**Cell wall inhibitors**

**Overview**

Some antimicrobial drugs selectively interfere with synthesis of the Bacterial cell walla structure that mammalian cells do not possess. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links. To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms; they have little or no effect on bacteria that are not growing and dividing. The most important members of this group of drugs are the Beta-lactam antibiotics (named after the β-lactam ring that is essential to their activity) and *vancomycin*. Figure 31.1 shows the classification of agents affecting cell wall synthesis

2. **PENICILLINS**

The penicillins are among the most widely effective and the least toxic drugs known, but increased resistance has limited their use. Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue (Figure 31.2). The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, cross-hypersensitivity, and susceptibility to bacterial degradative enzymes (Beta-lactamases).

1. **Mechanism of action**

The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins. These drugs are thus bactericidal. The success of a penicillin antibiotic in causing cell death is related to the antibiotic’s size, charge, and hydrophobicity. Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall. Consequently, they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses.

1. **Penicillin-binding proteins:** Penicillins inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium. Exposure to these antibiotics can therefore not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria. The number of PBPs varies with the type of organism. Alterations in some of these target molecules provide the organism with resistance to the penicillins. [Note: *Methicillin* resistant Staphylococcus aureus (MRSA) arose because of such an

alteration.]

**2. Inhibition of transpeptidase:** Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains (Figure 31.3). Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity. As a result of this blockade of cell wall synthesis, the “Park nucleotide” (formerly called the “Park peptide”), UDP-acetylmuramyl-L-Ala-DGln- L-Lys-D-Ala-D-Ala, accumulates.

**3. Production of autolysins:** Many bacteria, particularly the grampositive cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall. In the presence of a penicillin, the degradative action of the autolysins proceeds in the absence of cell wall synthesis. Thus, the antibacterial eff ect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysins.

**B. Antibacterial spectrum**

The antibacterial spectrum of the various penicillins is determined, in part, by their ability to cross the bacterial peptidoglycan cell wall to reach the PBPs in the periplasmic space. Factors that determine the susceptibility of PBPs to these antibiotics include the size, charge, and hydrophobicity of the particular β-lactam antibiotic. In general, grampositive microorganisms have cell walls that are easily traversed by penicillins and, therefore, in the absence of resistance are susceptible to these drugs.Gram-negative micro organisms have an outer lipopolysaccharide membrane (envelope) surrounding the cell wall that presents a barrier to the water-soluble penicillins. However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-fi lled channels (called porins) to permit transmembrane entry. [Note: Pseudomonas aeruginosa has restrictive porins, making this organism intrinsically resistant to many antimicrobial agents.]

**1. Natural penicillins:** These penicillins, which include those classifi ed as antistaphylococcal, are obtained from fermentations of the mold Penicillium chrysogenum. Other penicillins, such as *ampicillin*, are called semisynthetic, because the diff erent R groups are attached chemically to the 6-aminopenicillanic acid nucleus obtained from fermentation broths of the mold. *Penicillin* [pen-i-SILL-in] *G* (*benzylpenicillin*) is the cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes (Figure 31.4). Penicillins are susceptible to inactivation by β-lactamases (penicillinases). *Penicillin V* has a spectrum similar to that of *penicillin G*, but it is not used for treatment of bacteremia because of its poor absorption. *Penicillin V* is more acidstable than *penicillin G* and is often employed orally in the treatment of infections.

**2. Antistaphylococcal penicillins:** *Methicillin* [meth-i-SILL-in], *nafcillin* [naf-SILL-in], *oxacillin* [ox-a-SILL-in], and *dicloxacillin* [dye-klox-a- SILL-in] are penicillinase-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including methicillin sensitive S. aureus (MSSA). [Note: Because of its toxicity (interstitial nephritis), *methicillin* is not used clinically except to identify resistant strains of S. aureus]. *Methicillin* resistant Staphylococcus aureus (MRSA) is currently a source of serious community and nosocomial (hospital-acquired) infections and is resistant to all commercially available β-lactam antibiotics, including antistaphylococcal penicillins. This organism is usually susceptible to glycopeptide *vancomycin.* The penicillinase-resistant penicillins have no activity versus gram-negative infections.

**3. Extended-spectrum penicillins:** *Ampicillin* [am-pi-SILL-in] and *amoxicillin* [a-mox-i-SILL-in] have an antibacterial spectrum similar to that of *penicillin G* but are more eff ective against gram-negative bacilli. Therefore, they are referred to as extended-spectrum penicillins (Figure 31.5A). *Ampicillin* (with or without the addition of *gentamicin*) is the drug of choice for the gram-positive bacillus Listeria monocytogenes and susceptible Enterococcal species. These extended-spectrum agents are also widely used in the treatment of respiratory infections, and *amoxicillin* is employed prophylactically by dentists for patients with abnormal heart valves who are to undergo extensive oral surgery. Resistance to these antibiotics is a major clinical problem because of inactivation by plasmidmediated

penicillinases. [Note: Escherichia coli and Haemophilus infl uenzae are frequently resistant.] Formulation with a β-lactamase inhibitor, such as *clavulanic acid* or *sulbactam*, protects *amoxicillin* or *ampicillin*, respectively, from enzymatic hydrolysis and extends their antimicrobial spectrum. For example, without the β-lactamase inhibitor, MSSA is resistant to *ampicillin* and *amoxicillin*.

**4. Antipseudomonal penicillins:** *Carbenicillin* [kar-ben-i-SILL-in], *ticarcillin* [tye-kar-SILL-in], and *piperacillin* [pip-er-a-SILL-in] are called antipseudomonal penicillins because of their activity against P. aeruginosa (Figure 31.5B). *Piperacillin* is the most potent of these antibiotics. They are eff ective against many gram-negative bacilli, but not against *Klebsiella* because of its constitutive penicillinase. Formulation of *ticarcillin* or *piperacillin* with *clavulanic acid* or *tazobactam*, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms. (Figure 31.6 summarizes of the stability of the penicillins to acid or the action of penicillinase.)

**5. Penicillins and aminoglycosides:** The antibacterial eff ects of all β-lactam antibiotics are synergistic with the aminoglycosides. Because cell wall synthesis inhibitors alter the permeability of bacterial cells, these drugs can facilitate the entry of other antibiotics (such as aminoglycosides) that might not ordinarily gain access to intracellular target sites. This can result in enhanced antimicrobial activity. [Note: Although the combination of a penicillin plus an aminoglycoside is used clinically, these drug types should never be placed in the same infusion fl uid because on prolonged contact, the positively charged aminoglycosides form an inactive complex withthe negatively charged penicillins.]

**C. Resistance**

Natural resistance to the penicillins occurs in organisms that either lack a peptidoglycan cell wall (for example, mycoplasma) or have cell walls that are impermeable to the drugs. Acquired resistance to the penicillins by plasmid transfer has become a significant clinical problem. Organisms may become resistant to several antibiotics at the same time due to acquisition of a plasmid that encodes resistance to multiple agents. Multiplication of such an organism will lead to increased dissemination of the resistance genes. By obtaining a resistance plasmid, bacteria may acquire one or more of the following properties, thus allowing it to withstand β-lactam antibiotics.

**1. β-Lactamase activity:** This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity (see Figure 31.2). They are the major cause of resistance to the penicillins and are an increasing problem. β-Lactamases are either constitutive or, more commonly, are acquired by the transfer of plasmids. Some of the β-lactam antibiotics are poor substrates for β-lactamases and resist hydrolysis, thus retaining their activity against β-lactamase producing organisms. [Note: Certain organisms may have chromosome-associated β-lactamases that are inducible by β-lactam antibiotics (for example, third and second generation cephalosporins).] Gram-positive organisms secrete β-lactamases extracellularly, whereas gram-negative bacteria confine the enzymes in the periplasmic space between the inner and outer membranes.

**2. Decreased permeability to the drug:** Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs. The presence of an efflux pump can also reduce the amount of intracellular drug.

**3. Altered PBPs:** Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This explains MRSA resistance to commercially available β-lactams.

**D. Pharmacokinetics**

**1. Administration:** The route of administration of a β-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.

**a. Routes of administration:** *Ticarcillin*, *piperacillin*, and the combinations of *ampicillin* with *sulbactam*, *ticarcillin* with *clavulanic acid*, and *piperacillin* with *tazobactam,* must be administered intravenously (IV) or intramuscularly (IM). *PenicillinV*, *amoxicillin*, and *amoxicillin* combined with *clavulanic acid* are available only as oral preparations. Others are effective by the oral, IV, or IM routes (see Figure 31.6).

**b. Depot forms:** *Procaine penicillin G* and *benzathine penicillin G* are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

**2. Absorption:** Most of the penicillins are incompletely absorbed afteroral administration, and they reach the intestine in sufficient amounts to aff ect the composition of the intestinal flora. However, *amoxicillin* is almost completely absorbed. Consequently, it is not appropriate therapy for the treatment of Shigella- or Salmonella-derived enteritis, because therapeutically effective levels do not reach the organisms in the intestinal crypts. Absorption of all the penicillinase-resistant penicillins is decreased by food in the stomach, because gastric emptying time is lengthened, and the drugs are destroyed in the acidic environment. Therefore, they must be administered 30 to 60 minutes before meals or 2 to 3 hours postprandial. Other penicillins are less affected by food.

**3. Distribution:** The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none has been shown to be teratogenic. However, penetration into certain sites, such as bone or cerebrospinal fluid (CSF), is insufficient for therapy unless these sites are inflamed (Figures 31.7 and 31.8). [Note: During the acute phase of infection, the inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the amount of drug in the central nervous system compared to the amount in the serum. As the infection abates, inflammation subsides, and permeability barriers are re-established in the meninges.] *Penicillin* levels in the prostate are insufficient to be effective against infections.

**4. Metabolism:** Host metabolism of the β-lactam antibiotics is usually insignificant, but some metabolism of *penicillin G* has been shown to occur in patients with impaired renal function.

**5. Excretion:** The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular fi ltration. Patients with impaired renal function must have dosage regimens adjusted. Thus, the half-life of *penicillin G* can increase in the

presence of renal dysfunction. *Probenecid* inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. *Nafcillin*, *dicloxacillin* and *oxacillin* are exceptions to the rule and are not eliminated by the kidneys. The penicillins are also excreted into breast milk.

**E. Adverse reactions**

Penicillins are among the safest drugs, and blood levels are not moni- tored. However, the following adverse reactions may occur (Figure 31.9).

**1. Hypersensitivity**: This is the most important adverse effect of the penicillins. The major antigenic determinant of penicillin hypersen- sitivity is its metabolite, penicilloic acid, which reacts with proteins and serves as a hapten to cause an immune reaction. Approximately five percent of patients have some kind of reaction, ranging from maculopapular rash (the most common rash seen with ampicil- lin hypersensitivity) to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Among patients with mononucleosis who are treated with ampicillin, the incidence of maculopapular rash approaches 100 percent. Cross-allergic reac- tions occur among the β-lactam antibiotics. To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.

**2. Diarrhea**: This effect, which is caused by a disruption of the nor- mal balance of intestinal microorganisms, is a common problem. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. As with most antibiotics, pseudomembranous colitis may occur.

**3. Nephritis**: All penicillins, but particularly methicillin, have the potential to cause acute interstitial nephritis. [Note: Methicillin is therefore no longer available.]

**4. Neurotoxicity**: The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk. When indicated, dosage adjustments for patients with renal dys- function further minimize the risk for seizure.

**5. Hematologic toxicities**: Decreased coagulation may be observed with high doses of piperacillin, ticarcillin and nafcillin (and, to some extent, with penicillin G). It is generally a concern when treating patients who are predisposed to hemorrhage (for example, uremics) or those receiving anticoagulants. Cytopenias may occur, but are associated with greater than 2 weeks of therapy. For this reason, a CBC should be monitored weekly for such patients. An additional toxicity is eosinophilia.

**6. Cation toxicity**: Penicillins are generally administered as the sodium or potassium salt. Toxicities may be caused by the large quantities of sodium or potassium that accompany the penicillin. For example, sodium excess may result in hypokalemia. This can be avoided by using the most potent antibiotic, which permits lower doses of drug and accompanying cations. Treatment with aqueous penicillin G has a high potassium load, which must be taken into account while monitoring electrolytes. The same is true for ticarcillin which has a high sodium load.

**III. CEPHALOSPORINS**

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins. Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid. Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be more resistant than the penicillins to Certain β-lactamases.

**A. Antibacterial spectrum** Cephalosporins have been classified as first, second, third, and fourth generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases (Figure 31.10). [Note: Commercially available cephalosporins are ineffective against MRSA, L. monocytogenes,

Clostridium difficile, and the enterococci.]

**1. First generation:** The first-generation cephalosporins act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase (that is, they cover MSSA) and also have activity against Proteusmirabilis, E. coli, and Klebsiella pneumoniae (the acronym PEcK hasbeen suggested).

**2. Second generation:** The second-generation cephalosporins Display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker (the acronym HENPEcK has been suggested with the second generation’s increased coverage). Antimicrobial coverage of *cefotetan* and *cefoxitin* also includes the anaerobe, Bacteroides fragilis. However, neither *cefotetan* nor *cefoxitin* is the preferred treatment because of the increasing prevalence of resistance amongst B. fragilis to both agents.

**3. Third generation:** These cephalosporins have assumed an important role in the treatment of infectious diseases. Although inferior to first-generation cephalosporins in regard to their activity against MSSA, the third generation cephalosporins have enhanced activity against gram-negative bacilli, including those mentioned above, as well as most other enteric organisms plus Serratia marcescens. *Ceftriaxone* [sef-trye-AKS-own] and *cefotaxime* [sef-oh-TAKS-eem] have become agents of choice in the treatment of meningitis. *Ceftazidime* [sef-TA-zi-deem] has activity against P. aeruginosa, however, resistance is increasing and appropriate use should be evaluated on a case-by-case basis. Third generation cephalosporins must be used with caution, as they are associated with "collateral damage," essentially meaning the induction and spread of antimicrobial resistance. [Note: fluoroquinolones use is also associated with collateral damage.]

**4. Fourth generation:** *Cefepime* [SEF-eh-peem] is classified as a fourthgeneration cephalosporin and must be administered parenterally. *Cefepime* has a wide antibacterial spectrum, being active against streptococci and staphylococci (but only those that are *methicillin*susceptible). *Cefepime* is also effective against aerobic gram-negative organisms, such as Enterobacter species, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa. When selecting an antibiotic that is active against P. aeruginosa, clinicians should refer to their local antibiograms

(laboratory testing for the sensitivity of an isolated bacterial strain to different antibiotics) for direction.

**B. Resistance**

Mechanisms of bacterial resistance to the cephalosporins are essentially the same as those described for the penicillins. [Note: Although they are not susceptible to hydrolysis by the staphylococcal penicillinase, cephalosporins may be susceptible to extended-spectrum β-lactamases (ESBLs). Organisms such as E. coli and K. pneumoniae are particularly associated with ESBLs.]

**C. Pharmacokinetics**

**1. Administration:** Many of the cephalosporins must be administered IV or IM (Figure 31.11) because of their poor oral absorption. Exceptions are noted in Figure 31.12.

**2. Distribution:** All cephalosporins distribute very well into body fl uids. However, adequate therapeutic levels in the CSF, regardless of infl ammation, are achieved only with select a few cephalosporins. For example, *ceftriaxone* or *cefotaxime* is eff ective in the treatment of neonatal and childhood meningitis caused by H. infl uenzae.

*Cefazolin* [se-FA-zo-lin] fi nds application as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing S. aureus. However, additional intraoperative

*cefazolin* doses may be required if the surgical procedure lasts longer than 3 hours. *Cefazolin* is eff ective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. All cephalosporins cross the placenta.

**3. Elimination:** Biotransformation of cephalosporins by the host is not clinically important. Elimination occurs through tubular secretion and/or glomerular filtration (see Figure 31.11). Therefore doses must be adjusted in cases of severe renal failure to guard against accumulation and toxicity. An exception is *ceftriaxone* which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

**D. Adverse effects**

The cephalosporins produce a number of adverse affects, some of which are unique to particular members of the group.

**1. Allergic manifestations:** Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins should not receive cephalosporins. The cephalosporins should be avoided or used with caution in individuals who are allergic to penicillins (about 8 to 10 percent is traditionally cited to show cross-sensitivity). Current data evaluation suggests a cross-reactivity between penicillin and cephalosporins to be around 3 to 5 percentand determined by similarity in the side chain, not the b-lactam structure. The rate of highest allergic cross sensitivity is between penicillin and first generation cephalosporins.

**IV. OTHER β-LACTAM ANTIBIOTICS**

**A. Carbapenems**

Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring (see Figure 31.2) has been externalized and replaced by a carbon atom (Figure 31.13). *Imipenem* [i-mi-PEN-em], *meropenem* [mer-oh-PEN-em],

*doripenem* [dore-i-PEN-em] and *ertapenem* [er-ta-PEN-em] are the drugs of this group currently available. *Imipenem* is compounded with *cilastatin*

to protect it from metabolism by renal dehydropeptidase.

**1. Antibacterial spectrum:** *Imipenem* resists hydrolysis by most

β-lactamases, but not the metallo-β-lactamases. This drug plays a role in empiric therapy because it is active against b-lactamase-producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa (although other pseudomonal strains are resistant, and resistant strains of P. aeruginosa have been reported to arise during therapy). *Meropenem* and *doripenem* have antibacterial activity similar to that of *imipenem* (Figure 31.14). However, *ertapenem* is not an alternative for P. aeruginosa coverage because most strains exhibit resistance. *Ertapenem* also lacks coverage versus Enterococcus species and Acinetobacter species.

**2. Pharmacokinetics:** *Imipenem/cilastatin* and *meropenem* are administered

IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. They are excreted by glomerular filtration. *Imipenem* undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. This enzyme forms an inactive metabolite that is potentially nephrotoxic. Compounding the *imipenem* with *cilastatin* protects the parent drug and, thus, prevents the formation of the toxic metabolite. *Meropenem, ertapenem,* and *doripenem* do not require co-administration of *cilistatin. Ertapenem* can be administered via IV or IM injection once daily. [Note: Doses of these agents must be adjusted in patients with renal insufficiency.]

**3. Adverse effects:** *Imipenem/cilastatin* can cause nausea, vomiting, and diarrhea. Eosinophilia and neutropenia are less common than with other β-lactams. High levels of *imipenem* may provoke seizures, but *meropenem* is possibly less likely to do so. *Doripenem* has notdemonstrated any potential to cause seizures in animal studies.

**B. Monobactams**

The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the β-lactam ring is not fused to another ring (see

Figure 31.13). *Aztreonam* [az-TREE-oh-nam], which is the only commercially available monobactam, has antimicrobial activity directed primarily against the Enterobacteriaceae, including P. aeruginosa. It lacks activity against gram-positive organisms and anaerobes. This narrow antimicrobial spectrum precludes its use alone in empiric therapy (see p. 370). *Aztreonam* is resistant to the action of most β-lactamases, with the exception of the extended-spectrum β-lactamases (ESBLs). It is administered either IV or IM and can accumulate in patients with renal failure. *Aztreonam* is relatively nontoxic, but it may cause phlebitis, skin rash, and occasionally, abnormal liver function tests. This drug has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic and unable to tolerate penicillins and/or cephalosporins.

**V. β-LACTAMASE INHIBITORS**

Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic. β-Lactamase inhibitors, such as *clavulanic* [cla-vue-LAN-ick] *acid*,

*sulbactam* [sul-BACK-tam], and *tazobactam* [ta-zoh-BACK-tam], contain a β-lactam ring, but by themselves, do not have significant antibacterial activity. Instead, they bind to and inactivate β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The β-lactamase inhibitors are therefore formulated in combination with β-lactamase sensitive antibiotics. For example, Figure 31.15 shows the effect of *clavulanic acid* and *amoxicillin* on the growth of β-lactamase producing E. coli. [Note: *Clavulanic acid* alone is nearly devoid of antibacterial activity.]

**VI. VANCOMYCIN**

*Vancomycin* [van-koe-MYE-sin] is a tricyclic glycopeptide that has become increasingly important because of its effectiveness against multiple drugresistant organisms, such as MRSA and enterococci. The medical community is presently concerned with emergence of *vancomycin* resistance in these organisms. Two examples are *vancomycin* resistant enterococci (VRE) and increased MICs of MRSA. [Note: *Bacitracin* [bass-i-TRAY-sin] is a mixture of polypeptides that also inhibits bacterial cell wall synthesis. It is active against a wide variety of gram-positive organisms. Its use is restricted to topical application because of its potential for nephrotoxicity with systemic use.]

**A. Mechanism of action**

*Vancomycin* inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization in a time-dependant fashion by binding to the D-Ala-D-Ala side chain of the precursor pentapeptide. This prevents the transglycosy lation step in peptidoglycan polymerization, thus weakening the cell wall and damaging the underlying cell membrane.

**B. Antibacterial spectrum**

*Vancomycin* is eff ective against gram-positive organisms (Figure 31.16). It has been lifesaving in the treatment of MRSA and *methicillin*-resistant Staphylo coccus epidermidis (MRSE) infections as well as enterococcal infections. With the emergence of resistant strains, it is important to curtail the increase in *vancomycin*-resistant bacteria (for example, Enterococcus faecium and Enterococcus faecalis) by restricting the use of *vancomycin* to the treatment of serious infections caused by β-lactam resistant, gram-positive microorganisms or for patients with

gram-positive infections who have a serious allergy to the β-lactams. Oral *vancomycin* is limited to treatment for potentially life-threatening, antibiotic-associated colitis due to C. diffi cile. Intravenous *vancomycin* is used in individuals with prosthetic heart valves and in patients undergoing implantation with prosthetic devices, especially in those hospitals

where there is a problem with MRSA or MRSE. *Vancomycin* acts synergistically with the aminoglycosides, and this combination can be used in the treatment of enterococcal endocarditis. *Daptomycin*, a cyclic lipopeptide antibiotic, and two protein synthesis inhibitors—*quinopristin/ dalfopristin* and *linezolid*—are currently available for the treatment of *vancomycin*-resistant organisms.]

**C. Resistance**

*Vancomycin* resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules. [Note: An example of the latter is caused by the replacement of a D-Ala by D-lactate in resistant organisms.]

**D. Pharmacokinetics**

Slow IV infusion (60–90 minutes) of *vancomycin* is employed for treatment of systemic infections or for prophylaxis. Because *vancomycin* is not absorbed after oral administration, this route is employed only for the treatment of antibiotic-induced colitis due to C. diffi cile. Infl ammation allows the intravenous formulation to penetrate into the meninges. However, it is often necessary to combine *vancomycin* with other antibiotics, such as *ceftriaxone* for synergistic eff ects when treating meningitis. Metabolism of the drug is minimal, and 90 to 100 percent is excreted by glomerular fi ltration (Figure 31.17). [Note: Dosage must be adjusted in renal dysfunction, because the drug will accumulate. The normal half-life of *vancomycin* is 6 to 10 hours, compared to over 200 hours in end-stage renal disease.]

**E. Adverse effects**

Side effects are a serious problem with vancomycin and include fever, chills, and/or phlebitis at the infusion site. Flushing (“red man syn- drome”) and shock result from histamine release associated with a rapid infusion. If an infusion-related reaction occurs, slow the infusion rate to administer vancomycin over 2 hours, increase the dilution volume, and/or pre-treat with an antihistamine 1 hour prior to administration. Additionally, reactions can be treated with antihistamines and steroids (Figure 31.18). This reaction is not an allergy and clinicians must be careful not to mistake it for true hypersensitivity. Dose-related hearing loss has occurred in patients with renal failure who accumulate the drug. Ototoxicity and nephrotoxicity are more common when vancomycin is administered with another drug (for example, an aminoglycoside) that can also produce these effects.

**VII. DAPTOMYCIN**

Daptomycin [DAP-toe-mye-sin] is a cyclic lipopeptide antibiotic that is an alternative to other agents, such as linezolid and quinupristin/dalfopristin, for treating infections caused by resistant gram-positive organisms, including MRSA and vancomycin-resistant enterococci (VRE).

**A. Mechanism of action** Upon binding to the bacterial cytoplasmic membrane, daptomycin induces rapid depolarization of the membrane, thus disrupting multi- pleaspects of membrane function and inhibiting intracellular synthesis of DNA, RNA, and protein. Daptomycin is bactericidal, and bacterial killing is concentration dependent.

**B. Antibacterial spectrum**

Daptomycin has a spectrum of activity limited to gram-positive organ- isms, which includes MSSA, MRSA, penicillin-resistant Streptococcus pneumoniae, Streptococcus pyogenes, Corynebacterium jeikeium, E. faecalis, and E. faecium (including VRE). Daptomycin is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus, including those with right-sided infective endocarditis. Efficacy of treatment with daptomycin in left-sided endocarditis has not been demonstrated. Additionally, daptomycin is inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia.

**C.Pharmacokinetics**

Daptomycin is 90 to 95 percent protein bound and does not appear to undergo hepatic metabolism; however, the dosing interval needs to be extended from every 24 hours to every 48 hours in patients with creatinine clearance less than 30 mL/minute.

**D. Adverse effects**

The most common adverse effects reported in clinical trials included constipation, nausea, headache, myalgias and insomnia. Increased hepatic transaminases and also elevations in creatine phosphokinases occurred, suggesting weekly monitoring of these enzymes, while the patient is receiving daptomycin. Although no clinically significant inter- actions have been identified, it is recommended to temporarily discontinue 3-hydroxy-3-methylglutary coenzyme A reductase inhibitors (statins), while receiving *daptomycin* due to the potential for additive muscle toxicity.

**VIII. TELAVANCIN**

*Telavancin [tel-a-VAN-sin]* is a semi-synthetic *lipoglycopeptide* antibiotic that is a synthetic derivative of *vancomycin.* It is an alternative to *vancomycin, daptomycin, linezolid,* and *quinupristin*/*dalfopristin* in treating complicated skin and skin structure infections, caused by resistant gram-positive organisms, including MRSA.

**A. Mechanism of action**

Like *vancomycin*, *telavancin* inhibits bacterial cell wall synthesis. Unlike *vancomycin*, *telavancin* exhibits an additional mechanism of action similar to that of *daptomycin*, that involves disruption of the bacterial cell membrane, due to the presence of a lipophilic side chain moiety.

**B. Antibacterial spectrum**

*Telavancin* is bactericidal against methicillin-resistant Staphylococcus aureus (MRSA), Streptococcus pyogenes, Streptococcus agalactiae, penicillin-resistant Streptococcus pneumoniae, Streptococcus angiosus group, and vancomycin-susceptible Enterococcuss faecalis isolates. Although *telavancin* is an alternative to *vancomycin*, there is no evidence it is more eff ective. *Telavancin* is not known to be eff ective versus E. faecium or VRE.

**C. Pharmacokinetics**

It is uncertain if *telavancin* undergoes hepatic metabolism, however, it has a half-life of 7 to 9 hours. *Telavancin* is administered at 10 mg/kg via a 60-minute infusion every 24 hours (Figure 31.20). In patients with a creatinine clearance between 30-50 mL/min, the dose is reduced to 7.5 mg/kg every 24 hours. In patients with a creatinine clearance between 10-29 mL/min, the recommended dose is 10 mg/kg with a dosing interval of 48 hours. Therefore, renal function should be monitored during therapy, but monitoring of serum concentration of *telavancin* is not necessary.

**D. Adverse Eff ects**

The most common adverse reactions reported with *telavancin* have included taste disturbances, nausea, vomiting, insomnia, and foamy urine (Figure 31.21). *Telavancin* is not recommended during pregnancy due to adverse developmental outcomes observed with animal data. In the United States, there is a boxed warning for women of childbearing age to have a pregnancy test prior to use. Because *telavancin* may prolong the QTc interval, use should be avoided in patients with a history of QTc prolongation, uncompensated heart failure, severe left ventricular hypertrophy, or patients receiving other medications that may prolong the QTc interval. *Telavancin* may also interfere with tests used to monitor coagulation (PT/INR, aPTT,ACT, coagulation based Xa tests). Thus, blood samples monitoringcoagulation should be collected as close to the next dose of *telavancin* as possible.