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

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• Gram positive bacteria • Vancomycin • Daptomycin
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VANCOMYCIN

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

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

Mechanism of Action

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

Antimicrobial Activity

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

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

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

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

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

Pharmacokinetics, Dosing, and Administration

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

except for cases in which the meninges are inflamed, in cases in which cerebrospinal fluid concentrations range from 7% to 21% of concomitant serum levels.[10–12] The bone-to-serum ratio of vancomycin concentration is 10%, which increases to 20% to 30% in infected bone.[13] Relatively poor penetration of vancomycin into respiratory secretions (eg, epithelial lining fluid) is reported (25% of plasma concentrations in pneumonia), in part as a function of high protein binding (50%–60%).[14]

Vancomycin retains activity at a pH between 6.5 and 8, and concentrations achieved in abscess fluid approach those obtained in serum.[15,16] Vancomycin is eliminated by glomerular filtration, with 80% to 90% of an administered dose appearing in the urine within 24 hours. The serum half-life in adults who have normal renal function is 4 to 8 hours after intravenous injection.[11] Several nomograms exist for initiating vancomycin dosing and adjusting dosage in renal insufficiency.[17,18] However, because nomograms assume a fixed volume of distribution and wide variations can occur, serum levels should be monitored. Desired peak and trough levels have traditionally ranged from 30 to 40 μg/mL and 5 to 10 μg/mL, respectively; however, numerous recent guidelines advocate higher desired trough levels of from 15 to 20 μg/mL.[19–21] Unfortunately, there are limited human data that document superior efficacy for vancomycin or the possibility that increases in trough levels can result in increased toxicity. Vancomycin has an alpha-phase (mostly distribution) half-life of 30 minutes; therefore, if peaks are drawn, the samples should be collected approximately 1 hour postinfusion, using a 1-hour infusion.

Unlike previous recommendations of 1 g every 12 hours as a standard initiation dose, typical adult dosing is now highly variable as a result of variation in desired target trough concentrations. Vancomycin dosages should be calculated using actual body weight[21]; however, caution should be used for individuals weighing more than 120 kg. Elderly patients might only require 1 g every 24 hours, whereas younger patients might require 1.5 g every 8 hours or more to achieve serum trough concentrations of 15 to 20 μg/mL, depending on renal function and weight. Additionally, using loading doses (eg, 25 mg/kg) may also be helpful in quickly achieving desired trough levels that may prevent elevations in MRSA MICs, or tolerance, from occurring during therapy.[22] Although the AUC/MIC ratio is now considered the most predictive pharmacodynamic parameter for vancomycin, (specifically a target AUC/MIC ratio of $\geq$400), the ratio's clinical utility does not appear practical.[21] Continuous infusion regimens do not appear to offer any therapeutic advantage.[20] Regardless of the dosing interval selected, critically ill patients should have their trough concentrations measured within the first day of therapy, even if the levels are not believed to be at steady state, to ensure that adequate levels are achieved quickly. Determining trough serum vancomycin concentrations is the most practical and accurate method for monitoring vancomycin effectiveness.[21] The recommended intravenous dosing schedules for pediatric patients vary according to age and site of infection.[23] In newborns, vancomycin is given at a dosage of 15 mg/kg every 12 hours for the first week of life, or every 8 hours in newborns 8 to 30 days of age; 10–15 mg/kg every 6 hours is recommended for older infants and children. For central nervous system infections, 15 mg/kg every 6 hours is recommended. The volume of distribution is increased and the elimination phase is prolonged in adults compared with children.

Vancomycin cannot be administered intramuscularly because it causes severe pain at the injection site. Orally administered vancomycin is poorly absorbed from the gastrointestinal tract. However, patients who have renal impairment and inflamed bowel can have significant absorption.[24] The oral drug in a dosage of 125 to 500 mg every 6 hours is used to treat *C difficile* enterocolitis, with stool concentrations of vancomycin ranging from 100 to 800 μg/g for the 125-mg dose.[25] Vancomycin is

rapidly absorbed into the general circulation after intraperitoneal administration and can be used to treat gram-positive bacterial infections related to continuous ambulatory peritoneal dialysis (CAPD). Therapeutic serum levels of vancomycin are attainable using this method.[26]

Hemodialytic removal of vancomycin depends on a variety of factors, including the filter being used, the flow rates, and the time on the dialysis circuit.[27] With the advent of high-flux filters, previous recommendations regarding vancomycin dosages of just 500 mg every week[5] may be outdated. Some patients now require 1 g of vancomycin after each dialysis session. Dosing recommendations at institutions should be individualized, and therapeutic drug monitoring should be used. Care should be taken so that levels are not obtained too soon after dialysis to avoid misinterpreting falsely low vancomycin levels. In such settings, falsely low vancomycin levels result from drug redistribution from tissues back into the serum after rapid removal of the drug in the serum during dialysis.[27]

Clinical Indications

Vancomycin is the drug of choice for methicillin-resistant strains of coagulase-negative and coagulase-positive staphylococcal infections, including bacteremia, endocarditis, pneumonia, cellulitis, and osteomyelitis.[15,28] For patients who are allergic to semisynthetic penicillins or cephalosporins, vancomycin is an alternative for methicillin-susceptible staphylococcal infections. However, in cases of serious infections caused by methicillin-susceptible organisms such as endocarditis, vancomycin may be less effective than semisynthetic antistaphylococcal penicillins[29] and should not be used for convenience alone. Some methicillin-susceptible strains that are deficient in autolysins may be tolerant to vancomycin, in which case the addition of gentamicin, rifampin, or both should be considered.

Vancomycin should be combined with gentamicin, rifampin, or both agents when treating prosthetic-device-related *Staphylococcus epidermidis* infections because cure rates are improved by using such combinations.[8] Foreign bodies may need to be removed if the patient has not responded to antibiotics or if infection relapses. *Staphylococcus epidermidis* infections of long-term intravenous catheters can usually be cured without removal of the device. Administration of the antibiotic should be rotated to alternating lumens in the case of multilumen catheters. Central nervous system shunt infections can often be treated using a combination of intravenous and intraventricular vancomycin, but in some cases, removal of the foreign body is necessary.[30] Vancomycin can be given intrathecally or intraventricularly at dosages of 3 to 5 mg per day in children if necessary.[31] In adults higher daily doses of 10 to 20 mg are needed.

Vancomycin is also the drug of choice for infections caused by penicillin-resistant streptococci, *Corynebacterium* group jeikeium, *Bacillus* spp, and penicillin-resistant enterococci. Accordingly, given the recent increased frequency of penicillin-resistant pneumococcal disease, vancomycin is now recommended as initial therapy for cases of proved, suspected, or possible pneumococcal meningitis, in combination with a third-generation cephalosporin, until susceptibility data are available. In cases of serious enterococcal infections, vancomycin should be combined with an aminoglycoside (gentamicin or streptomycin) unless high-level aminoglycoside resistance (MIC > 500 or 2000 μg/mL, respectively) is present.

In the treatment of *C difficile* enterocolitis, the use of oral vancomycin should be reserved for patients who do not respond to therapy using metronidazole, for patients who have severe, life-threatening infections, for patients who cannot tolerate metronidazole, and for those who have relapsing disease and who require long courses or multiple repeated courses of therapy. Although vancomycin has the advantages of

poor systemic absorption and fewer side effects, concern about the emergence of VRE isolates should limit its use to treat this condition. If oral vancomycin is used, it should not be combined with cholestyramine because that agent binds vancomycin.

Resistance

VRE are becoming an alarming problem. In all National Nosocomial Infections Surveillance System–participating hospitals, resistance frequency has increased, regardless of the hospital's size or teaching affiliation.[32,33] The VanA phenotype (vancomycin MIC > 256, teicoplanin resistant) is encoded by a gene located on a plasmid that is easily transferable to other enterococci using conjugation. The VanB phenotype is also transferable, and it codes for vancomycin resistance; however, these isolates retain susceptibility to teicoplanin. The transfer to and expression of enterococcal vancomycin-resistant genes in *Staphylococcus aureus* has been accomplished in the laboratory,[34] heightening concern that widespread vancomycin resistance in staphylococci will eventually emerge. The use of vancomycin and cephalosporin is a well-recognized risk factor for infection by VRE.[35] Thus, any program to control resistance must consider reducing unnecessary use of these antibiotics.

Reports to the US Centers for Disease Control and Prevention of glycopeptide-resistant enterococci (GRE) indicate an increase of more than 25 fold in the prevalence of GRE between 1989 and 1993.[28] The proportion of health care–associated GRE infections in intensive care units rose to 14%; although *E faecalis* is isolated at about four times the frequency of *E faecium*, the latter is responsible for most episodes of GRE.[28] Huycke and colleagues[28] reported that although vancomycin resistance varied between 1.3% and 2.3% between the years 1995 and 1997 in cases of *E faecalis* infection, resistance increased from 28% to 52% in *E faecium* during the same period. Although carriage of these organisms by health care professionals has been described, most infections arise from the patient's own flora. As could be expected, vancomycin use is believed to contribute to the increase in GRE[36]; however, the use of other antibiotics, such as third-generation cephalosporins, also has contributed to GRE selection.[37] Additional factors associated with the emergence of GRE are shown in **Box 1**.

Selection pressure by overuse of vancomycin can be enormous. Ena and colleagues[39] described a 20-fold increase in the use of vancomycin between 1981 and 1991 in a 900-bed university teaching hospital. In only one-third of cases was

Box 1
Factors associated with emergence of glycopeptide-resistant enterococci[38]

1. Current or recent vancomycin use
2. Gastrointestinal tract colonization by GRE
3. Duration of hospital stay
4. Proximity to patients who are infected by GRE
5. Intrahospital transfer of patients between wards or floors
6. Prior use of certain broad spectrum antimicrobials (antianaerobes).
7. Location in an intensive care unit
8. Hemodialysis, ventilator, catheter, and other invasive device use.
9. Large hospital size
10. Intra-abdominal surgery.

vancomycin used for specific culture-directed therapy. The remainder of the cases were divided between prophylactic use and empiric therapy. In addition, the authors found a failure to make adjustments in therapy in the majority of cases in which vancomycin use for prophylactic or empiric reasons was initiated. Strong efforts should be made to control vancomycin use in all medical centers, as recommended by the US Centers for Disease Control and Prevention report from the Hospital Infection Control Practices Advisory Committee.[38]

Methicillin-resistant *Staphylococcus epidermidis* infections that are clinically unresponsive to vancomycin therapy have been described. One such infection occurred in a patient who was treated using vancomycin for more than two months for CAPD-associated peritonitis.[40] Heterogeneous resistance was found, with an MIC range to vancomycin of 2 to 16 μg/mL. Population analysis showed some colonies that had vancomycin MICs of 25 to 50 μg/mL.

An analysis of a large surveillance database of 35,458 *Staphylococcus aureus* strains by Jones[41] found that the MIC required to inhibit the growth of 90% of organisms (MIC_{90}) for vancomycin is 1 μg/mL. Some researchers are reporting that a greater percentage of their MRSA isolates have elevated MICs to vancomycin but are still within the susceptible range, a phenomenon known as MIC creep.[41,42] The most alarming aspect of these findings is that infections caused by MRSA that have vancomycin MICs of 2 μg/mL have worse surrogate outcomes.[43,44] Recently, a study showed that after adjusting for a number of variables, mortality was also worse in the elevated MIC group.[45] These reports have formed the basis for consensus recommendations that trough serum concentrations should always be maintained at greater than 10 μg/mL to avoid the development of resistance and possibly improve clinical outcome.[21] Accordingly, total trough serum vancomycin concentrations of 15 to 20 μg/mL are recommended.[21] Unfortunately, there is also a lack of data on antibiotic therapy that is superior to vancomycin for these infections. One center reported the emergence of daptomycin-nonsusceptible isolates when patients were switched to daptomycin as a result of elevated vancomycin MICs.[46] Patients in that report had a mean duration of vancomycin therapy of 4 days prior to switching to daptomycin, which may have contributed to the development of daptomycin-nonsusceptible isolates.

Glycopeptide-intermediate-resistant *Staphylococcus aureus* (GISA) was first described in Japan in May 1996, in a child who had an MRSA wound infection that was clinically unresponsive to vancomycin.[47–49] According to the National Committee for Clinical Laboratory Standards, vancomycin-susceptible strains of *Staphylococcus aureus* have MICs of 2 μg/mL or less, GISA strains of 4 to 8 μg/mL, and resistant strains of 16 μg/mL or greater.[50]

Strains of apparently vancomycin-susceptible MRSA have also been detected that display subpopulations that have reduced sensitivity to vancomycin; they have been termed heterogeneous heteroresistant, vancomycin-intermediate *Staphylococcus aureus* (hVISA). Similar to cases of infection by MRSA that have MICs of 2 μg/mL to vancomycin, poor outcomes have been reported.[51] In some centers, rates of hVISA have been steadily rising since 1986, to as high as 8.3% between 2003 and 2007. However, there seems to be a lack of correlation between the trends for hVISA and vancomycin-intermediate *Staphylococcus aureus* (VISA) because the same researchers noted that the lowest rates of VISA, at 0.3%, were detected during the period from 2003 to 2007, which was down from 2.3% in the period preceding it.[52] Because this analysis was done retrospectively and vancomycin had been used as a mainstay of therapy in the hospitals reporting these results, it is unclear whether continued vancomycin use to treat infections caused by hVISA will promote the formation of VISA.

In 2002, the first naturally occurring vancomycin-resistant *Staphylococcus aureus* (VRSA) infection was described in a patient who had a nonhealing foot wound and who was receiving long-term hemodialysis in Michigan at an outpatient dialysis center.[53] Approximately 1 month later, an independent second case of VRSA was reported in an outpatient in Pennsylvania who also had nonhealing foot wounds.[54] Upon further analysis, it was determined that the VRSA from the Michigan patient carried the VanA gene coding for high-level vancomycin resistance and was most likely acquired from coexisting *E faecalis* present in the foot wound.[53] The first patient was cured of VRSA using a combination of antibiotic therapy (trimethoprim and sulfamethoxazole) and aggressive foot care.[53] The second patient was transiently colonized and did not require antimicrobial treatment. Common to both patients were repeated infections by *Staphylococcus aureus* and enterococci. An extensive contact tracing failed to show any spread beyond the index cases. However, if spread had occurred, the public health consequences of these difficult-to-treat, gram-positive infections would have been enormous.

Toxicity and Adverse Reactions

The ''red man'' syndrome is a nonimmunologically mediated histamine release associated with rapid infusion of vancomycin. Clinical signs and symptoms include pruritis, erythema and flushing of the upper torso, angioedema, and occasionally, hypotension. Slow administration (for at least 1 hour) and the administration of prophylactic antihistamines given two hours prior to infusion can protect against the development of this side effect.[55] A rapid bolus of vancomycin can also result in muscle spasms of the chest and back, which is known as the ''pain and spasm'' syndrome. Ototoxicity, which may continue to progress after discontinuation of therapy, may occur when serum levels of vancomycin are excessively high but rarely occurs when peak serum levels are 40 to 50 μg/mL or less. Deafness may be proceeded by tinnitus and high-tone hearing loss. Nephrotoxicity is similarly rare when vancomycin is used alone and at conventional dosages (eg, 1 g every 12 hours). Ototoxicity and nephrotoxicity may be potentiated when vancomycin and aminoglycosides are used in combination.[56] A recent retrospective report called into question the use of higher doses of vancomycin in light of the higher rates of nephrotoxicity seen in patients who received 4 g or more of vancomycin.[57] Care should be used when extrapolating these data because there may have been an unseen selection bias of giving patients higher doses of vancomycin when they were perceived by a clinician as having a more severe disease state, and the patients' underlying condition may have also contributed to the perceived toxicity.

Vancomycin-induced neutropenia is dose- and time-dependent, rare, and reversible after the drug is discontinued. It typically occurs when the duration of therapy exceeds 14 days.[58] Skin rash and drug fever occur in 4% to 5% of patients.[59]

TEICOPLANIN

Teicoplanin is a glycopeptide antibiotic with activity similar to that of vancomycin.[60] It is not commercially available in the United States.

QUINUPRISTIN/DALFOPRISTIN (SYNERCID)

Quinupristin-dalfopristin is a combination of two naturally occurring compounds isolated from *Streptomyces pristinaspiralis*.[61] This streptogramin class is water soluble[62] and contains quinupristin and dalfopristin in a 30:70 weight/weight ratio.[63]

Mechanism of Action

Quinupristin-dalfopristin exerts its activity through the inhibition of protein synthesis. Quinupristin and dalfopristin sequentially bind to different sites on the 50S ribosome, resulting in a stable, ternary drug-ribosome complex and interfering with different targets of 23S RNA. Newly synthesized peptide chains cannot be extruded from this complex.[61,64]

Pharmacokinetics, Dosing, and Administration

Quinupristin and dalfopristin are metabolized quickly after intravenous administration. Neither component is extensively protein bound. The recommended dosage is 7.5 mg/kg every 8 hours by the intravenous route for infections by VRE. The interval may be lengthened to every 12 hours for complicated skin and skin structure infections. There are no adjustments necessary for renal or hepatic impairment.[61] The combination has a postantibiotic effect for 6 to 8 hours. High intracellular concentrations are seen.[65] Excretion is primarily by way of the biliary tract. The drug combination is a potent inhibitor of the cytochrome P450 enzymes, with the potential for drug interactions.

Clinical Activity

The spectrum of activity of quinupristin-dalfopristin is similar to that of vancomycin. In a study of nearly 30,000 clinical isolates in the United States, susceptibility was seen for 97.7% of *Streptococcus pneumoniae* (including penicillin-resistant isolates), 97% of other streptococcal spp, 99% to 99.9% of *Staphylococcus aureus*, and 98% to 100% of coagulase-negative staphylococci. *E faecium* susceptibility varied by participating study region.[63] Overall, 0.2% of *E faecium* isolates were resistant to quinupristin/dalfopristin, with MICs greater than 4 μg/mL. The drug has no activity against *E faecalis*. It is bacteriostatic for *E faecium* and *Legionella* spp.[65] Gram-negative anaerobes such as *Fusobacterium* spp and *Bacteroides* spp are also susceptible.[61] VRSA isolates retained susceptibility to quinupristin-dalfopristin. In a study of 274 South African enterococcal isolates, 19.7% of *E faecium* strains were resistant. *Staphylococcus aureus* MICs were similar to those for vancomycin.[66] The main use for quinupristin-dalfopristin is in the treatment of vancomycin-resistant *E faecium*, and potentially for the treatment of GISA and VRSA. One case of successful therapy for VRE *faecium* prosthetic valve endocarditis has been described.[67]Superinfection by *E faecalis* during therapy has also been described.[68]

Resistance

Resistance may develop as the result of decreased ribosomal binding of either component, through enzymatic modification, or through efflux mechanisms and altered target.[61,69] A patient who developed quinupristin-dalfopristin–resistant *E faecium* bacteremia while receiving therapy using quinupristin-dalfopristin has been described.[70] In addition to clinical failures, resistant isolates have been recovered from human stool samples.[69] No cross-resistance to other currently available antimicrobials occurs. When used in combination with doxycycline, resistance to the streptogramin may be prevented.[71]

Toxicity and Adverse Events

Side effects of quinupristin-dalfopristin include venous irritation and elevation of conjugated bilirubin. The most troublesome side effect seen is the development of arthralgias and myalgias, which can be severe.

OXAZOLIDINONES

The oxazolidinones are a synthetic class of antimicrobial agents that were discovered in 1987. Although there are a number compounds in development, linezolid is the only commercially available product.

Mechanism of Action

Linezolid exerts its effect early in protein synthesis by inhibiting the initiation complex at the 30S ribosome.[72,73] The agent interacts with a translational component that is either directly or indirectly involved in binding mRNA during the start of translation.[73] Because of this unique action, no cross-resistance with other currently available antimicrobials occurs.

Antimicrobial Activity

The antimicrobial spectrum of the oxazolidinones is similar to that of vancomycin, with activity against most gram-positive organisms, including MRSA and penicillin-resistant pneumococci.[74,75] The compounds also have activity against gram-negative anaerobes and mycobacteria.[75] They are bacteriostatic for enterococci and staphylococci, but bactericidal for *Streptococcus pyogenes* and *Bacteroides fragilis*.[76]

Pharmacokinetics, Dosing, and Administration

Maximum peak plasma levels are achieved within 1 to 2 hours after administration. Linezolid has 100% oral bioavailability.[77,78] Linezolid differs from vancomycin by its enhanced penetration into respiratory secretions. Rapid penetration into bone, fat, and muscle is also reported, achieving levels of 4 μg/mL or greater in excess of the MIC of most susceptible organisms.[79] Urinary concentrations of linezolid are high, achieving bactericidal activity against urinary pathogens such as enterococci.[80] There is a short postantibiotic effect of about 1 hour; however, inhibition of virulence-factor expression by gram-positive cocci continues after exposure to subinhibitory concentrations of linezolid.[81] No synergy with aminoglycosides for gram-positive bacteria exists. Isolates of enterococci and streptococci are considered sensitive if their MICs are 2 μg/mL or less, and 4 μg/mL or less for staphylococci. The recommended dosage is 600 mg every 12 hours. The 24-hour AUC-MIC ratio is the pharmacodynamic parameter that bests predicts clinical efficacy.[9]

Clinical Indications

Although initially used to mainly treat patients who were infected by VRE, linezolid's role in treating MRSA infections has grown significantly. Linezolid is currently used for the treatment of pneumonia and skin and skin-structure infections caused by MRSA.[74,82] The high penetration of the drug into respiratory secretions is believed to contribute to linezolid being a very effective agent for the treatment of pneumonia caused by *Staphylococcus aureus* and *Streptococcus pneumoniae*.[83] A recent retrospective analysis of 339 patients who had documented *Staphylococcus aureus* pneumonia, including 160 patients who had MRSA pneumonia, suggested the superior efficacy of linezolid rather than vancomycin.[84] Additional prospective studies are required to confirm these findings. Similarly, several reports of superior activity for ceftriaxone in bacteremic pneumococcal pneumonia have appeared.[85,86]

Given the excellent bioavailability of linezolid and its activity against MRSA and methicillin-resistant, coagulase-negative staphylococci, reports have appeared of efficacy and cost-savings accompanying the early switch and early discharge of

patients who were treated using oral linezolid.[87–90] These studies, combined with the prevalence of community-acquired MRSA skin and skin-structure infections, have greatly increased the use of linezolid. It is apparent that parenteral linezolid is now being considered as a first-line therapy for multisite infections caused by MRSA organisms without vancomycin resistance. Although evidence of clinical equivalence has been published, many experts continue to reserve linezolid for vancomycin-resistant organisms, refractory infections, and vancomycin-intolerant patients.

Resistance

In gradient plate experiments, there was no increase in the MICs to linezolid upon serial passage of either MRSA or methicillin-resistant *Staphylococcus epidermidis* strains.[91–94] The previously described VRSA isolates retained susceptibility to linezolid. However, linezolid resistance has been described in enteroccci, even in patients who had no prior exposure to this novel antibiotic.[93,94] Additionally, reports of MRSA resistant to linezolid have emerged.[95]

Toxicity and Adverse Events

Increases in the levels of hepatic enzymes and creatinine can occasionally occur. Skin rash has been reported. Linezolid has the potential for monoamine oxidase inhibition. In preclinical animal studies, reversible time- and dose-dependent myelosuppression occurred, particularly thrombocytopenia. Gerson and colleagues[96] concluded that hematological abnormalities associated with linezolid use were mild and reversible and not significantly different from those of comparator drugs. Thrombocytopenia occurred in 2.2% of patients, usually after 2 weeks of therapy. Long-term use is, however, associated with an incidence of up to 10%. In a study of 686 seriously ill patients who had nosocomial pneumonia, observed in multiple intensive care units, patients treated using linezolid rarely developed thrombocytopenia, which was no more frequent than with the use of vancomycin.[97]

DAPTOMYCIN

Daptomycin is a naturally occurring cyclic lipopeptide antibiotic that is a fermentation byproduct of *Streptomyces roseosporus*.[98] It consists of a 10-membered amino acid ring with a 10-carbon decanoic acid attached to a terminal L-tryptophan.[98]

Mechanism of Action

Daptomycin is rapidly bactericidal in a novel, concentration-dependent manner. It exhibits its action by binding to the cell membrane in a calcium-dependent manner, causing depolarization of the bacterial membrane potential, resulting in the termination of bacterial DNA, RNA, and protein synthesis and the termination of intracellular potassium release, thus causing cell death.[99]

Antimicrobial Activity

The spectrum of activity includes *Staphylococcus aureus*, streptococci, and enterococcal species, including those with multidrug resistance.[100,101] This includes vancomycin-, quinupristin-dalfopristin–, and linezolid-resistant gram-positive organisms. Daptomycin also demonstrates clinical activity against vancomycin-resistant *Leuconostoc* spp.[102] Neither *Listeria* nor *Clostridium* spp are susceptible. Daptomycin in combination with gentamicin is synergistic in killing staphylococci and enterococci.[99] Data regarding the addition of rifampin have been positive or indifferent.[103]

Pharmacokinetics, Dosing, and Administration

Daptomycin is available in intravenous form. It is administered once daily and exhibits linear pharmacokinetics at doses of up to 12 mg/kg.[99] Daptomycin is highly protein bound (92%) and is excreted in the kidney as intact drug.[99] Dosage adjustment for patients who have a creatinine clearance of less than 30 mL/min is recommended. It has a postantibiotic effect that lasts for about 2.5 to 5 hours.[104] Bactericidal activity is dose-dependent. Streptococci and staphylococci are considered sensitive if the MIC is 1 μg/mL or less, and enterococci are considered sensitive when the MIC is 4 μg/mL or less.

Clinical Indications

Daptomycin is approved by the US Food and Drug Administration for the treatment of complicated skin and soft-tissue infections caused by staphylococci (methicillin-susceptible *Staphylococcus aureus* and MRSA), *Streptococcus* spp, and *E faecalis*, at a dose of 4 mg/kg/day administered intravenously. A trial was completed that led to its approval for use in *Staphylococcus aureus* bloodstream infections, including right-sided endocarditis, using daptomycin at 6 mg/kg/day.[105] In the MRSA arm (99 patients) of this trial, success rates were numerically higher but not statistically significant in favor of daptomycin rather than the comparator vancomycin with 4 days of gentamicin. The toxicity of daptomycin was less than that of the vancomycin-gentamicin combination. Among patients who had treatment failure, six daptomycin-treated patients and one vancomycin-gentamicin–treated patient developed reduced susceptibility to their primary therapy. The length of bacteremia infection was similar between the two groups. Patients should not be treated using daptomycin for pneumonia because the drug binds to surfactant, inhibiting its activity.

Resistance

VRSA and VRE isolates are susceptible to daptomycin. However, some hVISA and VISA isolates have shown reduced susceptibility to daptomycin without previous exposure to daptomycin but with exposure to vancomycin.[106–108] Resistance in MRSA has rarely been reported. However, only recently have the various automated systems used by many hospitals incorporated daptomycin into standard panels. One health system recently reported reduced susceptibility to daptomycin for MRSA isolates.[109] All of the isolates that showed reduced susceptibility had vancomycin MICs of 2 μg/mL. The correlation of MRSA with reduced susceptibility to vancomycin and reduced cross-susceptibility to daptomycin requires further study.

Toxicity and Adverse Events

Two major causes of toxicity for daptomycin are elevated levels of creatine phosphokinase and myopathy, both of which resolve after discontinuation of the drug. Weekly monitoring of creatine phosphokinase values during daptomycin therapy and discontinuation if creatine phosphokinase elevation is 5 times the upper limit of normal or greater is recommended. These effects are more common when divided doses are used compared with once-daily dosing.[110] Constipation and other gastrointestinal side effects have also been noted to occur.

DALBAVANCIN AND TELAVANCIN

Dalbavancin and telavancin are two new antimicrobial agents that are structurally and mechanistically related to vancomycin. Neither agent is currently licensed by the US Food and Drug Administration. Their respective spectrums of activity are similar to

those of vancomycin, with the most notable exception being that these two agents have lower MICs against MRSA isolates, with MICs of 2 μg/mL to vancomycin and to VISA isolates. Both agents also have lower MICs to VRE isolates, but the MICs are considerably higher for non–vancomycin-resistant isolates. Both agents have longer half-lives than vancomycin, which allows for simpler dosing regimens. In clinical trials, dalbavancin has been tested using once-weekly infusions, whereas telavancin has been studied using daily infusions. Studies have been completed that used both agents for the treatment of skin and soft-tissue infections. If approved by the Food and Drug Administration, the clinical role for both agents will likely be in the treatment of infections caused by *Staphylococcus aureus* that have reduced susceptibility to vancomycin or to simplify the intravenous regimens for patients who are being discharged and will receive long-term outpatient antimicrobial therapy.[111–114]

SUMMARY

Gram-positive bacteria have shown a propensity to develop resistance to all of the available antibiotics in use. Additionally, the superiority data for any one agent rather than another is lacking, with the possible exception of linezolid, rather than vancomycin, for the treatment of MRSA pneumonia. Selecting the appropriate therapy is also complicated by differences in local susceptibility patterns, particularly as they relate to diminished susceptibility to vancomycin and daptomycin, site of infection, propensity to induce resistance, toxicity, dosage form availability, and only if the proceeding factors are similar, costs. Despite the increasing prevalence of gram-positive infections, judicious use of these agents and strict infection-control practices to preserve the activity of these agents is warranted.

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