

Cell wall inhibitors 2

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.
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- 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,
 - fourth, and
 - advanced generation,
- based largely on their bacterial **susceptibility** patterns and **resistance** to β -lactamases
- [Note: Most Commercially available cephalosporins are ineffective against MRSA,
L. monocytogenes, C. difficile, and the enterococci.]

- **1. First generation:**
- act as *penicillin G* substitutes.
- They are **resistant** to the staphylococcal penicillinase (that is, they cover MSSA)
- and also have activity against Gram (–) rods
 - *Proteus mirabilis*,
 - *E. coli*, and
 - *K. pneumoniae*.

- **2. Second generation:**
- **greater activity** against three additional **gram-negative** organisms:
 - H. influenzae,
 - Enterobacter aerogenes,
 - and some Neisseria species,
- whereas activity against **gram-positive** organisms is **weaker**.
- Antimicrobial coverage of the cephamycins :
 - *cefotetan* [sef-oh-TEE-tan] and
 - *cefoxitin* [sef-OX-i-tin]) also includes anaerobes (for example, Bacteroides fragilis).
 - They are the only cephalosporins commercially available with appreciable activity against **gram-negative anaerobic** bacteria.
 - However, neither drug is first line because of the increasing prevalence of resistance among B. fragilis to both agents.

- **3. Third generation:**

- have assumed an important role in the treatment of infectious diseases.
- Although they are **less potent than first-generation cephalosporins against MSSA,**
- They 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-TAKSeem] 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 use should be evaluated on a case-by-case basis.

- Third-generation cephalosporins must be used with caution, as they are associated with significant **“collateral damage,”** essentially meaning the induction and spread **of antimicrobial resistance.** [Note: Fluoroquinolone use is also associated with collateral damage.]

- **4. Fourth generation:**

- *Cefepime* [SEF-eh-peem] is classified as a fourth-generation cephalosporin and must be administered parenterally.
- *Cefepime* has a wide antibacterial spectrum, with activity 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.

- **5. Advanced generation:**
- *Ceftaroline* [sef-TAR-oh-leen] is a broadspectrum, advanced-generation cephalosporin that is administered IV as a prodrug, *ceftaroline fosamil*.
- It is the only *commercially available* β -lactam in the United States with activity against MRSA and is indicated for the treatment of
 - complicated skin and skin structure infections and
 - community-acquired pneumonia.
- The unique structure allows *ceftaroline* to bind to PBP2a found with MRSA and PBP2x found with *Streptococcus pneumoniae*.
- In addition to its broad gram-positive activity, it also has similar gram negative activity to the third-generation cephalosporin *ceftriaxone*.
- Important gaps in coverage include *P. aeruginosa*, extended spectrum β -lactamase (ESBL)-producing Enterobacteriaceae, and *Acinetobacter baumannii*.
- The twice-daily dosing regimen also limits use outside of an institutional setting.

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 **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 38.11) because of their poor oral absorption.
- Exceptions are noted in Figure 38.12.

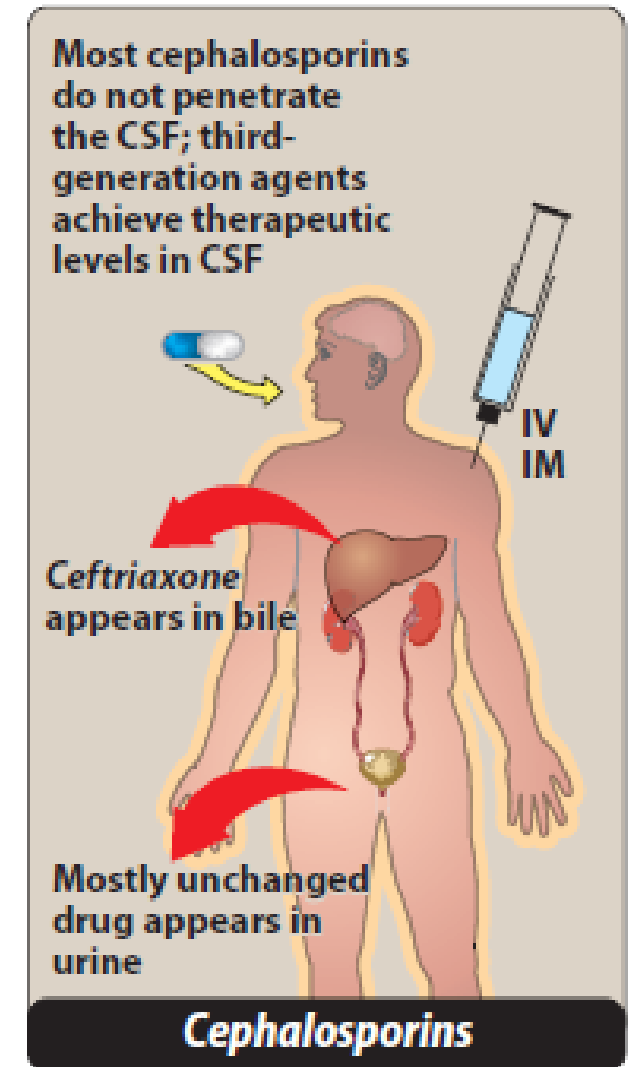


Figure 38.11

Administration and fate of the cephalosporins.
(CSF = cerebrospinal fluid.)

- **2. Distribution:**

- All cephalosporins distribute very well into body fluids.
- However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few cephalosporins.
- For example, *ceftriaxone* and *cefotaxime* are effective in the treatment of neonatal and childhood **meningitis** caused by *H. influenzae*.
- *Cefazolin* [se-FA-zo-lin] is commonly used as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing *S. aureus*.
- *Cefazolin* is effective for most surgical procedures, including **orthopedic surgery** because of its ability to **penetrate bone**.
- All cephalosporins cross the **placenta**.

- **3. Elimination:**

- Cephalosporins are eliminated through tubular secretion and/or glomerular filtration .
- Therefore, doses must be **adjusted in cases of renal dysfunction** to guard against accumulation and toxicity.
- One 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

- Like the penicillins, the cephalosporins are **generally well tolerated**.
- However, allergic reactions are a concern. Patients who have had an
 - anaphylactic response,
 - Stevens-Johnson syndrome, or
 - toxic epidermal necrolysis to penicillins **should not receive cephalosporins**.
- Cephalosporins should be avoided or used with caution in individuals with penicillin allergy.
- Current data suggest that the cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the similarity in the side chain, not the β -lactam structure.
- The highest rate of allergic cross-sensitivity is between **penicillin and first-generation cephalosporins**.

First Generation

Cefazolin ←

This first-generation parenteral cephalosporin has a longer duration of action and a similar spectrum of action, compared to other first-generation drugs. It penetrates well into bone.

Cefadroxil

Cephalexin ←

This is the prototype of first-generation, oral cephalosporins. Oral administration twice daily is effective against pharyngitis.

Second Generation

Cefuroxime sodium ←

This prototype second-generation, parenteral cephalosporin has a longer half-life than similar agents. It crosses the blood-brain barrier, and it can be used for community-acquired bronchitis or pneumonia in the elderly and for patients who are immunocompromised.

Cefuroxime axetil ←

Administered twice daily, this drug is well absorbed and is active against β -lactamase-producing organisms.

Third Generation

Cefdinir
Cefixime ←

These are administered orally once daily.

Cefotaxime ←

This penetrates well into the CSF.

Ceftazidime ←

This is active against *Pseudomonas aeruginosa*.

Ceftibuten

This drug has the longest half-life of any cephalosporin (6 to 8 hours), which permits once-a-day dosing. High levels of the drug can be achieved in blood and CSF. It is effective against genital, anal, and pharyngeal penicillin-resistant *Neisseria gonorrhoeae*. The drug is excreted in bile and may be used in patients with renal insufficiency. It has good penetration into bone.

Ceftriaxone ←

Fourth Generation

Cefepime ←

This is active against *Pseudomonas aeruginosa*.

Figure 38.12

Therapeutic advantages of some clinically useful cephalosporins. [Note: Drugs that can be administered orally are shown in reverse type. More useful drugs shown in **bold**.] (CSF = cerebrospinal fluid.)

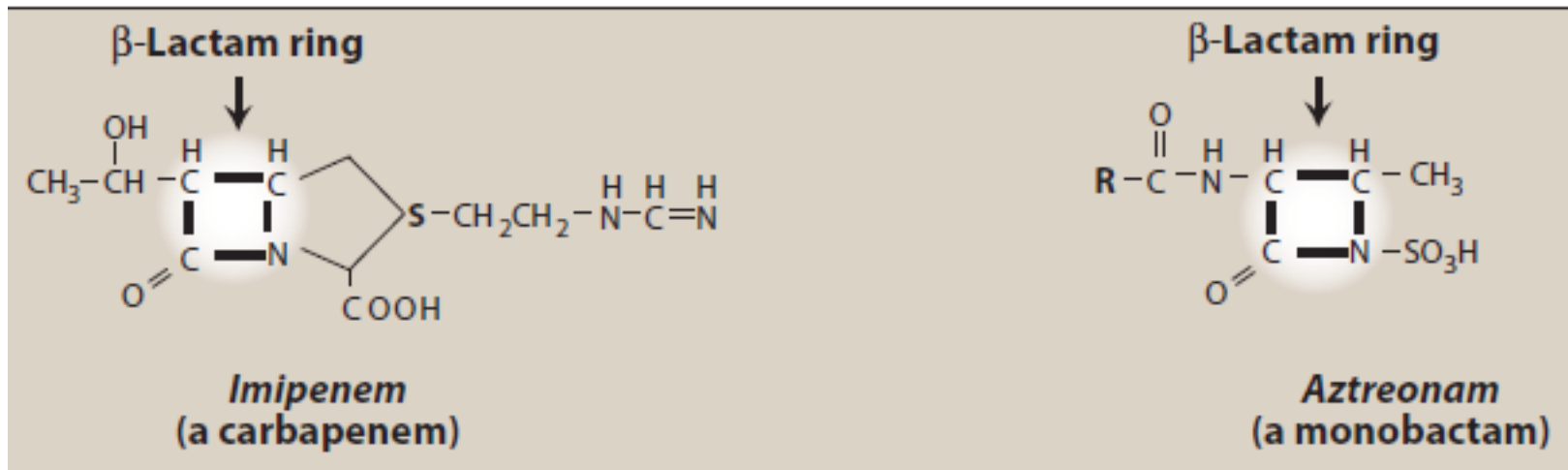
IV. OTHER β -LACTAM ANTIBIOTICS:

- **A. Carbapenems**

- *Imipenem* [i-mi-PEN-em],
- *meropenem* [mer-oh-PEN-em],
- *doripenem* [dore-i-PEN-em], and
- *ertapenem* [er-ta-PEN-em]

- **B. Monobactams**

- *Aztreonam* [az-TREE-oh-nam],



IV. OTHER β -LACTAM ANTIBIOTICS:

A. Carbapenems

- Carbapenems are synthetic β -lactam antibiotics that differ in structure from the penicillins.
- *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.

A. Carbapenems

- **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 β -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*
- Unlike other carbapenems, *ertapenem* lacks coverage against *P. aeruginosa*, *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.
- *Meropenem* is known to reach therapeutic levels in bacterial meningitis even without inflammation.
- 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.
- The other carbapenems do not require coadministration of *cilastatin*. *Ertapenem* can be administered via IV or IM injection once daily

- **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; however, the other carbapenems are less likely to do so.

IV. OTHER β -LACTAM ANTIBIOTICS:

B. Monobactams

- *Aztreonam* [az-TREE-oh-nam], which is the only commercially available monobactam,
- has antimicrobial activity directed primarily against **gram-negative pathogens, including the Enterobacteriaceae and *P. aeruginosa*.**
- It lacks activity against gram positive organisms and anaerobes.
- *Aztreonam* is resistant to the action of most β -lactamases, with the exception of the 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 to other penicillins, cephalosporins, or carbapenems.**

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 or cause any significant adverse effects.
- 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 drugs

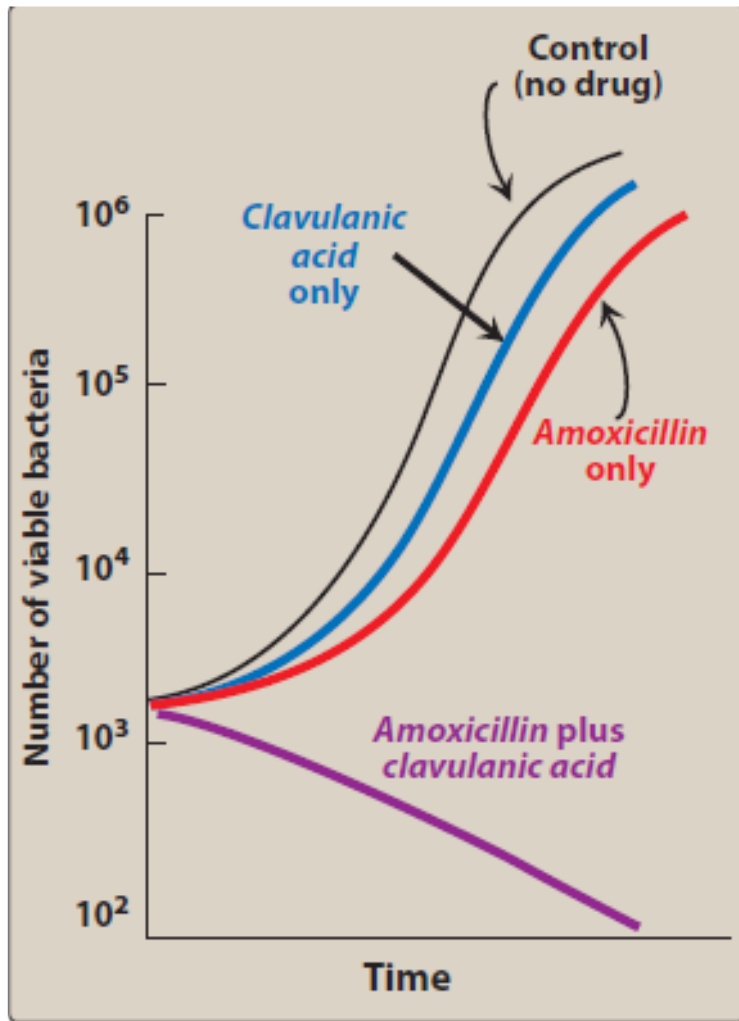


Figure 38.15

The in vitro growth of *Escherichia coli* in the presence of *amoxicillin*, with and without *clavulanic acid*.

VI. VANCOMYCIN

- *Vancomycin* [van-koe-MYE-sin] is a tricyclic glycopeptide that has become increasingly important in the treatment of **life-threatening MRSA** and *methicillin*-resistant *Staphylococcus epidermidis* (**MRSE**) infections, as well as enterococcal infections (Figure 38.16).
- 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 gram-positive infections in patients who have a serious allergy to the β -lactams.

- Intravenous *vancomycin* is used in individuals with prosthetic heart valves and in patients undergoing implantation with prosthetic devices, especially in those hospitals where there are high rates of MRSA or MRSE.
- Serum drug concentrations (troughs) are commonly measured to monitor and adjust dosages for safety and efficacy.
- *Vancomycin* is not absorbed after oral administration, so the use of the oral formulation is limited to the treatment of severe antibiotic associated *C. difficile* colitis.

VII. DAPTOMYCIN

- *Daptomycin [DAP-toe-mye-sin]*
- *is a bactericidal concentration-dependent 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
 - *vancomycinresistant enterococci (VRE)* (Figure 38.17).

- *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.

VIII. TELAVANCIN

- *Telavancin* [tel-a-VAN-sin] is a bactericidal concentration-dependent semisynthetic lipoglycopeptide antibiotic that is a synthetic derivative of *vancomycin*.
- Like *vancomycin*, *telavancin* inhibits bacterial cell wall synthesis.
- Moreover, *telavancin* exhibits an additional mechanism of action similar to that of *daptomycin*, which involves disruption of the bacterial cell membrane due to the presence of a lipophilic side chain moiety.
- It is an alternative to *vancomycin*, *daptomycin*, and *linezolid*, in treating complicated skin and skin structure infections caused by resistant gram-positive organisms (including MRSA).

- It is also an agent of last choice for hospital-acquired and ventilator-associated bacterial pneumonia when alternative treatments are not suitable.
- The use of *telavancin* in clinical practice is limited by significant adverse effects (for example, renal impairment),

	VANCOMYCIN	DAPTOMYCIN	TELAVANCIN
Mechanism of Action	Inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein	Inhibits bacterial cell wall synthesis; disrupts cell membrane
Pharmacodynamics	Time dependent Bactericidal	Concentration dependent Bactericidal	Concentration dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: <u>Staphylococcus aureus</u> (including MRSA), <u>Streptococcus pyogenes</u> , <u>S. agalactiae</u> , penicillin-resistant <u>S. pneumoniae</u> , <u>Corynebacterium jeikeium</u> , <u>vancomycin-susceptible Enterococcus faecalis</u> , and <u>E. faecium</u>		
Unique Antibacterial Spectrum	<u>Clostridium difficile</u> (oral only)	<u>Vancomycin-resistant E. faecalis</u> and <u>E. faecium</u> (VRE)	Some isolates of <u>vancomycin-resistant enterococci</u> (VRE)
Route	IV/PO	IV	IV
Typical Administration Time	60- to 90-minute IV infusion	2-minute IV push 30-minute IV infusion	60-minute IV infusion
Pharmacokinetics	Renal elimination Normal half-life: 6–10 hours Dose is adjusted based on renal function and serum trough levels	Renal elimination Normal half-life: 7–8 hours Dose is adjusted based on renal function	Renal elimination Normal half-life: 7–9 hours Dose is adjusted based on renal function
Unique Adverse Effects	Infusion related reactions due to histamine release: Fever, chills, phlebitis, flushing (red man syndrome); dose-related ototoxicity and nephrotoxicity	Myalgias, elevated hepatic transaminases and creatine phosphokinases (check weekly), and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while on therapy)	Taste disturbances, foamy urine, QTc prolongation, interferes with coagulation labs (PT/INR, aPTT, ACT), not recommended in pregnancy (box warning recommends pregnancy test prior to initiation)
Key Learning Points	Drug of choice for severe MRSA infections; oral form only used for <u>C. difficile</u> infection; resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of <u>vancomycin</u> to receptor molecules; monitor serum trough concentrations for safety and efficacy	<u>Daptomycin</u> is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia	Use with caution in patients with baseline renal dysfunction (CrCl < 50 mL/min) due to higher rates of treatment failure and mortality in clinical studies; any necessary coagulation labs should be drawn just prior to the <u>telavancin</u> dose to avoid interaction

IX. FOSFOMYCIN

- *Fosfomicin* [fos-foe-MYE-sin] is a bactericidal synthetic derivative of phosphonic acid. It blocks cell wall synthesis by inhibiting the enzyme UDP-*N*-acetylglucosamine enolpyruvyl transferase, which catalyzes the first step in peptidoglycan synthesis.
- It is indicated for urinary tract infections caused by *E. coli* or *E. faecalis*.
- Due to its unique structure and mechanism of action, cross resistance with other antimicrobial agents is unlikely.

- *Fosfomycin* is rapidly absorbed after **oral administration** and distributes well to the kidneys, bladder, and prostate.
- The drug is excreted in its active form in the urine and feces.
- **It maintains high concentrations in the urine over several days**, allowing for a one-time dose for the treatment of urinary tract infections.
- The most commonly reported adverse effects include diarrhea, vaginitis, nausea, and headache.

X. POLYMYXINS

- The polymyxins are **cation polypeptides** that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria.
- They have a detergent-like effect that disrupts cell membrane integrity.
- Polymyxins are concentration-dependent bactericidal agents with **activity against most clinically important gram-negative bacteria**, including *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *Acinetobacter* species, and *Enterobacter* species.
- However, **alterations in the cell membrane lipid polysaccharides** allow many species of *Proteus* and *Serratia* to be intrinsically **resistant**.

- Only two forms of polymyxin are in clinical use today,
 - *polymyxin B* and
 - *colistin* (*polymyxin E*).
- *Polymyxin B* is available in
 - parenteral,
 - ophthalmic,
 - otic, and
 - topical preparations.
- *Colistin* is only available as a prodrug, *colistimethate sodium*, which is administered
 - IV or
 - inhaled via a nebulizer.

- The **use** of these drugs has been **limited** for a long time, due to the increased risk of **nephrotoxicity and neurotoxicity** (for example, slurred speech, muscle weakness) when used systemically.
- However, with the increase in gram-negative resistance, they have seen a resurgence in use and are now commonly used as salvage therapy for **patients with multidrug-resistant infections**.
- **Careful dosing and monitoring of adverse effects** are important to maximize the safety and efficacy of these agents.