008;42:213–217.
78. Sakoulas G, Golan Y, Lamp KC, et al. Daptomycin in the treatment of bacteremia. *Am J Med*. 2007;120:S21–S27.
79. Mave V, Garcia-Diaz J, Islam T, et al. Vancomycin-resistant enterococcal bacteraemia: is daptomycin as effective as linezolid? *J Antimicrob Chemother*. 2009;64:175–180.
80. Twilla JD, Finch CK, Usery JB, et al. Vancomycin-resistant *Enterococcus* bacteremia: an evaluation of treatment with linezolid or daptomycin. *J Hosp Med*. 2012;7:243–248.
81. Britt NS, Potter EM, Patel N, et al. Effect of continuous and sequential therapy among veterans receiving daptomycin or linezolid for Vancomycin-resistant *Enterococcus faecium* bacteremia. *Antimicrob Agents Chemother*. 2017;61.
82. Britt NS, Potter EM, Patel N, et al. Comparative effectiveness and safety of standard-, medium-, and high-dose daptomycin strategies for the treatment of Vancomycin-resistant enterococcal bacteremia among veterans affairs patients. *Clin Infect Dis*. 2017;64: 605–613.
83. Chuang YC, Lin HY, Chen PY, et al. Effect of daptomycin dose on the outcome of Vancomycin-resistant, daptomycin-susceptible *Enterococcus faecium* bacteremia. *Clin Infect Dis*. 2017;64:1026–1034.
84. Shukla BS, Shelburne S, Reyes K, et al. Influence of minimum inhibitory concentration in clinical outcomes of *Enterococcus faecium* bacteremia treated with daptomycin: is it time to change the breakpoint? *Clin Infect Dis*. 2016;62:1514–1520.
85. Moise PA, Sakoulas G, McKinnell JA, et al. Clinical outcomes of daptomycin for Vancomycin-resistant *Enterococcus* bacteremia. *Clin Ther*. 2015;37: 1443–1453.e2.
86. Chong PP, van Duin D, Bangdiwala A, et al. Vancomycin-resistant enterococcal bloodstream infections in hematopoietic stem cell transplant recipients and patients with hematologic malignancies: impact of daptomycin MICs of 3 to 4 mg/L. *Clin Ther*. 2016;38:2468–2476.
87. Sakoulas G, Bayer AS, Pogliano J, et al. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother*. 2012;56:838–844.
88. Vena A, Falcone M, Comandini E, et al. Daptomycin plus trimethoprim/sulfamethoxazole combination therapy in post-neurosurgical meningitis caused by linezolid-resistant *Staphylococcus epidermidis*. *Diagn Microbiol Infect Dis*. 2013;76:99–102.
89. Mueller SW, Kiser TH, Anderson TA, et al. Intraventricular daptomycin and intravenous linezolid for the treatment of external ventricular-drain-associated ventriculitis due to vancomycin-resistant *Enterococcus faecium*. *Ann Pharmacother*. 2012;46:e35.
90. Jaspan HB, Brothers AW, Campbell AJ, et al. Multidrug-resistant *Enterococcus faecium* meningitis in a toddler: characterization of the organism and successful treatment with intraventricular daptomycin and intravenous tigecycline. *Pediatr Infect Dis J*. 2010;29:379–381.
91. Grandgirard D, Oberson K, Buhlmann A, et al. Attenuation of cerebrospinal fluid inflammation by the nonbacteriolytic antibiotic daptomycin versus that by ceftriaxone in experimental pneumococcal meningitis. *Antimicrob Agents Chemother*. 2010;54:1323–1326.
92. Pertel PE, Bernardo P, Fogarty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. *Clin Infect Dis*. 2008;46:1142–1151.
93. Singh KV, Weinstock GM, Murray BE. An *Enterococcus faecalis* ABC homologue (Lsa) is required for the resistance of this species to clindamycin and quinupristin-dalfopristin. *Antimicrob Agents Chemother*. 2002;46:1845–1850.
94. Deshpande LM, Fritsche TR, Moet GJ, et al. Antimicrobial resistance and molecular epidemiology of vancomycin resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. *Diagn Microbiol Infect Dis*. 2007;58:163–170.
95. Berenger R, Bourdon N, Auzou M, et al. In vitro activity of new antimicrobial agents against glycopeptide-resistant *Enterococcus faecium* clinical isolates from France between 2006 and 2008. *Med Mal Infect*. 2011;41: 40540–40549.
96. Weisblum B. Insights into erythromycin action from studies of its activity as inducer of resistance. *Antimicrob Agents Chemother*. 1995;39:797–805.
97. Drinkovic D, Fuller ER, Shore KP, et al. Clindamycin treatment of *Staphylococcus aureus* expressing inducible clindamycin resistance. *J Antimicrob Chemother*. 2001;48:315–316.
98. Bearden DT. Clinical pharmacokinetics of quinupristin/dalfopristin. *Clin Pharmacokinet*. 2004;43:239–252.
99. Moellering RC, Linden PK, Reinhardt J, et al. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*. Synercid Emergency-Use Study group. *J Antimicrob Chemother*. 1999;44:251–261.
100. Linden PK, Moellering RC Jr, Wood CA, et al. Treatment of vancomycin-resistant *Enterococcus faecium* infections with quinupristin/dalfopristin. *Clin Infect Dis*. 2001;33:1816–1823.
101. Drew RH, Perfect JR, Srinath L, et al. Treatment of methicillin-resistant *Staphylococcus aureus* infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. For the Synercid Emergency-Use Study Group. *J Antimicrob Chemother*. 2000;46: 775–784.
102. Rubinstein E, Prokocimer P, Talbot GH. Safety and tolerability of quinupristin/dalfopristin: administration guidelines. *J Antimicrob Chemother*. 1999;44:37–46.
103. Winston DJ, Emmanouilides C, Kroeber A, et al. Quinupristin/dalfopristin therapy for infections due to vancomycin-resistant *Enterococcus faecium*. *Clin Infect Dis*. 2000;30:790–797.
104. Garey KW, Tesoro E, Muggia V, et al. Cerebrospinal fluid concentrations of quinupristin-dalfopristin in a patient with vancomycin-resistant *Enterococcus faecium* [correction of *faecalis*] ventriculitis. *Pharmacotherapy*. 2001;21:748–750.
105. Fagon J, Patrick H, Haas DW, et al. Treatment of gram positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial pneumonia group. *Am J Respir Crit Care Med*. 2000;161:753–762.