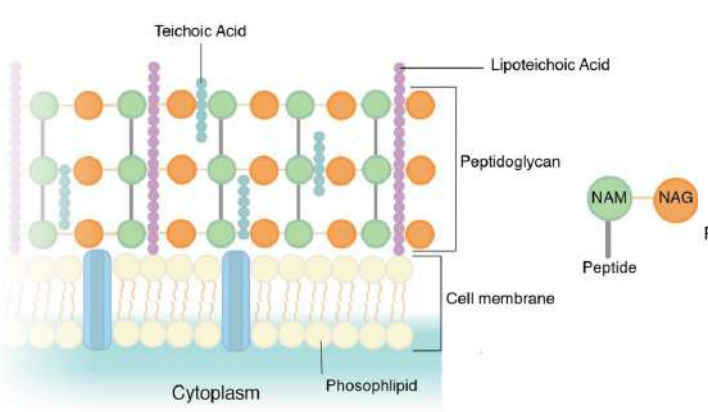
Cell Wall Inhibitors

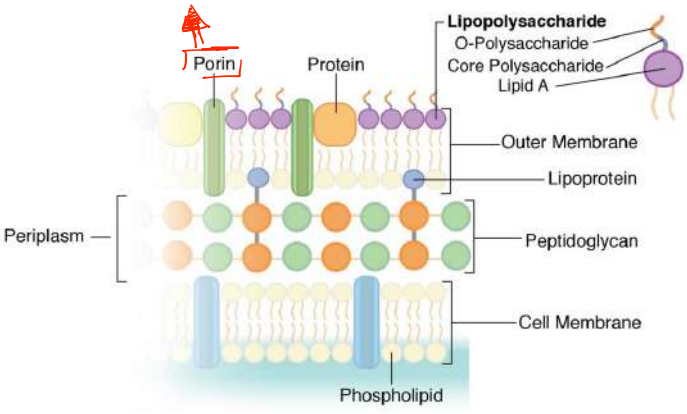
Pharmacology and Toxicology
General Pharmacology
Second Year Medical Students
Tareq Saleh, MD, PhD
Faculty of Medicine
The Hashemite University
Textbook: Chapter 29 pp 369- 383

Overview: Bacterial Cell Wall

Allow some cell wall inhibitors to cross them



Gram Positive Bacteria Cell Wall



Gram Negative Bacteria Cell Wall

Overview: Synthesis of Bacterial Cell Wall

1. Cytoplasmic Stage:

- Synthesis of glycan precursors: UDP-MurNAc-pentapeptide, UDP-GlcNAc

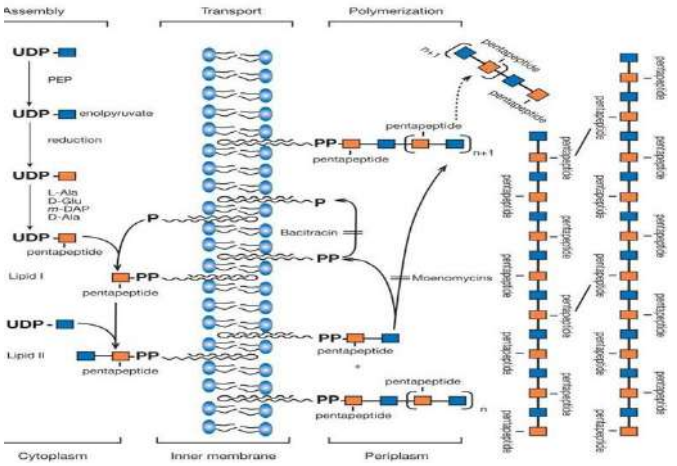
2. Cytoplasmic membrane Stage:

- Transfer to membrane receptors

3. Extracellular membrane stage:

- Transpeptidation via PBP

Penicillin binding protein.



Penicillins

Tareq Saleh ©
Copyright © 2018 Wolters Kluwer • All Rights Reserved
Wolters Kluwer

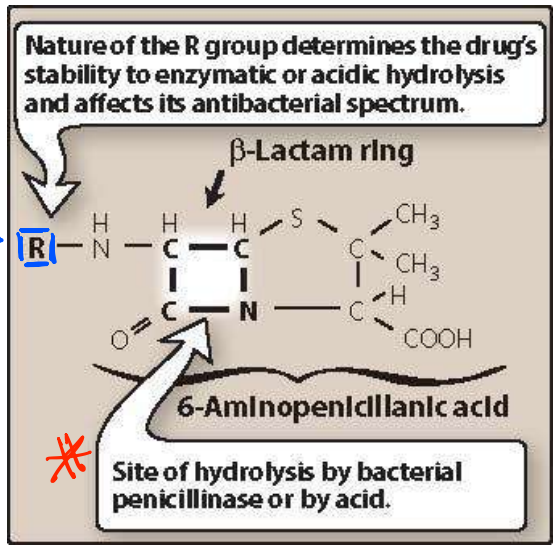
R-group ⇒ Differs between antibiotics.
Determines the Anti-bacterial spectrum.
Affect susceptibility & Resistance.

Penicillins

PENICILLINS

- *Amoxicillin* AMOXIL
- *Ampicillin* PRINCIPEN
- *Dicloxacillin* DYNAPEN
- *Nafcillin*
- *Oxacillin*
- *Penicillin G* PFIZERPEN
- *Penicillin V*
- *Piperacillin*
- *Ticarcillin*

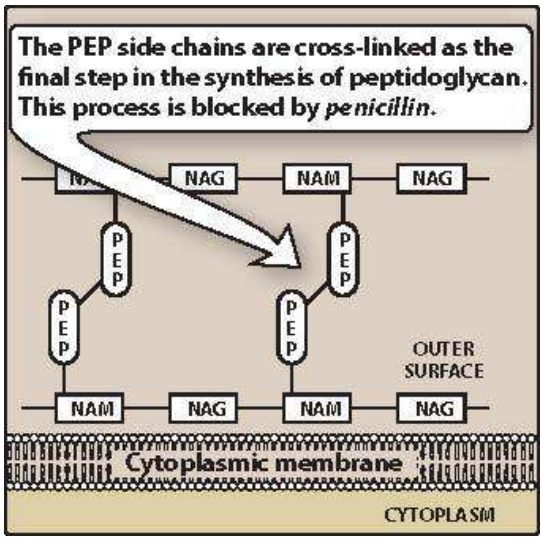
differ in



Quick Microbiology Reminder

Penicillin-binding proteins:

- Penicillins bind and inactivate bacterial cell membrane proteins called: penicillin-binding proteins (PBPs).
- Bacterial enzymes involved in cell wall synthesis
- Variable among different species
- Involved in resistance

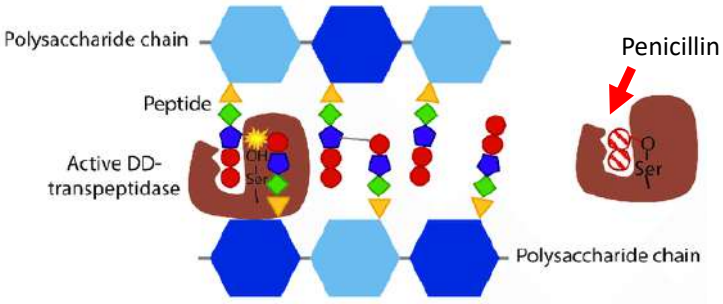


Penicillins interfere with the last step of bacterial cell wall synthesis, which Is the cross-linking of adjacent peptidoglycan strands by a process known as transpeptidation. Since penicillins structurally resemble the terminal portion of the peptidoglycan strand, they compete for and bind to enzymes called penicillin-binding proteins (PBPs), which catalyze transpeptidase and facilitate cross-linking of the cell wall (Figure 29.3). The result is the formation of a weakened cell wall and ultimately cell death. For this reason, penicillins are regarded as bactericidal and work in a time-dependent fashion.

Penicillins

Mechanism of action

- Inhibit transpeptidation or cross-linkage (*last step* of bacterial wall synthesis)
- Prevent cross-linking catalyzed by the PBP transpeptidase



What is the basis of selective toxicity?

Penicillins

What are the *consequences of transpeptidation inhibition*?

- Bacterial cell lysis Fluids shift to inside bacteria, leads to bacteria swelling & Rupture
- Bactericidal
- Time-dependent
- Effective against rapidly growing bacteria The rapidly growing bacteria, the rapidly cell wall synthesis. because it targets penicillin

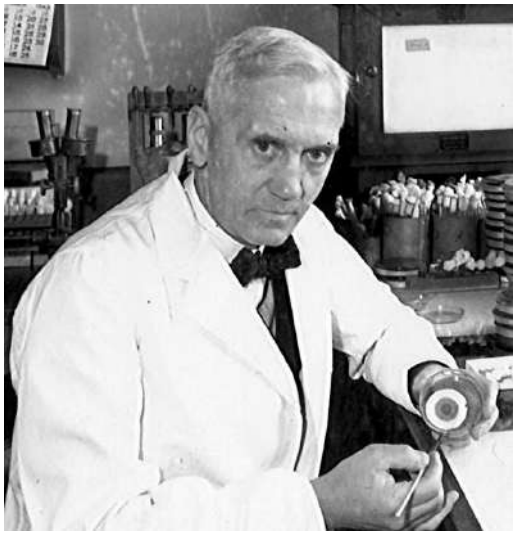
* Penicillin is poorly apsorbed by GIT, like Penicillin G
it's hydrolysed in GIT
So it's gived IM

Penicillins

Antibacterial spectrum

1. Natural penicillins:

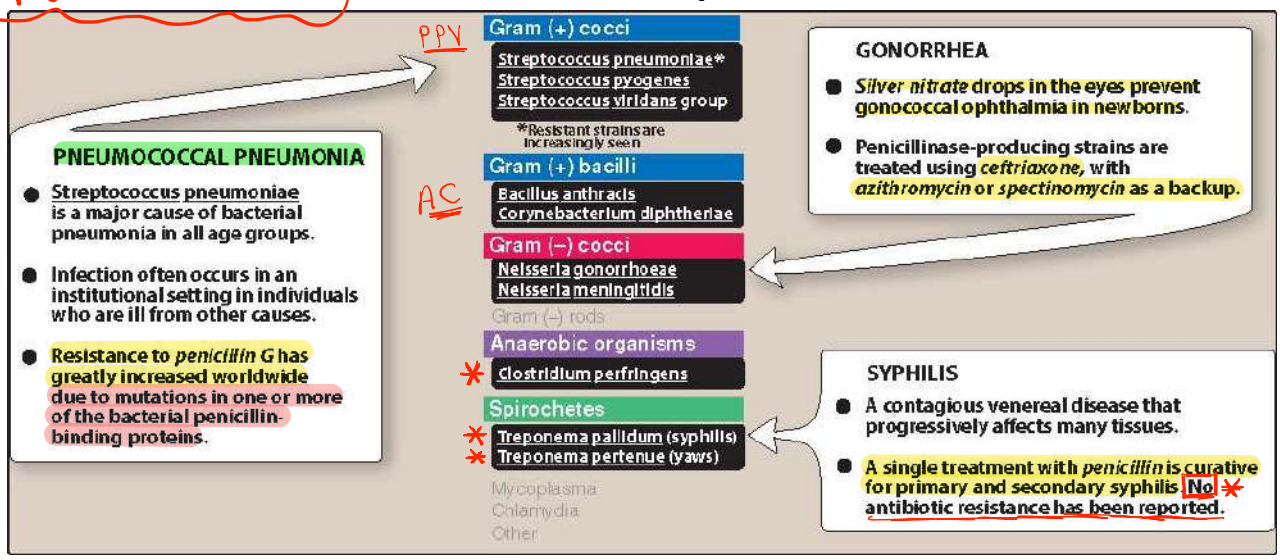
- Penicillin G, Penicillin V: *Penicillium chrysogenum* A fungus that produces penicillin
- Drugs of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum). (Treated by penicillin G)
- Penicillin V is the oral form of penicillin



Penicillins

Penicillin G

Antibacterial spectrum



Penicillins

Antibacterial spectrum:

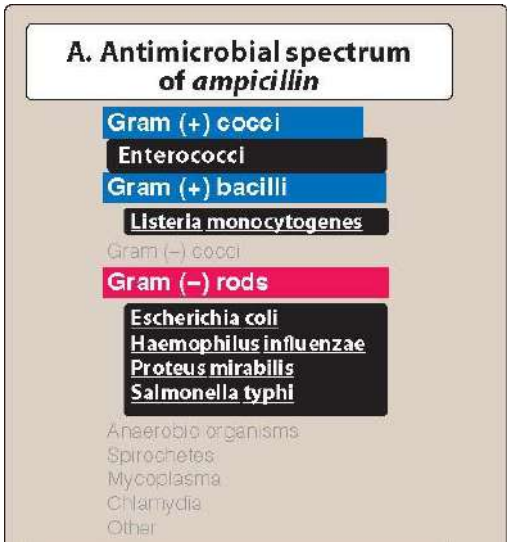
2. Extended-spectrum penicillins:

- Semisynthetic: ampicillin, amoxicillin
- Spectrum: extended to include gram-negative bacilli *

❑ Ampicillin: **drug of choice** for gram-positive bacillus *L. monocytogenes*

**Also for enterococci, resp infections*

❑ Amoxicillin: Ear, nose, and throat infections, dental prophylaxis *



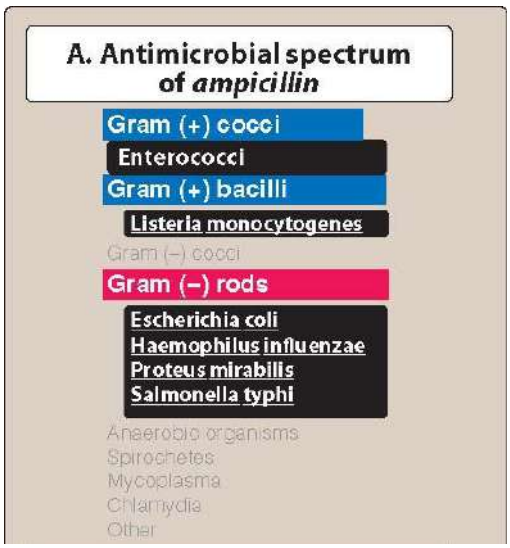
Penicillins

Antibacterial spectrum:

2. Extended-spectrum penicillins:

- Combined with β-lactamase inhibitors

e.g., MSSA is resistant to ampicillin and amoxicillin IF given without a β-lactamase inhibitors *



Naturall penicillin } Alone aren't effective against
Semisynthetic penicillin } Any staphylococcal species

Penicillins

Antibacterial spectrum

3. Antistaphylococcal penicillins:

- Methicillin, nafcillin, oxacillin, dicloxacillin
- Effective against penicillinase-producing staphylococci (MSSA)
- Minimal activity against gram-negative
- Methicillin not used clinically (toxic)

Just in lab use!

→ Cause Sever Kidney injury (interstitial nephritis)

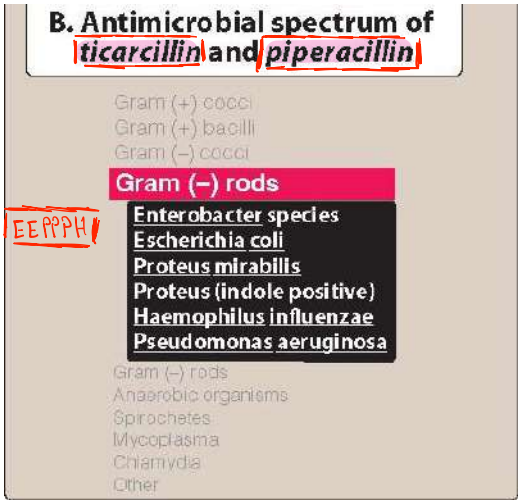
Penicillins

Antibacterial spectrum:

4. Antipseudomonal penicillins:

- Piperacillin
- Effective against gram-negative bacilli (but not against *Klebsiella*)
- Common combinations:

Piperacillin + tazobactam



Penicillins

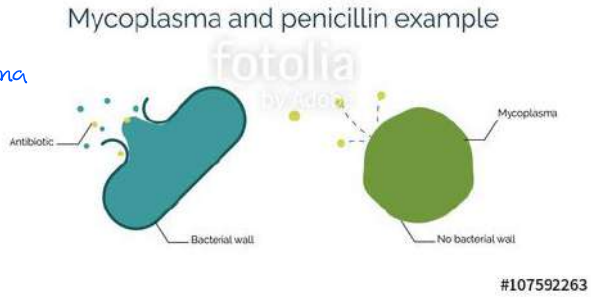
Mechanisms of resistance

- **Intrinsic Resistance:**

- Microorganisms that lack peptidoglycans cell walls e.g., *M. pneumoniae*

Mycoplasma

- Microorganisms that have impermeable cell walls



Penicillins

Mechanisms of resistance

- **Acquired Resistance:**

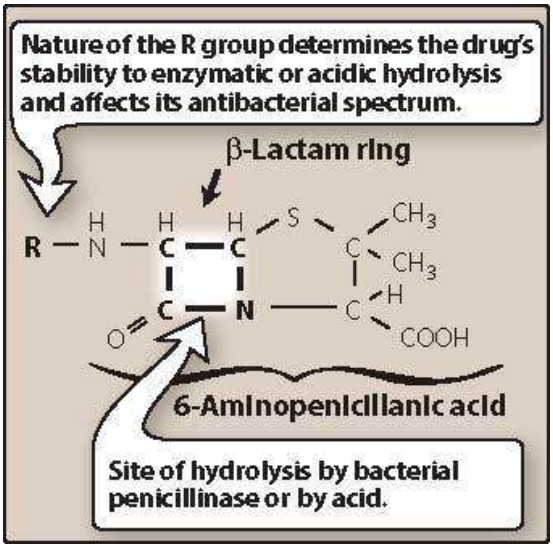
1. **β-Lactamase activity:**

- Enzymes that *hydrolyze* the cyclic amide bond of the β-lactam ring

- Mostly acquired (plasmids)

- **Gram-positive**: secrete β-lactamases extracellularly

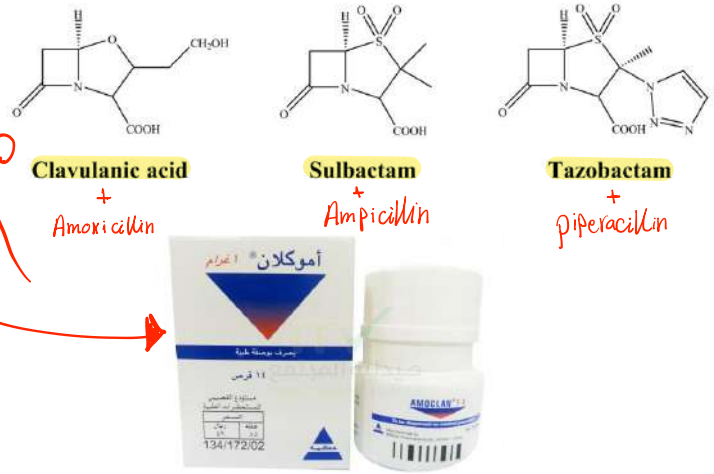
- **Gram-negative**: periplasmic β-lactamases

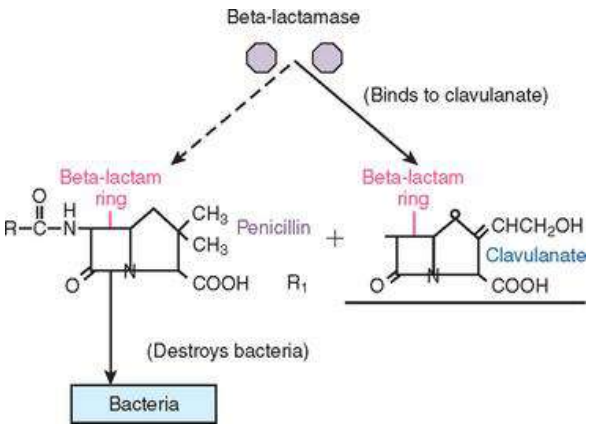


Production of β-Lactamases is the main resistance mechanism against β-Lactams.

How is this problem solved?

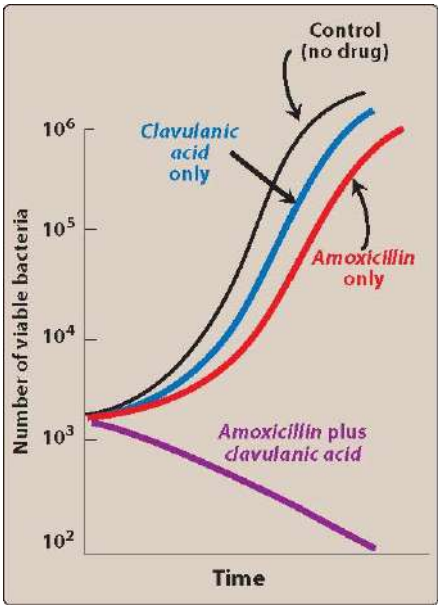
β-Lactamase Inhibitors





β-Lactamase Inhibitors

- Contain β-Lactam rings
- BY THEMSELVES, no antibacterial activity
- Protect antibiotics that are normally substrates for β-Lactamases
- Example……?



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

Penicillins

Mechanisms of resistance

- **Acquired Resistance:**

2. Decreased permeability to the drug:

- Reduced permeability e.g., *Pseudomonas aeruginosa*
- Efflux pump e.g., *Klebsiella pneumoniae*.

3. Altered PBPs:

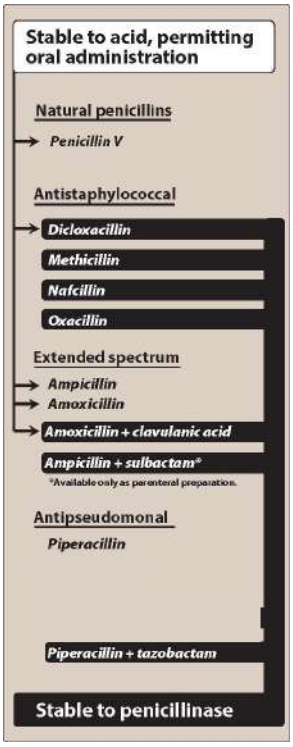
- Modified PBPs with lower affinity for β-lactams e.g., MRSA resistance to most β-lactams.

Penicillins

Pharmacokinetics

- **Routes of administration**
- **IV, IM only**: ampicillin+sulbactam, piperacillin+tazobactam, nafcillin, oxacillin
- **Oral only**: Penicillin V, amoxicillin, amoxicillin+clavulanic acid, dicloxacillin
- **Depot forms**: Procaine penicillin G and benzathine penicillin G (IM)

*Slow releasing form (Sustained release)

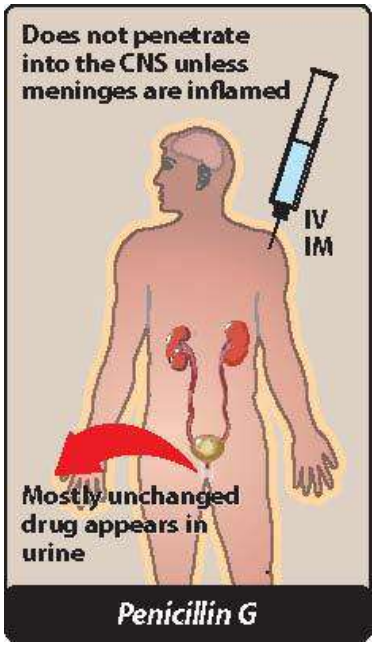


* Why penicillin G is given for neonatal meningitis ?!
Because Neonatal BBB isn't well developed & there is inflammation

Penicillins

Pharmacokinetics

- **Absorption**
- Most penicillins are incompletely absorbed after oral administration
- Empty stomach?
- **Distribution**
- Good distribution e.g., cross placenta
- (but no teratogenic effect)
- Insufficient penetration to bone or CSF (unless inflamed)

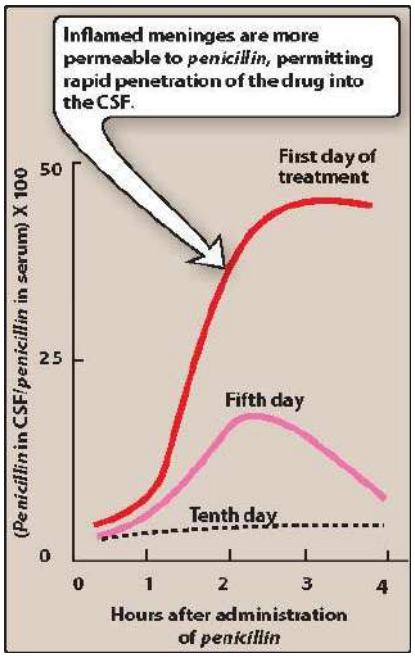


Absorption: The acidic environment within the intestinal tract is unfavorable for the absorption of penicillins. In the case of penicillin V, only one-third of an oral dose is absorbed under the best of conditions. Food decreases the absorption of the penicillinase resistant penicillin dicloxacillin because as gastric emptying time increases, the drug is destroyed by stomach acid. Therefore, it should be taken on an empty stomach. Conversely, amoxicillin is stable in acid and is readily absorbed from the gastrointestinal (GI) tract.

Penicillins

Pharmacokinetics

- **Absorption**
- Most penicillins are incompletely absorbed after oral administration
- Empty stomach?
- **Distribution**
- Good distribution e.g., cross placenta (but no teratogenic effect)
- Insufficient penetration to bone or CSF (unless inflamed)



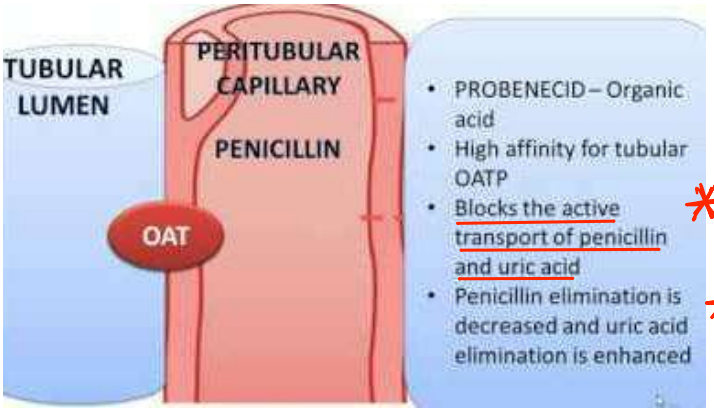
Excretion: The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Because nafcillin and oxacillin are primarily metabolized in the liver, they do not require dose adjustment for renal insufficiency. Probenecid inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. The penicillins are also excreted in breast milk.

→ *Used to treat gout, it interferes with uric acid reabsorption

Penicillins

Pharmacokinetics

- **Metabolism**
- Insignificant metabolism
- Exceptions? Anti staphylococcal penicillin
- **Excretion:**
- Renal: tubular secretory system
- *Probenecid* is an inhibitor of renal tubular excretion of penicillin



Angioedema ⇒ 

* Naturally drugs are associated with ⇒ Allergy

Penicillins

Adverse effects

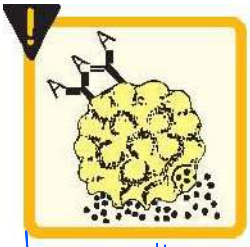
In very rare cases steven-johnson syndrom

1. Hypersensitivity:

- 5-10% percent of patients (simple rash to angioedema to anaphylaxis)
- Cross-allergy Here should switch to another family rather than penicillin
- Always inquire about penicillin allergy

2. Diarrhea:

- Caused by intestinal flora imbalance *
- More with extended-spectrum agents



Hypersensitivity

Diarrhea

Hypersensitivity: Approximately 10% of patients self-report allergy to penicillin. Reactions range from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Cross-allergic reactions occur among the Beta-lactam antibiotics. To determine whether treatment with a ~-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.

Penicillins

Adverse effects

3. Nephritis:

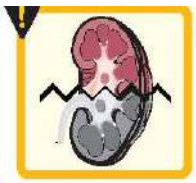
- Methicillin: no longer used because of this

4. Neurotoxicity:

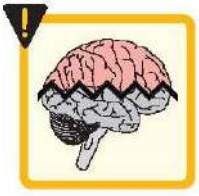
- If injected intrathecally

5. Hematological toxicities

- Decreased coagulation
- Cytopenias



Nephritis



Neurotoxicity

Hematologic toxicities

Quick Revision

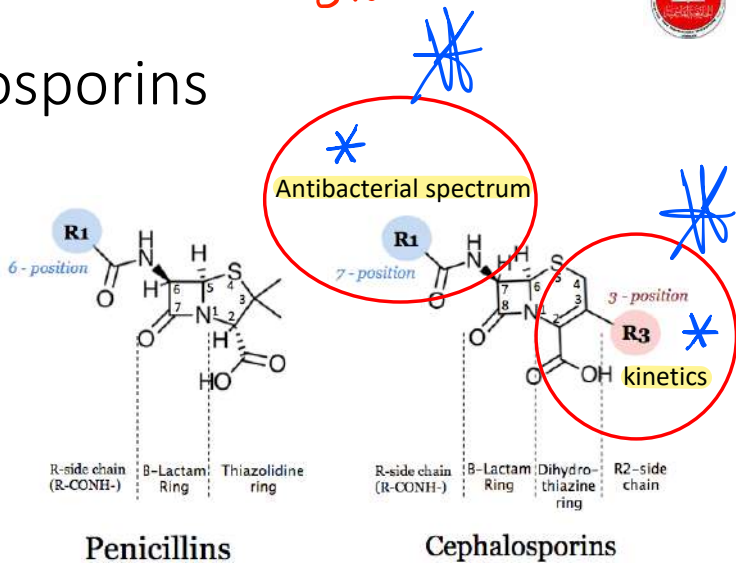
- Name a penicillin that is effective against penicillinase-producing S. aureus (MSSA)? Methicillin, dicloxacillin, Nafcillin & oxacillin
- Name a penicillin that is effective against penicillinase-producing S. aureus (MRSA)? Until this moment no

Cephalosporins

function of every side chain

Cephalosporins

- β-lactams
- Structurally/functionally related to penicillins
- Semisynthetic
- More resistant to certain β-lactamases



Cephalosporins

- Classified into generations:

-first

-second

-third

-fourth

-advanced

CEPHALOSPORINS
Cefaclor CECLOR
Cefadroxil DURACEF
Cefazolin KEFZOL
Cefdinir OMNICEF
Cefepime MAXIPIME
Cefixime SUPRAX
Cefotaxime CLAFORAN
Cefotetan CEFOTAN
Cefoxitin MEFOXIN
Cefprozil CEFZIL
Ceftaroline TEFLARO
Ceftazidime FORTAZ
Ceftibuten CEDAX
Ceftizoxime CEFIZOX
Ceftriaxone ROCEPHIN
Cefuroxime CEFTIN
Cephalexin KEFLEX

First-generation cephalosporins

ZLD

Cefazoline ⇒ Can penetrate bone
Cephalexin
Cefadroxil

Gram (+) cocci

SAEPP

- Staphylococcus aureus*
- Staphylococcus epidermidis
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) rods

PKE

- Escherichia coli
- Klebsiella pneumoniae
- Proteus mirabilis

Second-generation cephalosporins

PUXT

Cefprozil
Cefuroxime
Cefoxitin
Cefotetan

Gram (+) cocci

APPS

- Staphylococcus aureus*
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) cocci

- Neisseria gonorrhoeae

Gram (–) rods

HEEKP

- Enterobacter aerogenes
- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Proteus mirabilis

Anaerobic organisms**

Third-generation cephalosporins

DORA

Cefdinir
Cefotaxime] effective in neonatal meningitis caused by H. influenza
Ceftriaxone]
Ceftazidime → Eliminated in bile

Gram (+) cocci

SPP

- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) cocci

- Neisseria gonorrhoeae

Gram (–) rods

SEKAPP

- Enterobacter aerogenes
- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Proteus mirabilis
- Pseudomonas aeruginosa†
- Serratia marcescens

Fourth-generation cephalosporins

Antibacterial coverage comparable to that of the third-generation class; however, demonstrate greater stability against β-lactamases

Cephalosporins

Antibacterial spectrum

- **First-generation cephalosporins:**

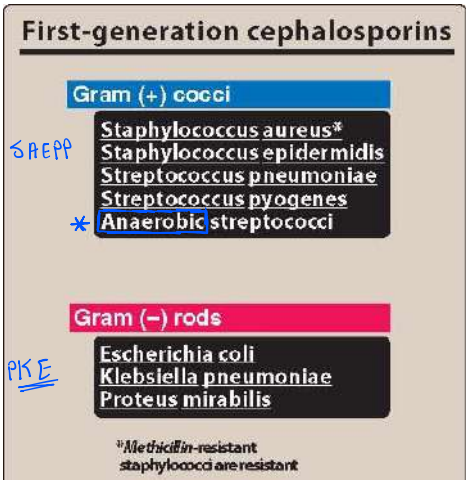
- penicillin G substitutes in allergy situations
- They cover MSSA (resistant to penicillinase) but not MRSA

for ENT infections (ear, tonsils, nasal)

- Cefazolin
- Cephalexin
- cefadroxil

Most of them are in oral form

Z, l, d



*Not MRSA

Cephalosporins

Antibacterial spectrum

- **Second-generation cephalosporins:**

- Wider gram-negative spectrum: *H. influenzae*, *Klebsiella*, *Proteus*, *Moraxella catarrhalis*, and some *Neisseria* species

- Cefotetan
- Cefuroxime
- Cefoxitin
- Cefprozil

They are given oral

PUXT

Non are first line

Cephalosporins

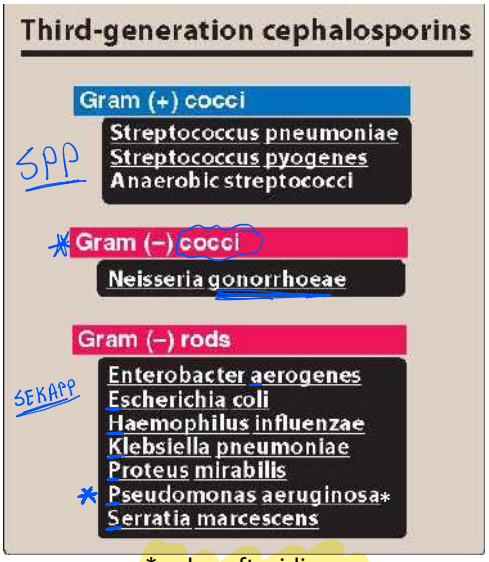
Antibacterial spectrum

- **Third-generation cephalosporins:**
- Greater activity against gram-negative bacilli (broad-spectrum)
- Drugs of choice for the treatment of meningitis
- Must be used with caution "collateral damage"

Treat meningitis
Ceftriaxone
Cefotaxime
Ceftazidime
Cefdinir
DORA

Anti-pseudomonas

* Very important, because they are first-line for several infection
* They are gived parenteral



* Collateral damage ⇒ like pseudomembranous colli, infection in colon with bloody diarrhea

Tareq Saleh ©

Cephalosporins

Antibacterial spectrum

- **Fourth-generation cephalosporins:**
- Broad-spectrum
- Active against strep and staph species (not MRSA)
- Active against aerobic gram-negative species including P. aeruginosa

Cefepime

Antibacterial spectrum

- **Advanced-generation cephalosporins:**
- Broad-spectrum
- Only β-lactam that is active against MRSA
- Indicated for complicated skin MRSA infections and pneumonia
- How about pseudomonas? ESBL? NO
- *What are the limitations for using ceftaroline?*

Ceftaroline

Tareq Saleh ©

Quick Exercise

Which of the following cell wall synthesis inhibitors is effective against MRSA?

-amoxicillin

-ampicillin

-amoxicillin/clavulanate

-cefazolin

-cephalexin

-ceftriaxone

-cefepime

-ceftaroline

Has same Penicillin target PBPs

Cephalosporins

Mechanisms of resistance

- Similar to penicillins

Susceptible to

Penicillinases (*staph*)

Extended spectrum beta-lactamase ESBL (*E.coli, Klebsiella*)

ESBL

a group of plasmid-mediated, diverse, complex and rapidly evolving enzymes which share the ability to hydrolyze third-generation cephalosporins and aztreonam

Rawat et al, 2010

Cephalosporins

3rd is gived oral ??

Pharmacokinetics 1st, 2nd ⇒ Are given oral

- **Administration:**

- Poor oral absorption, mostly given IV, IM

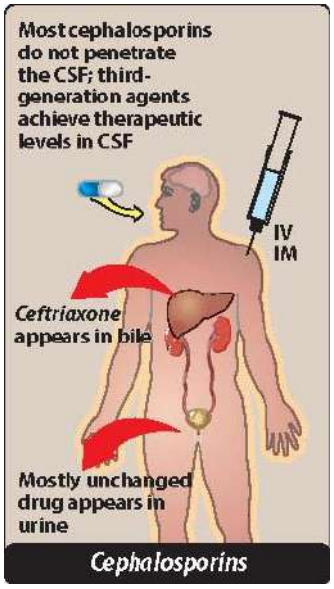
- **Distribution:**

- To CSF: ceftriaxone and cefotaxime are effective in the treatment of neonatal meningitis caused by *H. Infuenzae*

-cefazolin can penetrate bone is gived in bone infection

- **Elimination:**

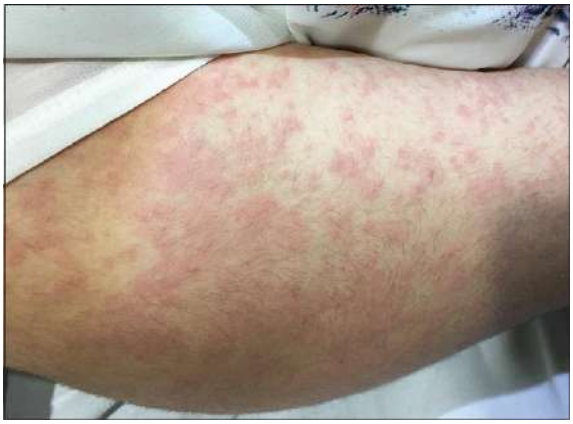
-Renal tubular secretion (except ceftriaxone, eliminated in bile)

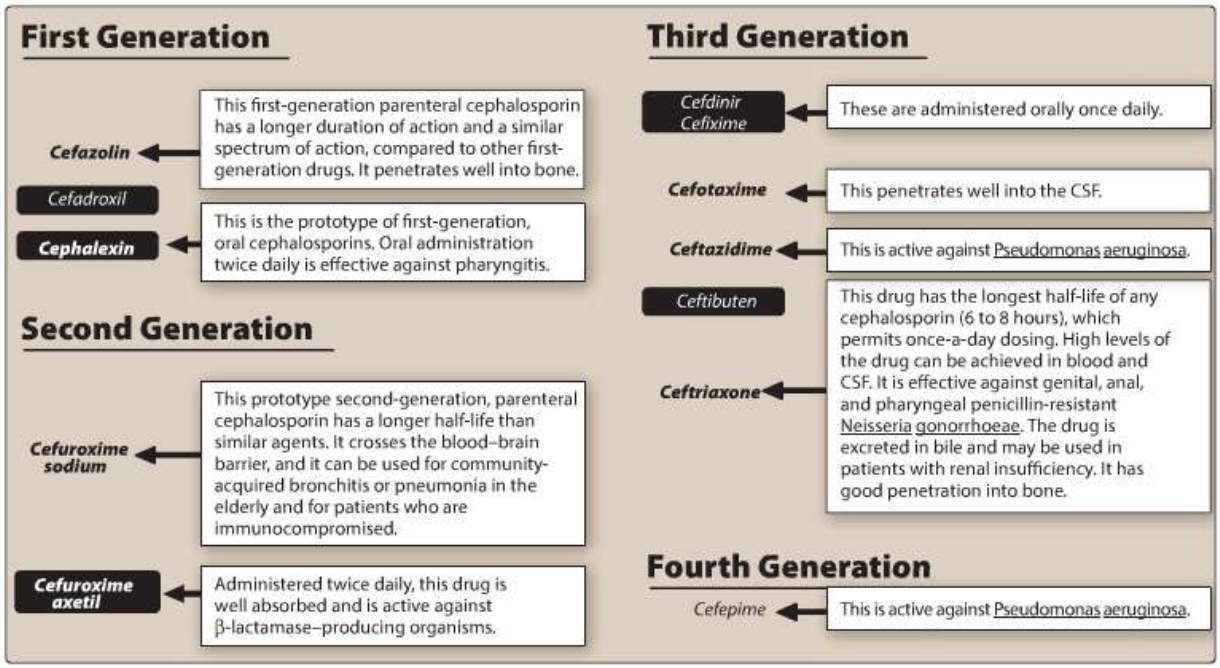


Cephalosporins

Adverse effects

- Hypersensitivity (cross-reactivity with penicillin)
- Highest rate of allergic cross-sensitivity with penicillin→1st generation
- Remember: broad-spectrum antibiotics are associated with superinfections





Other β-Lactams

Tareq Saleh ©
Copyright © 2018 Wolters Kluwer • All Rights Reserved
Wolters Kluwer

1- All of these drugs are synthetic

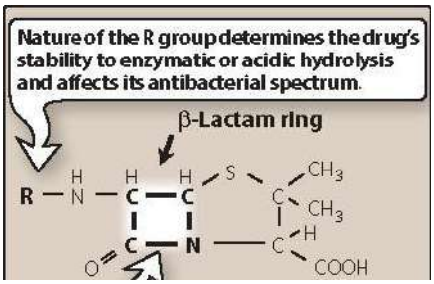
2- Cell wall synthesis inhibitors

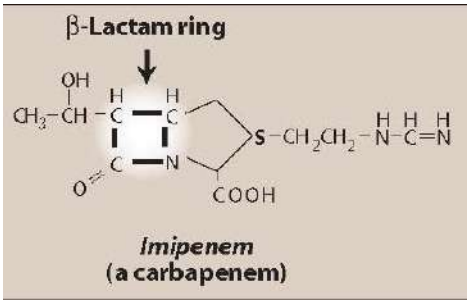
3- Used as the last option

Carbapenems

CARBAPENEMS	
Doripenem	DORIBAX
Ertapenem	INVANZ
Imipenem/cilastatin	PRIMAXIN
Meropenem	MERREM

back to brand name





Carbapenems are synthetic beta-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring (Figure 29.2) has been externalized and replaced by a carbon atom (Figure 29.14). Imipenem [i-mi-PEN-em], meropenem [mer-oh-PENem], doripenem [dore-i-PEN-em], and ertapenem [er-ta-PEN-em] are drugs in this group.

*Can be combined with β-lactamase inhibitors

Pharmacokinetics: Imipenem, meropenem, and doripenem 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. These agents are excreted by glomerular filtration. Imipenem undergoes* cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. Compounding imipenem with cilastatin protects the parent drug from renal dehydropeptidase and, thus, prolongs its activity in the body. The other carbapenems do not require coadministration of cilastatin. Ertapenem is administered IV once daily. [Note: Doses of these agents must be adjusted in patients with renal insufficiency.]

Carbapenems

Antibacterial spectrum

- Broad-spectrum (used for empiric therapy)
- Resist β-lactamases
- Effective against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa

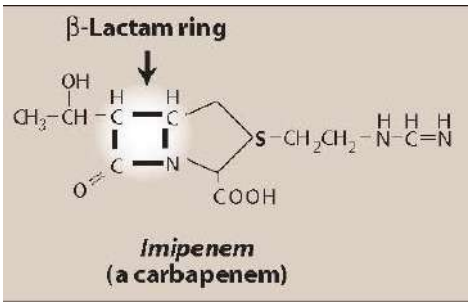
*Not MRSA

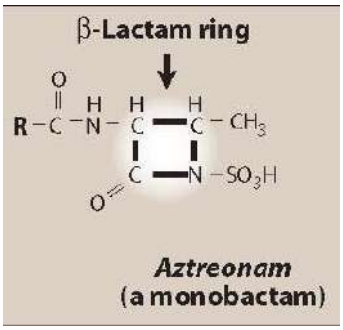
The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the 13-lactam ring is not fused to another ring (Figure 29.14). Aztreonam [az-TREE-oh-nam], which is the only commercially available monobactam, has antimicrobial activity directed primarily against gram-negative pathogens, including the Enterobacteriaceae and .P. aerugjnosa. It lacks activity against grampositive organisms and anaerobes. Aztreonam 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 13-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems

Monobactams

MONOBACTAMS

Aztreonam AZACTAM





-Effective against gram-negative (including P. aeruginosa)

-Lacks activity against gram-positive

-Susceptible to ESBLs Extended Spectrum Beta-Lactamase

-Relatively non-toxic

-little cross-reactivity with other β-lactams

So, can be given to patients with Penicillin resistance

Can Cephalosporins and Carbapenems Be Combined with β-lactamase inhibitors?

- Ceftolozane + tazobactam: used for multidrug resistant P. aeruginosa and some ESBLs-producing bacteria
- Ceftazidime + avibactam: used against ESBL-producing bacteria

(1)

***both indicated for the management of complicated intra-abdominal and urinary tract infections caused by multidrug resistant bacteria

(2)

- Meropenem + vaborbactam: used against ESBL-producing bacteria

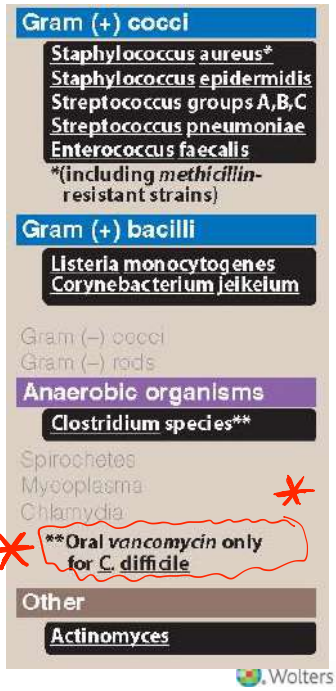
***indicated for the management of complicated urinary tract infections

1-Not B-lactames
2-Cell wall synthesis inhibitor
3-Doesn't target PBPs
4-Binds to peptidoglycans precursers

Vancomycin

- tricyclic glycopeptide
- **What is the mechanism of action of vanco?**
- Effective against gram-positive bacteria INCLUDING MRSA and MRSE
- Oral and IV
- IV vanco used in patients with MRSA skin infections, infective endocarditis, ...
- Oral vanco used for severe antibiotic associated pseudomembranous colitis
- Vanco is not absorbed after oral administration

Used in systemic infections



Vancomycin [van-koe-MYE-sin] is a tricyclic glycopeptide active against aerobic and anaerobic gram-positive bacteria, including MRSA, methicillin-resistant Staphylococcus epidermidis (MRSE), Enterococcus spp., and Clostridium difficile (Figure 29.17). Following cell entry, it binds to peptidoglycan precursors, disrupting polymerization and cross-linking required for maintenance of cell wall integrity. This interaction results in bactericidal activity. Due to an increase in MRSA, vancomycin is commonly used in patients with skin and soft tissue infections, infective endocarditis, and nosocomial pneumonia. Frequency of administration is dependent on renal function. Therefore, monitoring of creatinine clearance is required to optimize exposure and minimize toxicity. Optimal cure rates are observed when trough concentrations are maintained between 1 0 and 20 mcg/ml. [Note: The area under the curve/minimum inhibitory concentration ratio (AUC/MIC) is the best predictor of vancomycin activity against .S. aureus, with an AUC/MIC of greater than or equal to 400 associated with treatment success.] Initial trough concentrations are attained prior to the fourth or fifth vancomycin dose to ensure appropriate dosing. Common adverse events include nephrotoxicity, infusion-related reactions (red man syndrome and phlebitis), and ototoxicity. Emergence of resistance is uncommon within Streptococcus and Staphylococcus spp., but frequently observed in Enterococcus faecium infections. Resistance is driven by alterations in binding affinity to peptidoglycan precursors. Due to the prevalence of resistance, prudent use of vancomycin is warranted. Lastly, vancomycin has poor absorption after oral administration, so use of the oral formulation is limited to the management of Clostridium difficile infection in the colon.

Vancomycin

- Bactericidal
- Time- and concentration-dependent

Homework: What is the best predictor of vancomycin's antistaph activity?

Adverse effects

- Nephrotoxicity
- Red man syndrome
- Ototoxicity

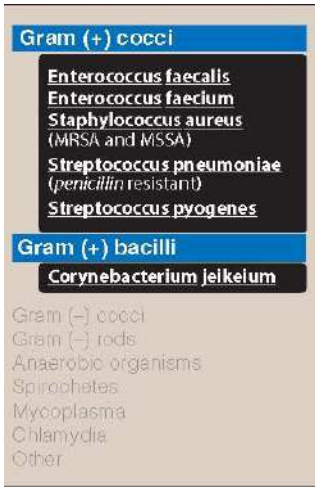
Mechanisms of resistance:

- Alteration in binding affinity to peptidoglycan precursors

Daptomycin [DAP-toe-mye-sin] is a bactericidal concentration-dependent cyclic lipopeptide antibiotic that is an alternative to other agents, such as vancomycin or linezolid, for treating infections caused by resistant gram-positive organisms, including MRSA and vancomycin-resistant enterococci (VRE) (Figure 29.18). 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. Daptomycin is dosed IV once daily. Figure 29.19 provides a comparison of important characteristics of vancomycin, daptomycin, and lipoglycopeptides.

Daptomycin

- cyclic lipopeptide
- bactericidal
- concentration-dependent
- Effective against gram-positive INCLUDING MRSA vancomycin-resistant enterococci (VRE)
- Not used for pneumonia. WHY?



	VANCOMYCIN	DAPTOMYCIN
Mechanism of Action	Inhibits bacterial cell wall synthesis	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein
Pharmacodynamics	Combination of time and concentration-dependent Bactericidal	Concentration dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: Staphylococcus aureus (including MI S. agalactiae, penicillin-resistant S. pneumoniae, Corynebacterium jeikeium, *vanc* faecalis, and E. faecium	
Unique Antibacterial Spectrum	Clostridium difficile (oral only)	*Vancomycin*-resistant E. faecalis and E. faecium (VRE)
Route	IV/PO orally	IV

	VANCOMYCIN	DAPTOMYCIN
Typical Administration Time	60- to 90-minute IV infusion	2-minute IV push 30-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
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)
Key Learning Points	Drug of choice for severe MRSA infections; oral form only used for C. difficile infection; resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules; monitor serum trough concentrations for safety and efficacy	*Daptomycin* is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia

Lipoglycopeptides

Telavancin

- Bactericidal
- Concentration-dependent
- Similar antibacterial spectrum as vancomycin (but better)
- Alternative to vancomycin for the treatment of ABSSSIs and nosocomial pneumonia caused by MRSA
- More toxic: nephrotoxicity and cardiotoxicity

hospital-acquired pneumonia

Acute bacterial skin and skin-structure infections (ABSSSI)

Can't be given for someone that has just survived from heart attack or cardiac arrhythmia

Fosfomycin

- Derivative of phosphoric acid
- Bactericidal
- **MOA**: blocks cell wall synthesis by inhibiting the enzyme UDP-N-acetylglucosamine *enolpyruvyl transferase* (*first step* in peptidoglycan synthesis)
- First line therapy for acute cystitis (Urinary bladder inflammation)
- Cross-resistance is unlikely

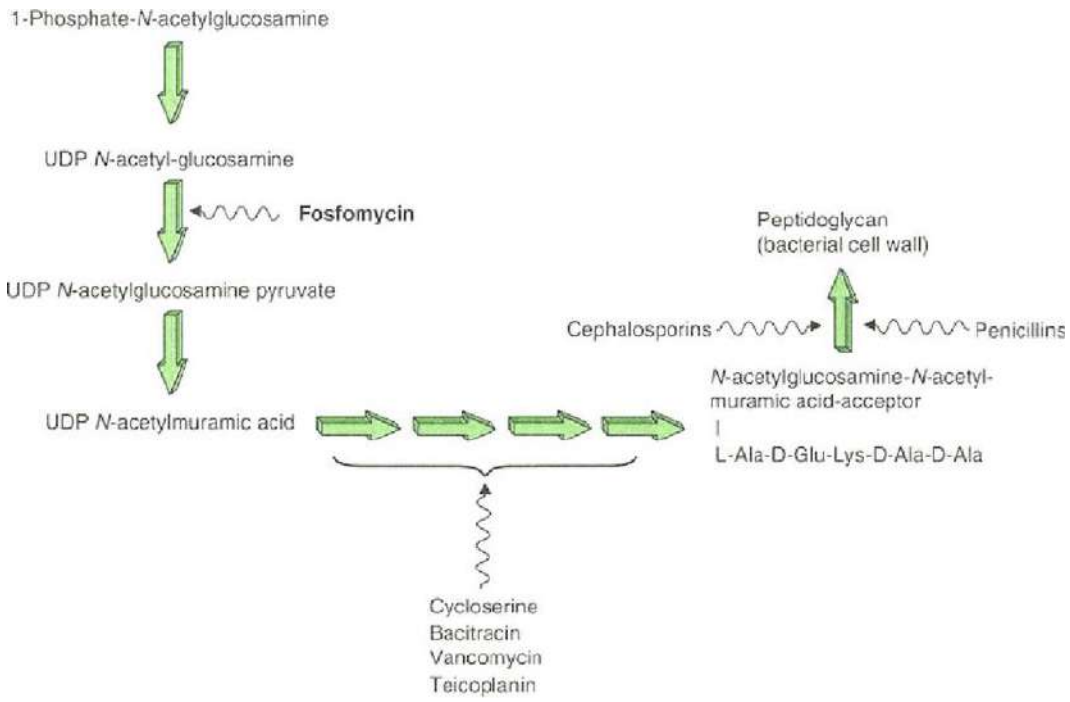
Polymyxin B (Colistin)

- Cation polypeptides
- **MOA**: bind phospholipids on the bacterial cell membrane of gram-negative bacteria (disrupt cell membrane not cell wall)
- Active against most gram-negative bacteria including P. aeruginosa
- Bactericidal (→ Acetinobacter)
- Concentration-dependent
- Limited use because of nephrotoxicity/neurotoxicity
- **Spared for multi-drug resistant infections**

In Jordan

- We are starting to see bacterial infections (mainly gram-negative) that are resistant to almost all antibiotics except for colistin.
- 76.8% of Acetinobacter *baumannii* isolates were MDR and 99.2% were carbapenem-resistant. has many resistance in countries where there is wars
- Resistance patterns indicated
  - **high resistance** for most cephalosporins, carbapenems, and fluoroquinolones
  - **moderate resistance** for trimethoprim/sulfamethoxazole and ampicillin/sulbactam,
  - **low resistance** for aminoglycosides and tetracyclines, while colistin and tigecycline, have the lowest resistance rates

Al-Tamimi *et al*. 2022

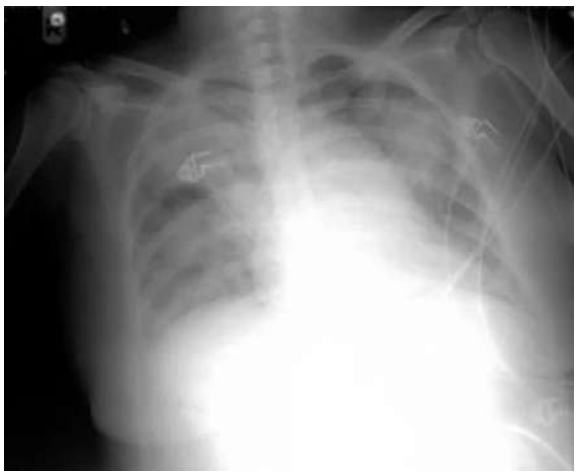


Quick Exercise

Name five cell wall synthesis inhibitors that have antipseudomonal activity.

1. _____
2. _____
3. _____
4. _____
5. _____

A 55-year-old male patient has been hospitalized for the last 3 days after suffering from severe upper gastrointestinal bleeding. While in the hospital, and possibly due to aspiration, the patient started developing fever, dyspnea, and productive cough, with pleuritic chest pain. On examination, the patient had purulent sputum and auscultatory signs of pulmonary consolidation. Radiography showed widespread pulmonary infiltrates suggestive of MRSA infection. Your initial evaluation highly favors the possibility of nosocomial aspiration pneumonia. Which of the following antibiotics must be included in your empiric therapy regimen?



Linezolid
Daptomycin
Ceftriaxone
Cefepime
Nafcillin