Cell Wall Inhibitors

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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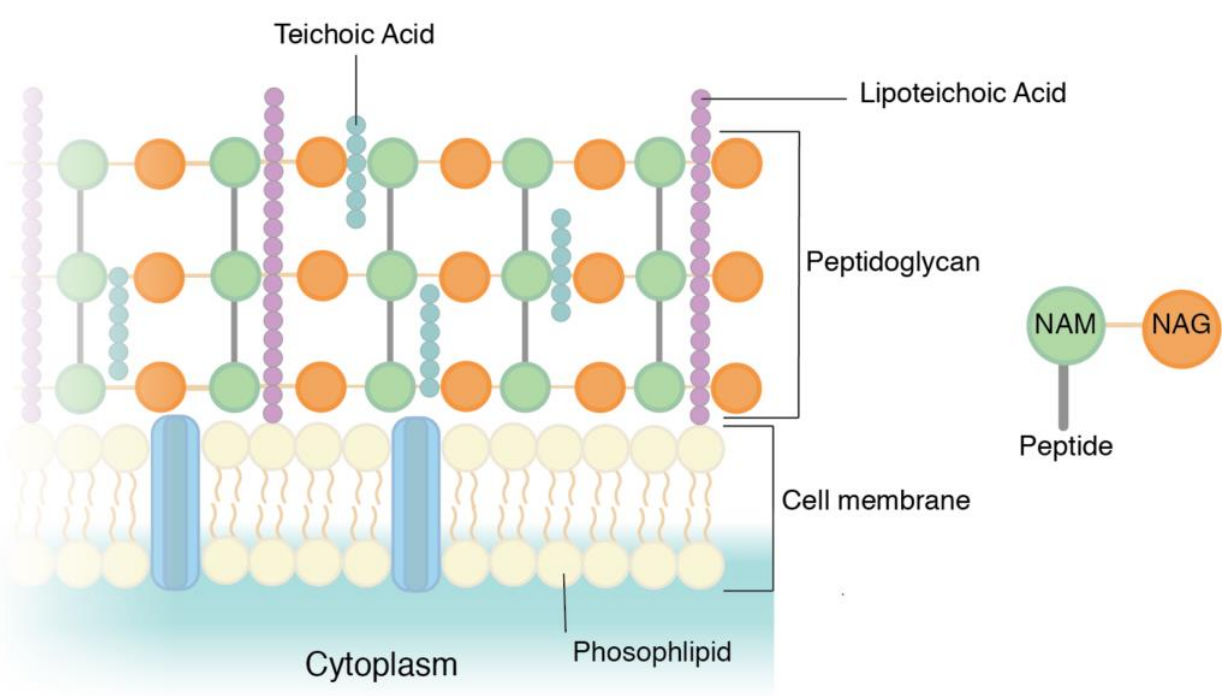
Faculty of Medicine

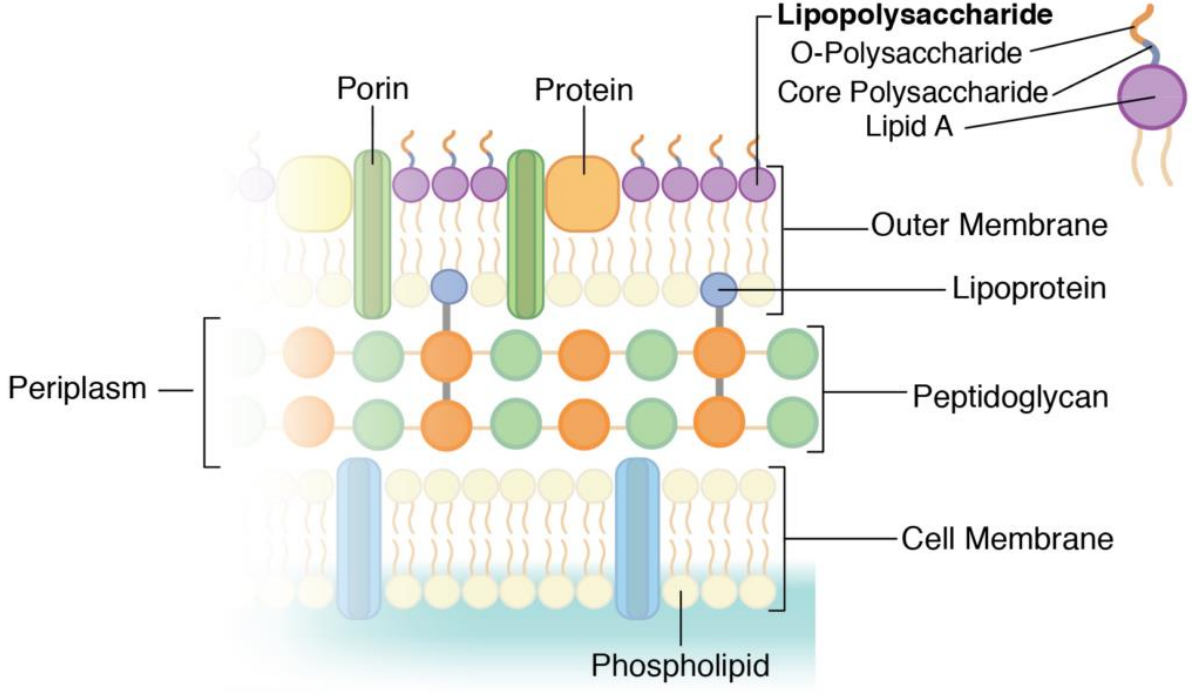
The Hashemite University

Textbook: Chapter 29 pp 369- 383

Overview: Bacterial Cell Wall



Gram Positive Bacteria Cell Wall



Gram Negative Bacteria Cell Wall

Overview: Synthesis of Bacterial Cell Wall

1. Cytoplasmic Stage:

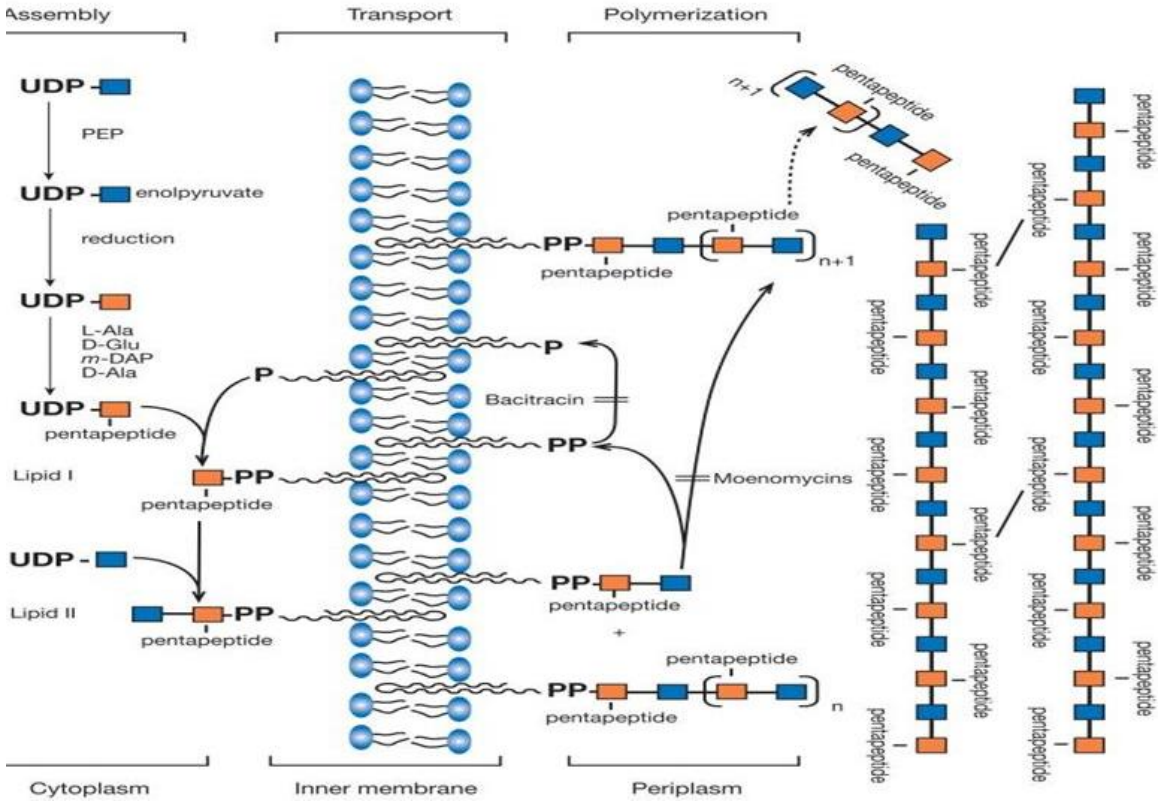
- Synthesis of glycan precursors: UDP-MurNAc-pentapeptide, UDP-GlcNAc

2. Cytoplasmic membrane Stage:

- Transfer to membrane receptors

3. Extracellular membrane stage:

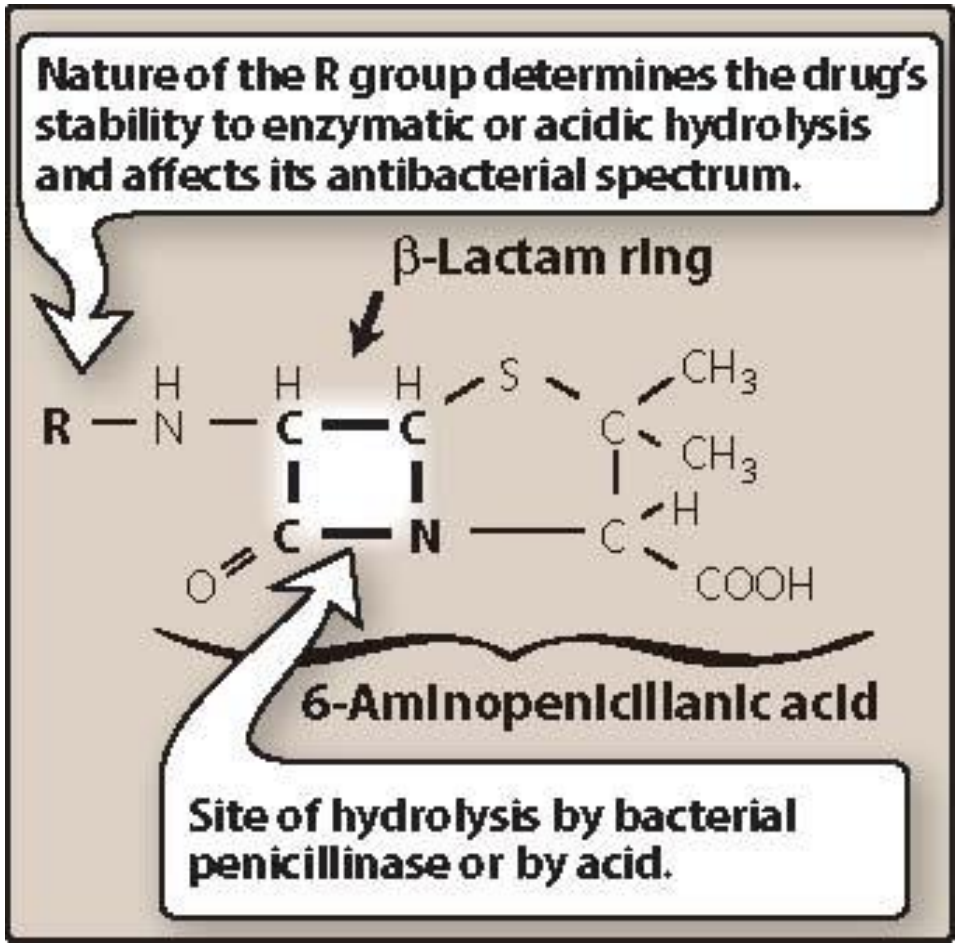
- Transpeptidation via PBP



Penicillins

Penicillins

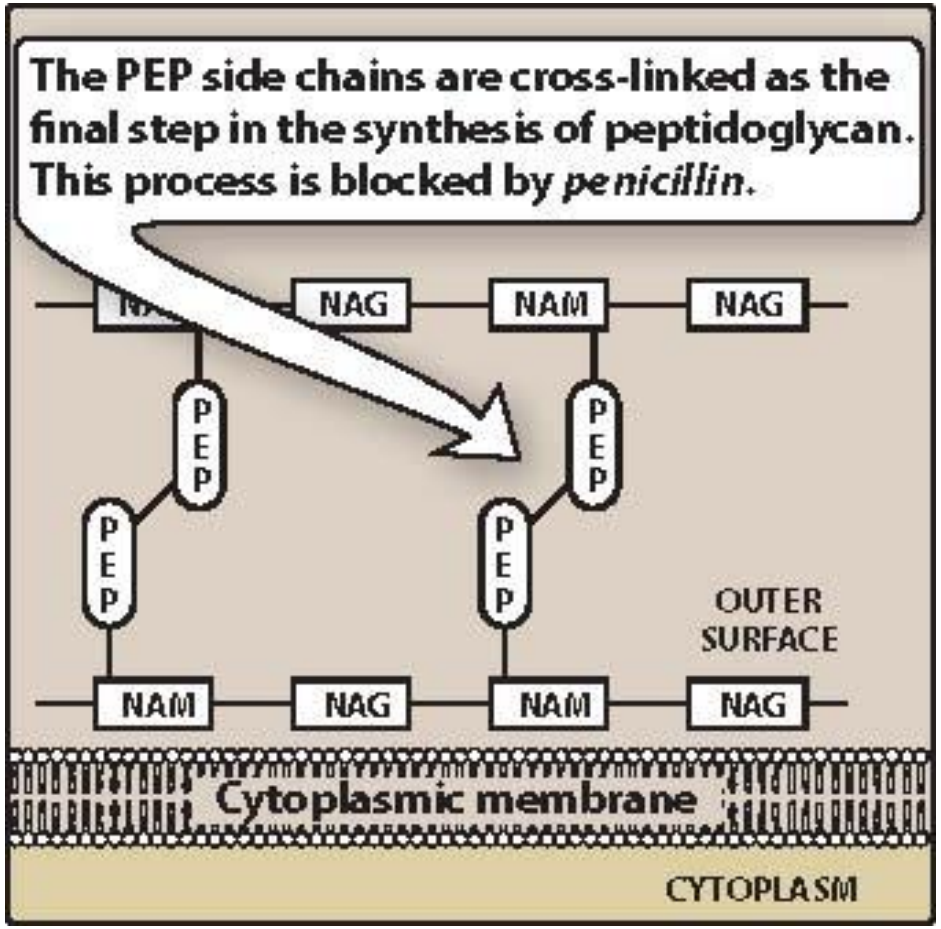
PENICILLINS
Amoxicillin AMOXIL
Ampicillin PRINCIPEN
Dicloxacillin DYNAPEN
Nafcillin
Oxacillin
Penicillin G PFIZERPEN
Penicillin V
Piperacillin
Ticarcillin



Quick Microbiology Reminder

Penicillin-binding proteins:

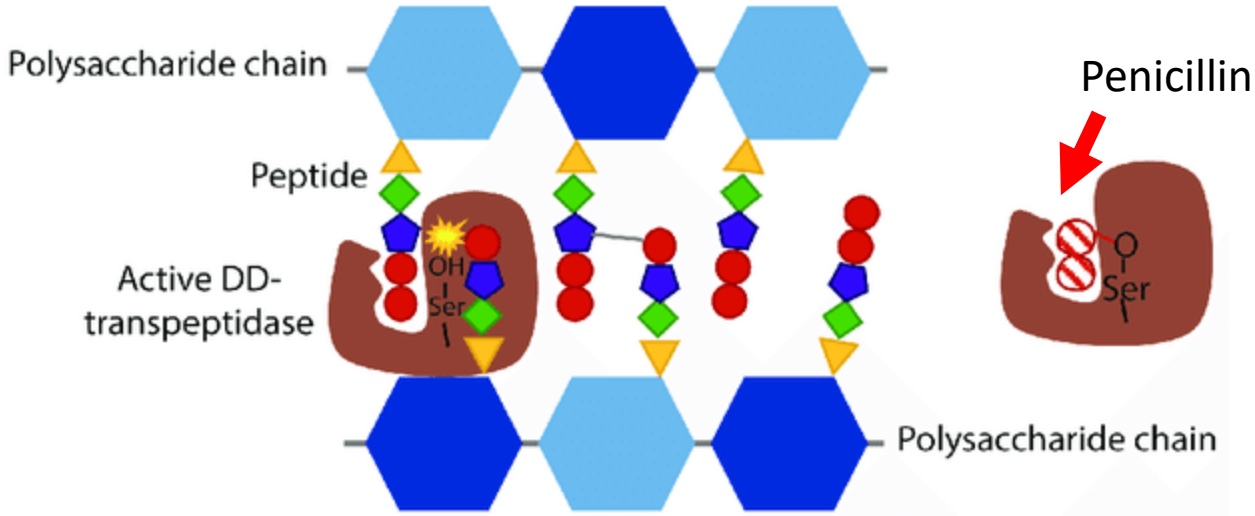
- Penicillins bind and inactivate bacterial cell membrane proteins called: penicillin-binding proteins (PBPs).
- Bacterial enzymes involved in cell wall synthesis
- Variable among different species
- Involved in resistance



Penicillins

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?*

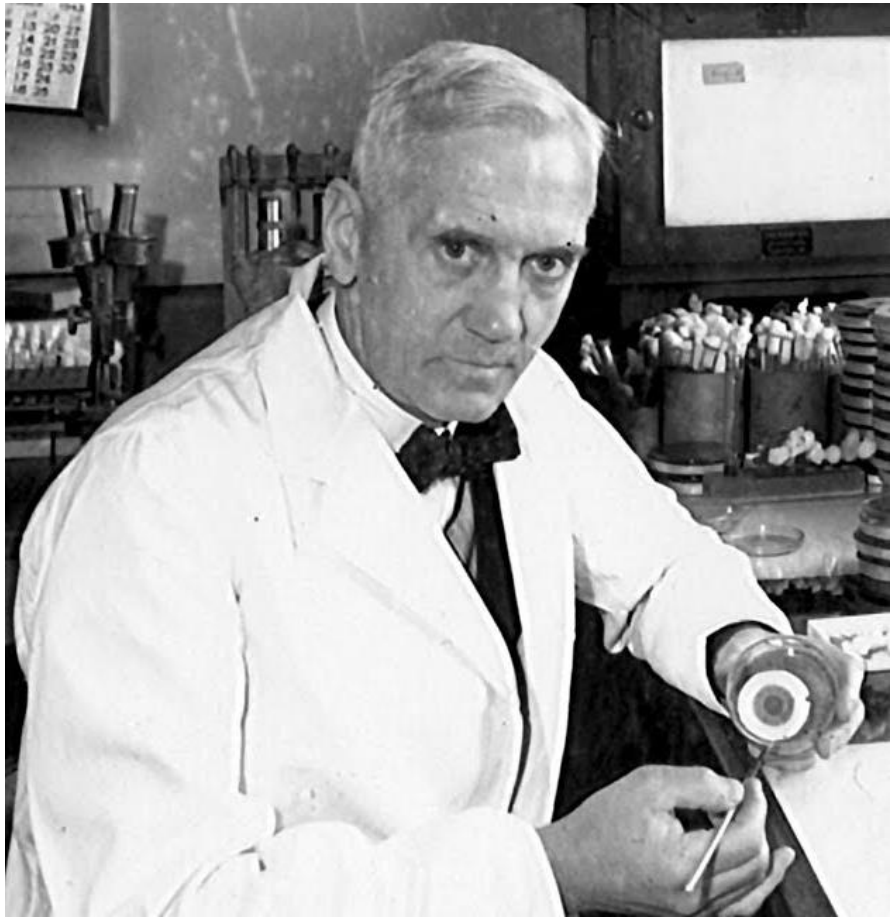
- Bacterial cell lysis
- Bactericidal
- Time-dependent
- Effective against rapidly growing bacteria

Penicillins

Antibacterial spectrum

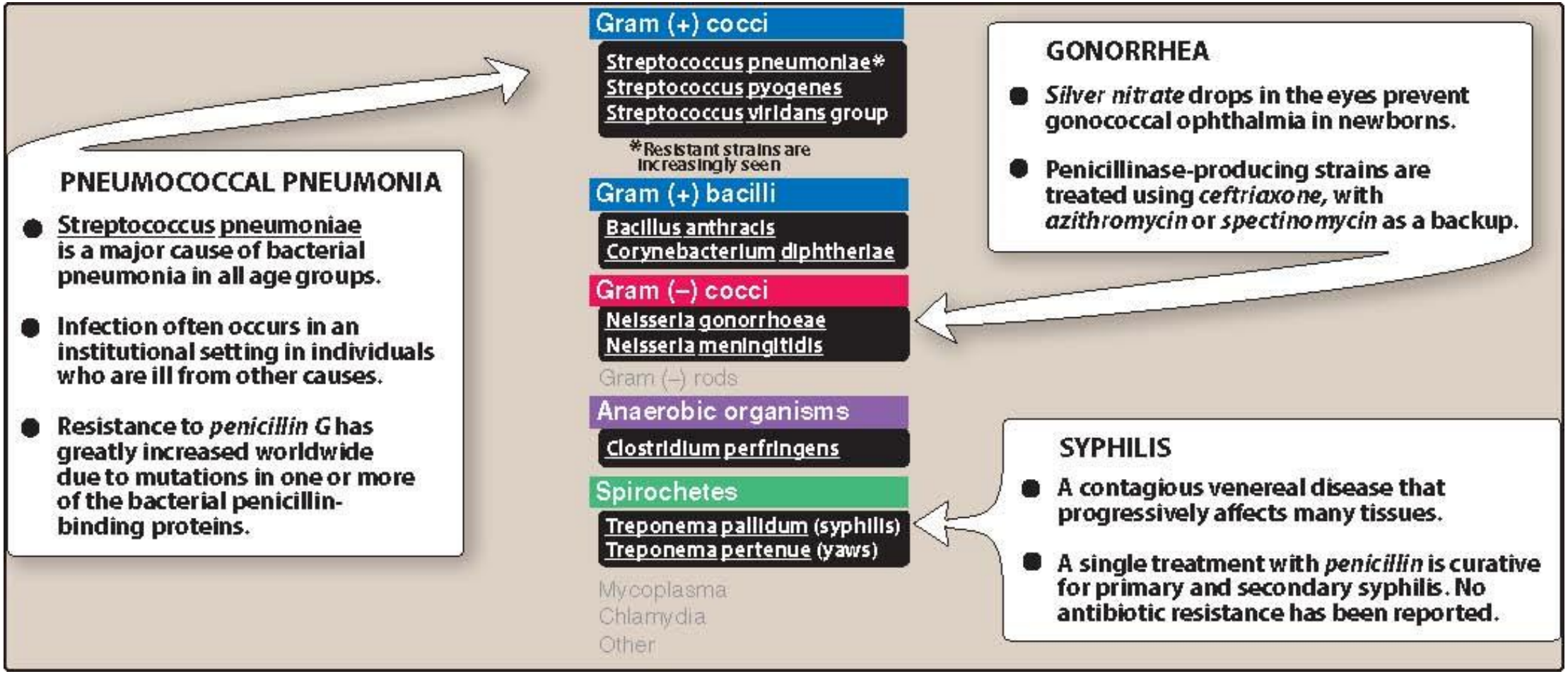
1. Natural penicillins:

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



Penicillins

Antibacterial spectrum



Penicillins

Antibacterial spectrum:

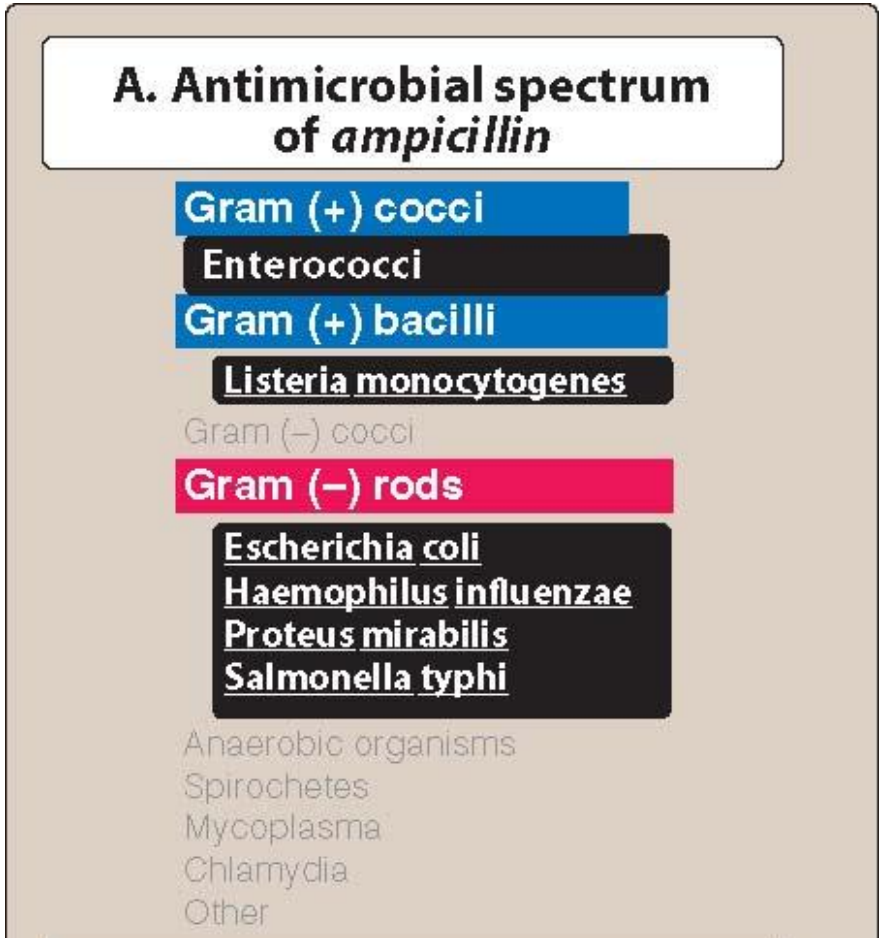
2. Extended-spectrum penicillins:

- 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



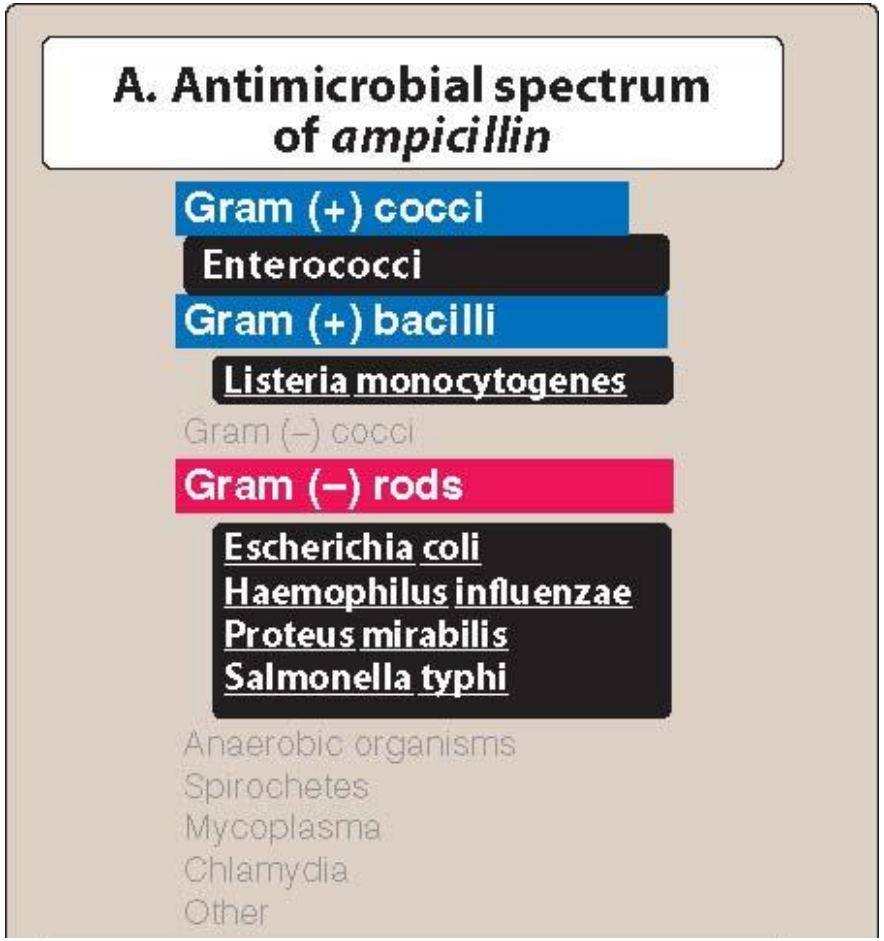
Penicillins

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



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)

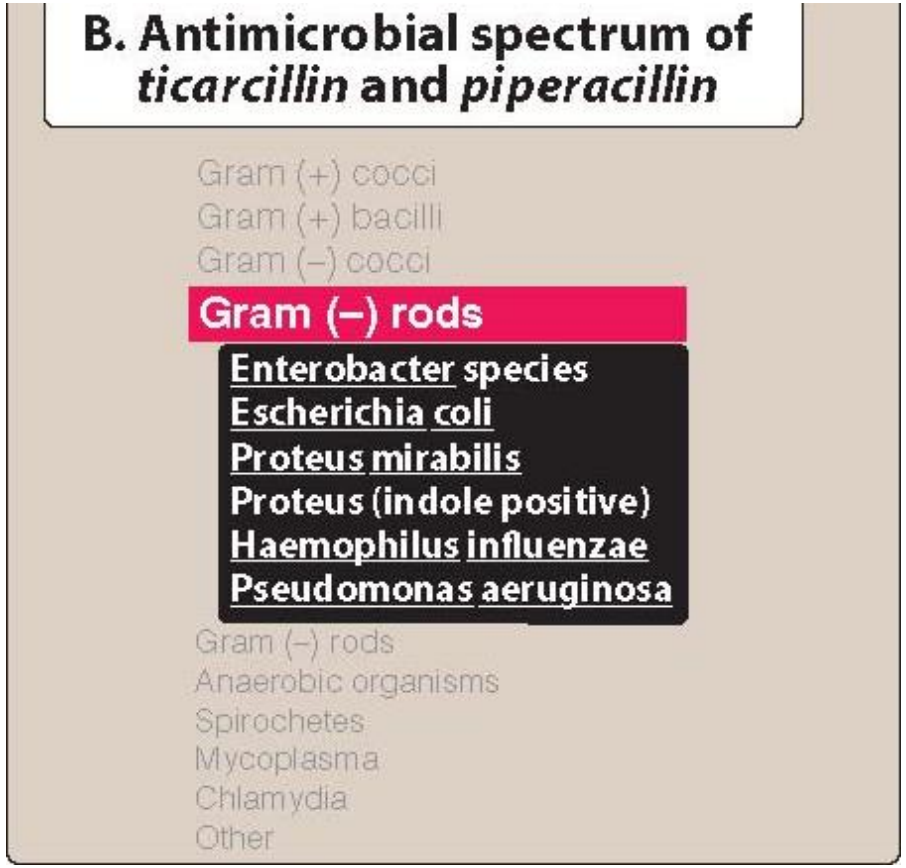
Penicillins

Antibacterial spectrum:

4. Antipseudomonal penicillins:

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

Piperacillin + tazobactam

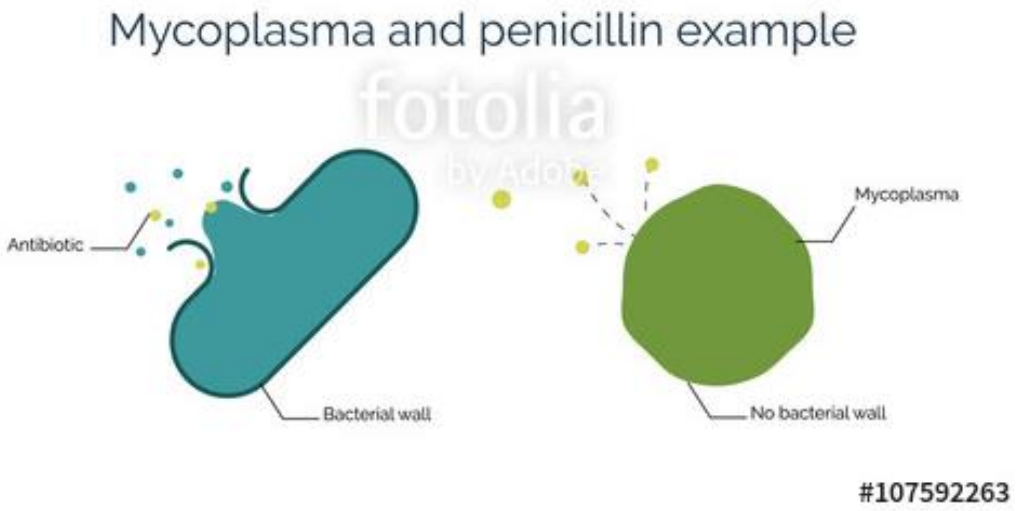


Penicillins

Mechanisms of resistance

- **Intrinsic Resistance:**

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



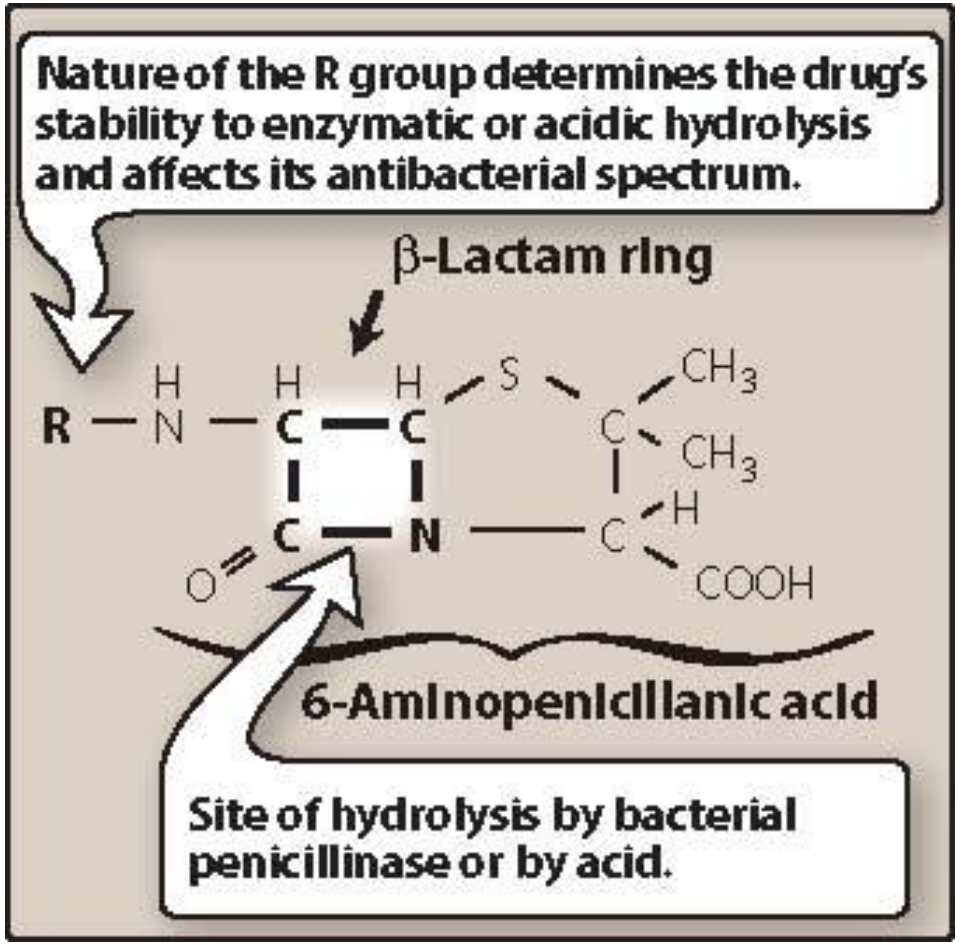
Penicillins

Mechanisms of resistance

- **Acquired Resistance:**

1. β-Lactamase activity:

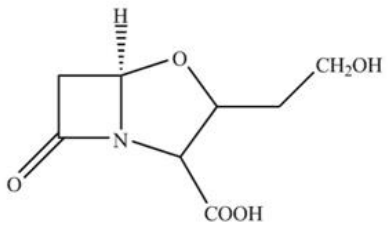
- Enzymes that *hydrolyze* the cyclic amide bond of the β-lactam ring
- Mostly acquired (plasmids)
- **Gram-positive**: secrete β-lactamases extracellularly
- **Gram-negative**: periplasmic β-lactamases



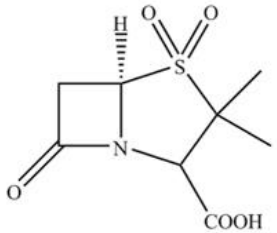
Production of β-Lactamases is the main resistance mechanism against β-Lactams.

How is this problem solved?

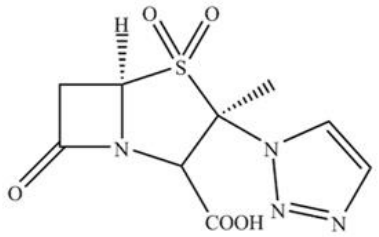
β-Lactamase Inhibitors



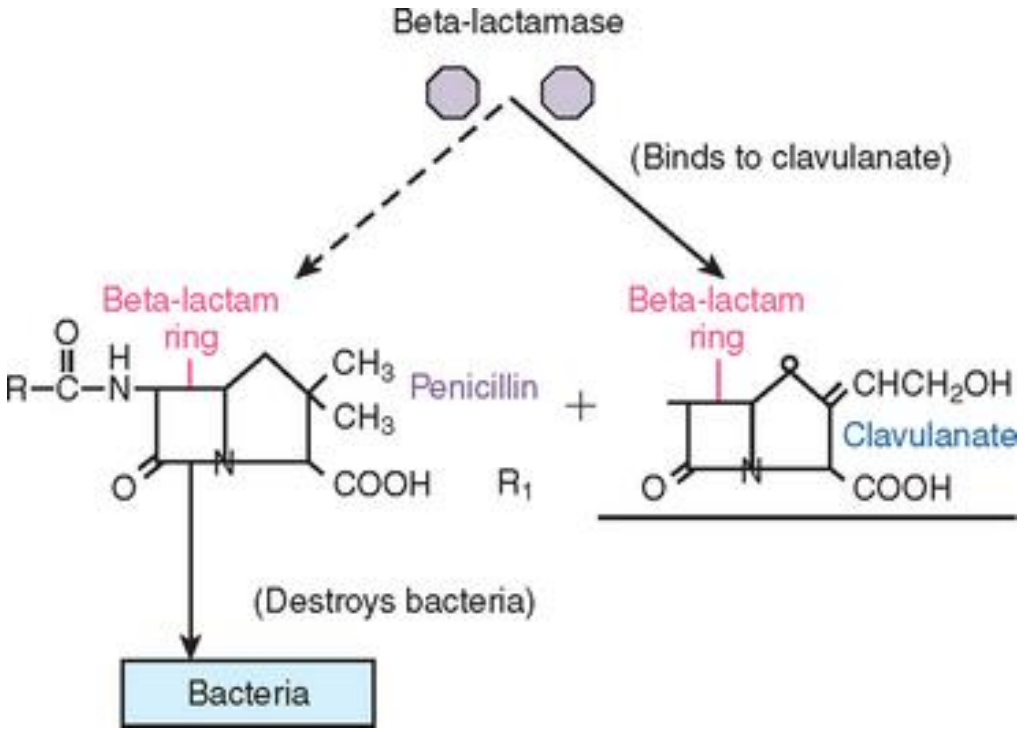
Clavulanic acid



Sulbactam

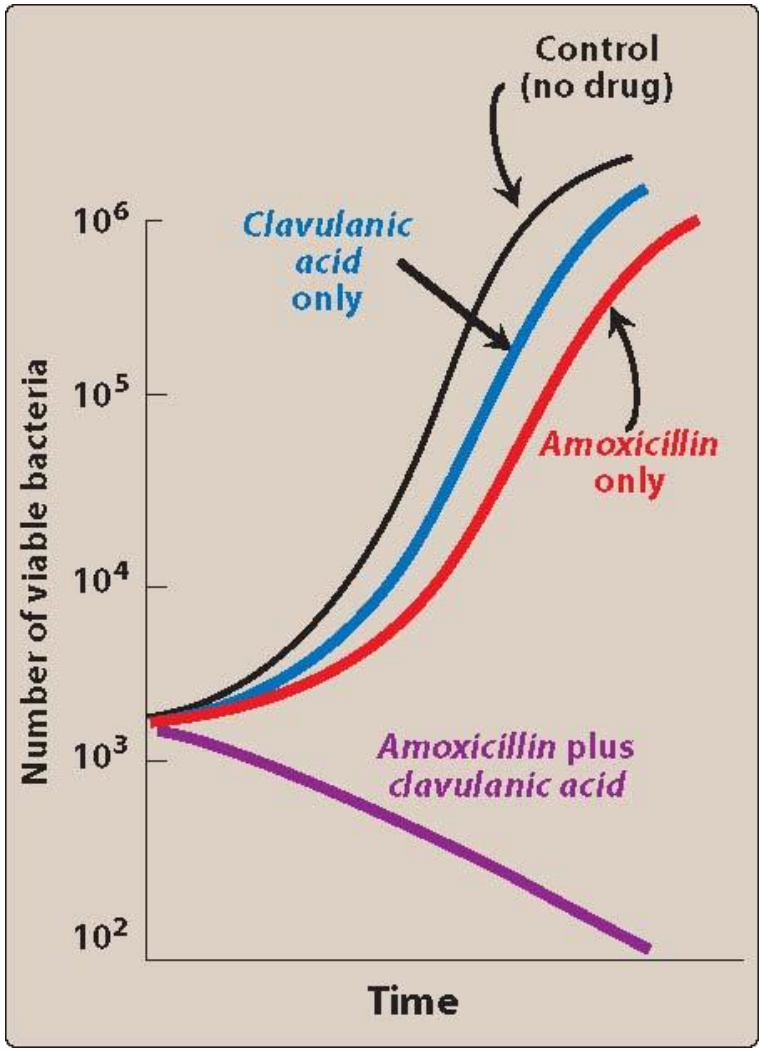


Tazobactam



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:

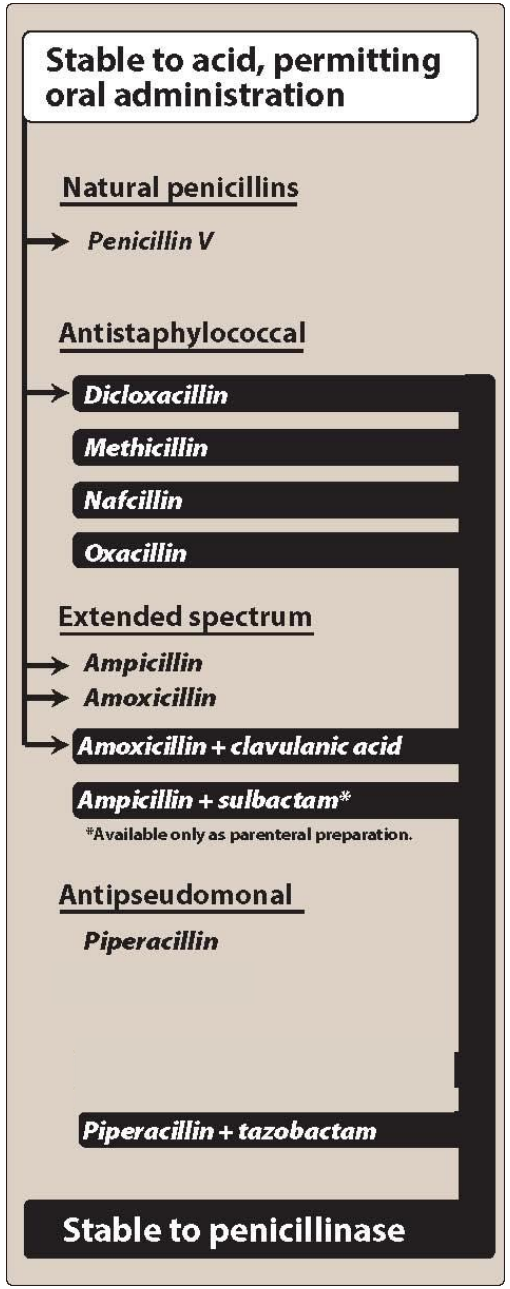
- Modified PBPs with lower affinity for β-lactams e.g., MRSA resistance to most β-lactams.

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)



Penicillins

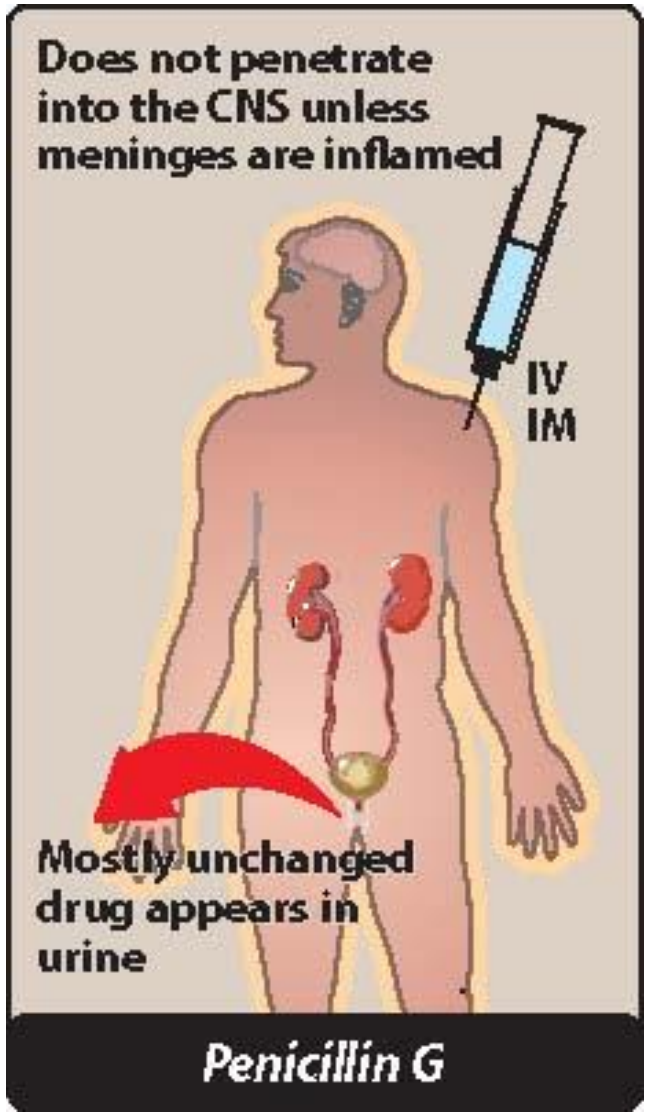
Pharmacokinetics

- **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)



Penicillins

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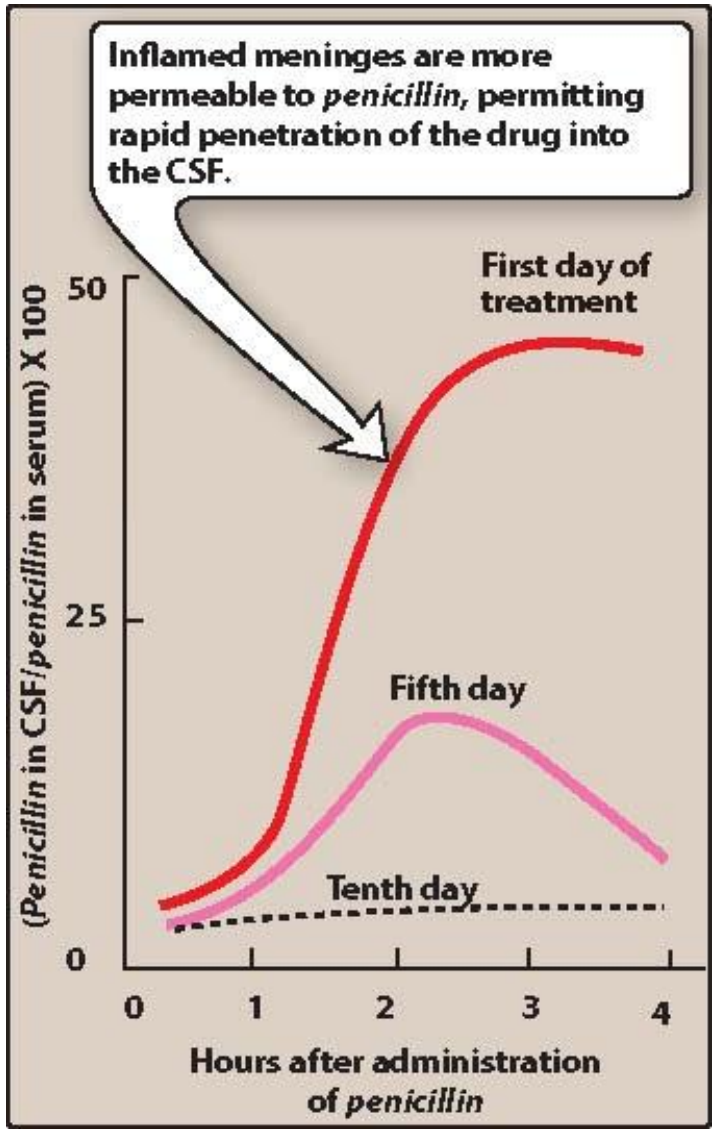


Penicillins

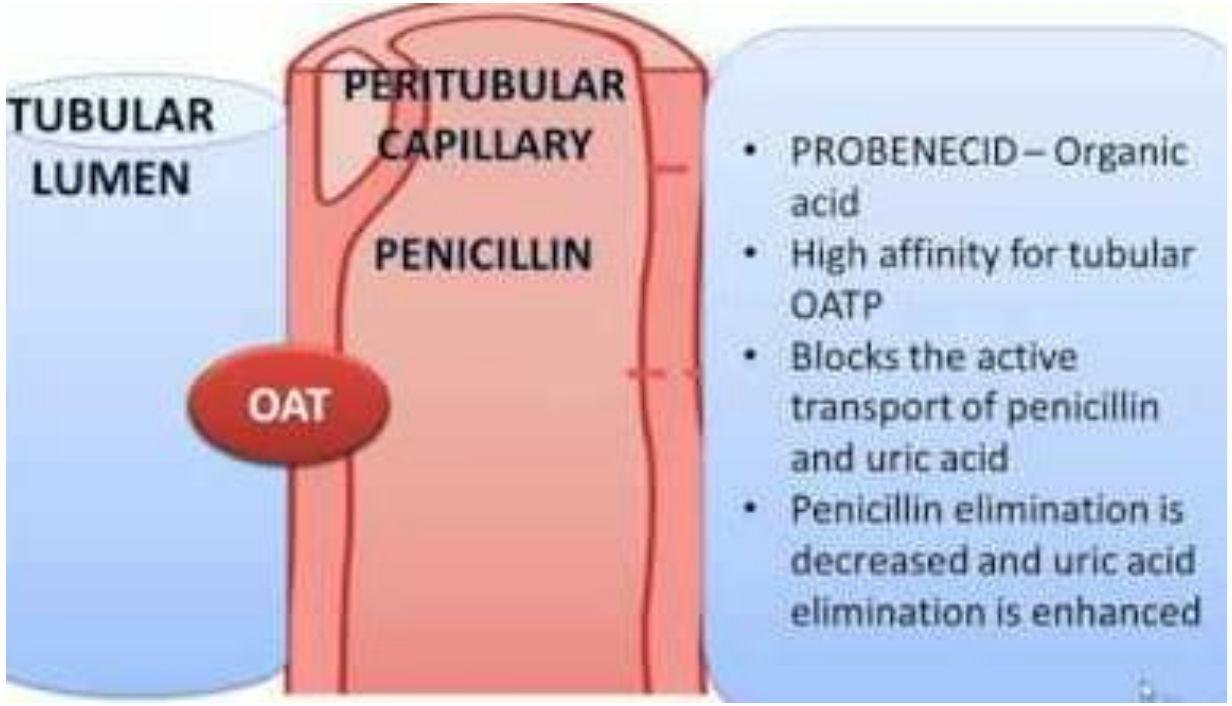
Pharmacokinetics

- **Metabolism**

- Insignificant metabolism
- Exceptions?

- **Excretion:**

- Renal: tubular secretory system
- *Probenecid* is an inhibitor of renal tubular excretion of penicillin



Penicillins

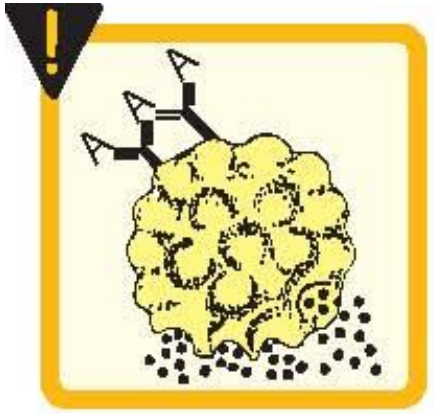
Adverse effects

1. Hypersensitivity:

- 5-10% percent of patients (simple rash to angioedema to anaphylaxis)
- Cross-allergy
- Always inquire about penicillin allergy

2. Diarrhea:

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



Hypersensitivity

Diarrhea

Penicillins

Adverse effects

3. Nephritis:

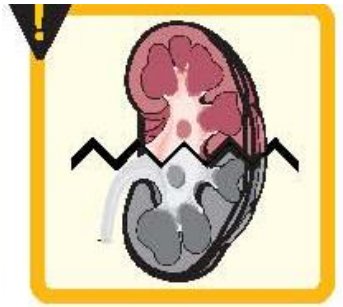
- Methicillin: no longer used because of this

4. Neurotoxicity:

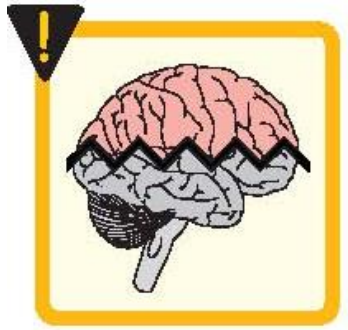
- If injected intrathecally

5. Hematological toxicities

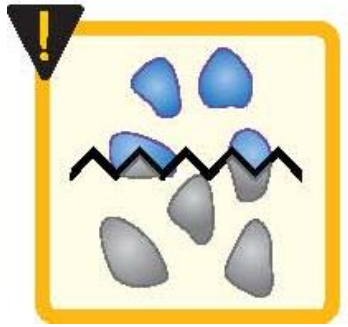
- Decreased coagulation
- Cytopenias



Nephritis



Neurotoxicity



Hematologic toxicities

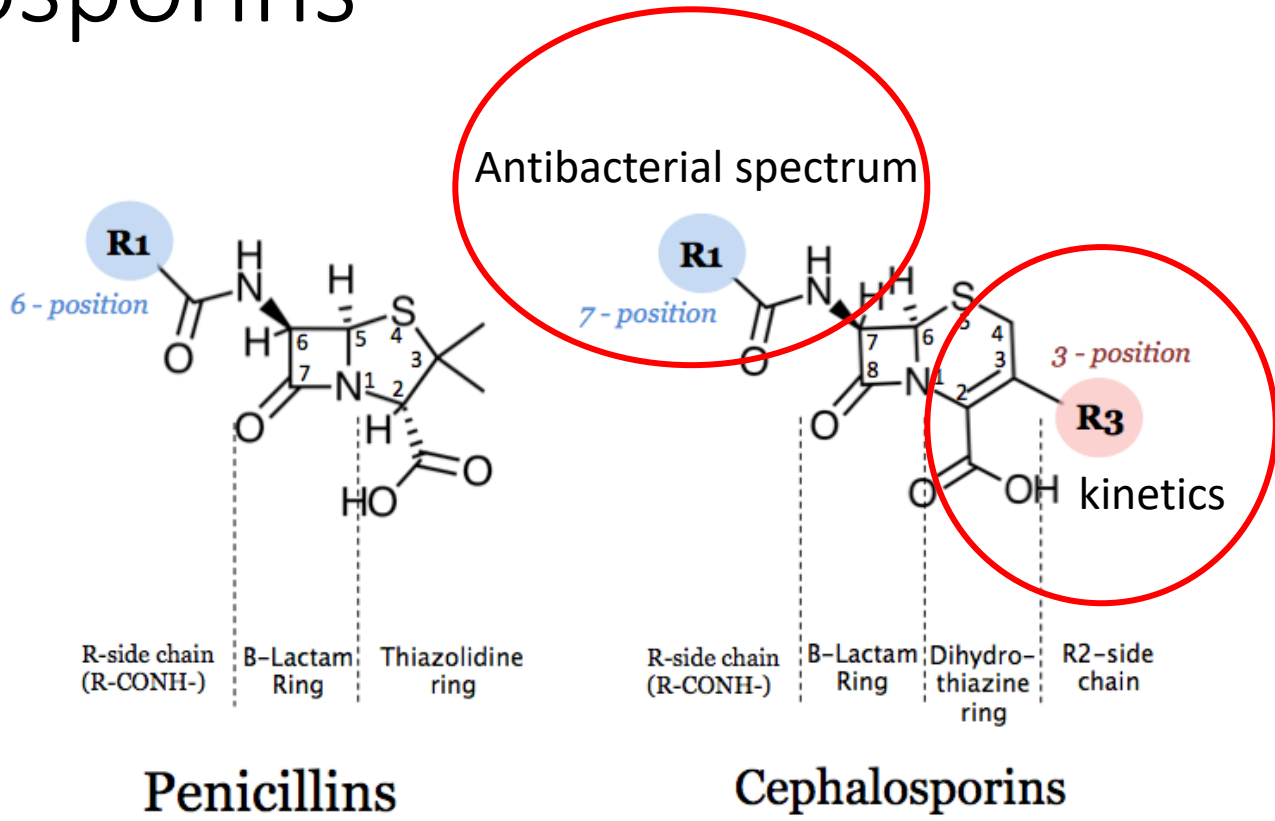
Quick Revision

- Name a penicillin that is effective against penicillinase-producing S. aureus (MSSA)? _____
- Name a penicillin that is effective against penicillinase-producing S. aureus (MRSA)? _____

Cephalosporins

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

Cephalosporins

Antibacterial spectrum

- **First-generation cephalosporins:**

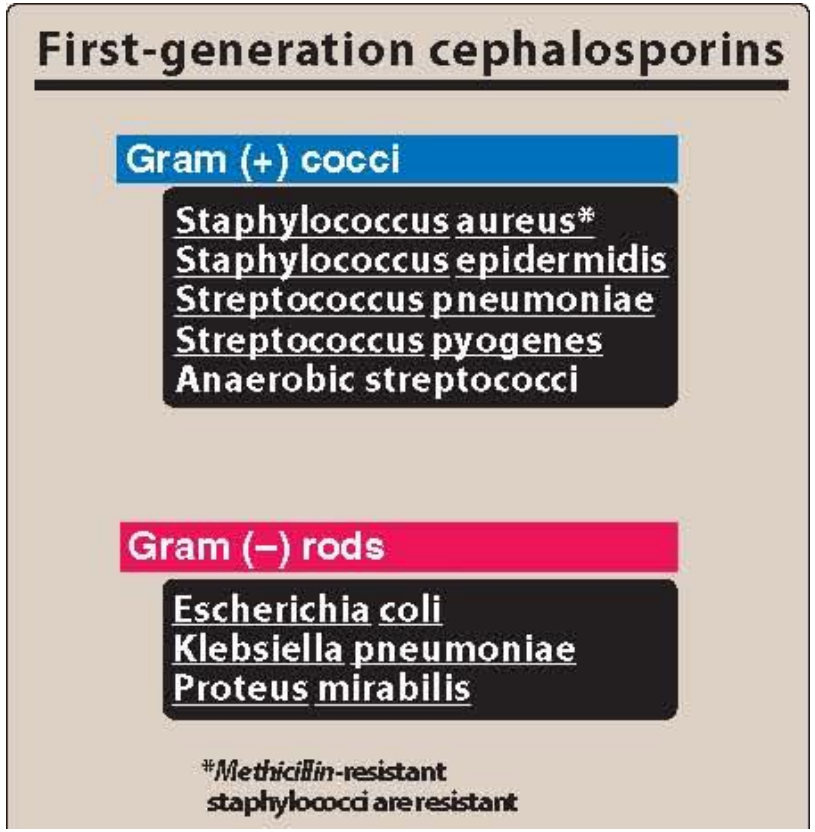
- penicillin G substitutes

- They cover MSSA (resistant to penicillinase) but not MRSA

Cefazolin

Cephalexin

cefadroxil



*Not MRSA

Cephalosporins

Antibacterial spectrum

- **Second-generation cephalosporins:**

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

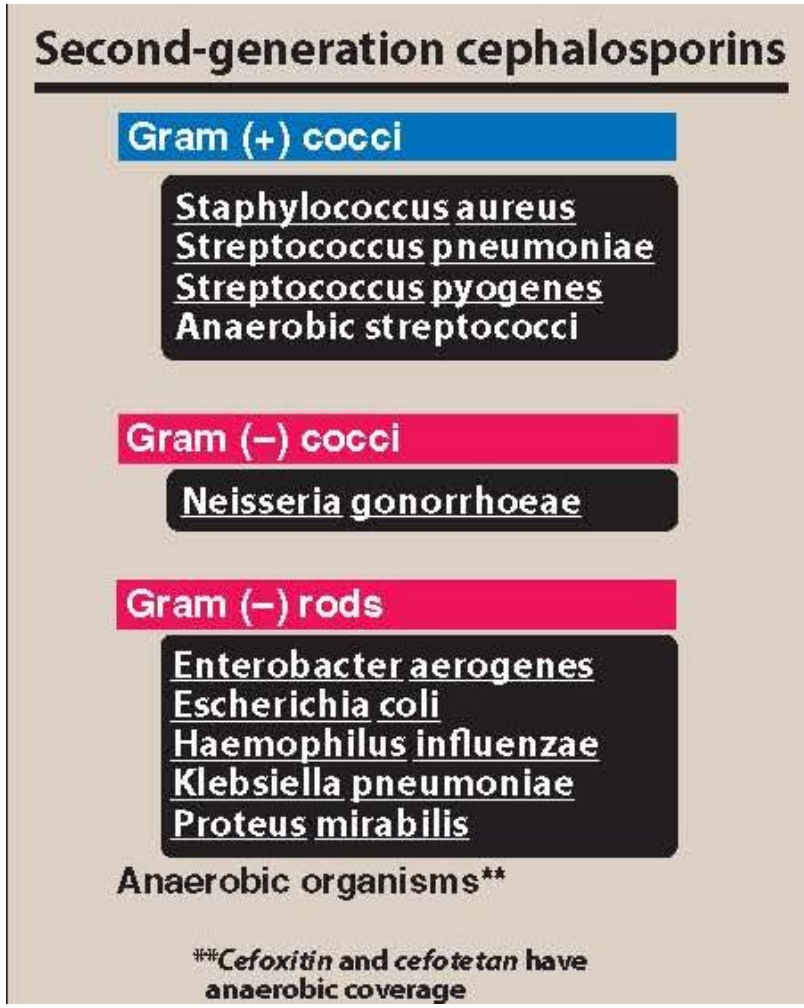
Cefotetan

Cefuroxime

Cefoxitin

Cefprozil

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”

Ceftriaxone

Cefotaxime

Ceftazidime

Cefdinir

*only ceftazidime

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?
- *What are the limitations for using ceftaroline?*

Ceftaroline

Quick Exercise

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

-amoxicillin

-ampicillin

-amoxicillin/clavulanate

-cefazolin

-cephalexin

-ceftriaxone

-cefepime

-ceftaroline

Cephalosporins

Mechanisms of resistance

- Similar to penicillins

<u>Susceptible to</u>

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

Pharmacokinetics

- **Administration:**

- Poor oral absorption, mostly given IV, IM

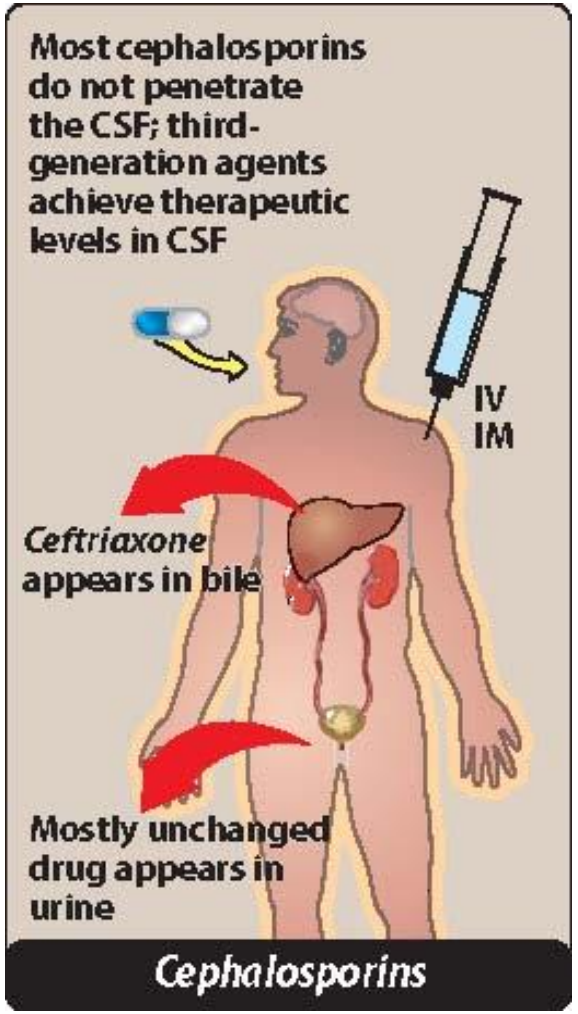
- **Distribution:**

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

-cefazolin can penetrate bone

- **Elimination:**

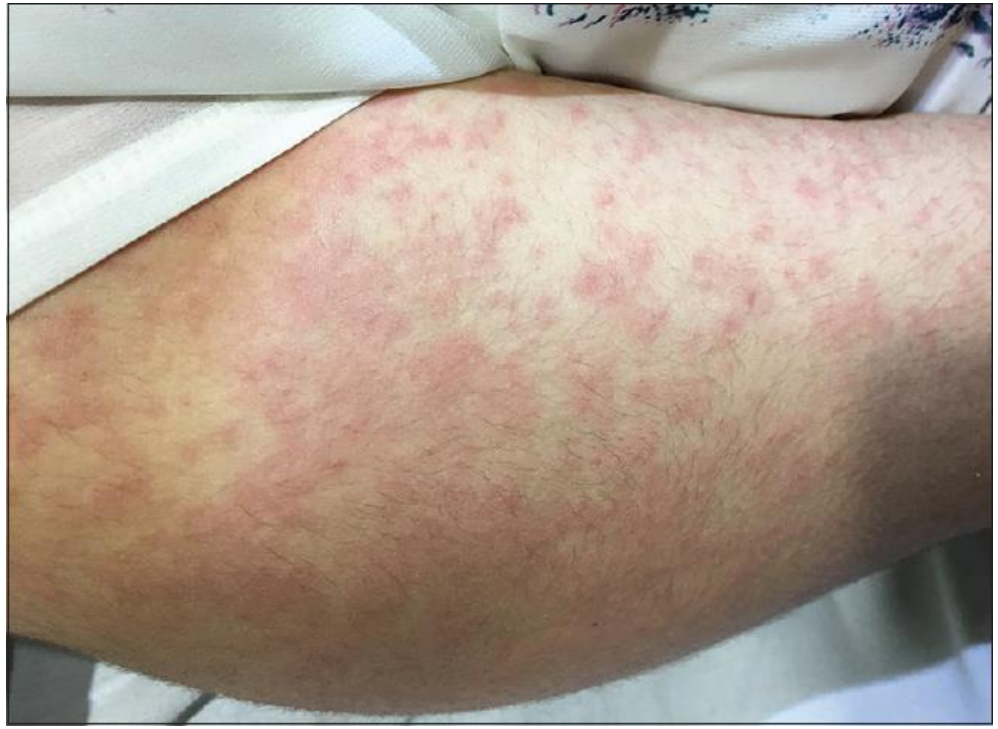
-Renal tubular secretion (except ceftriaxone, eliminated in bile)

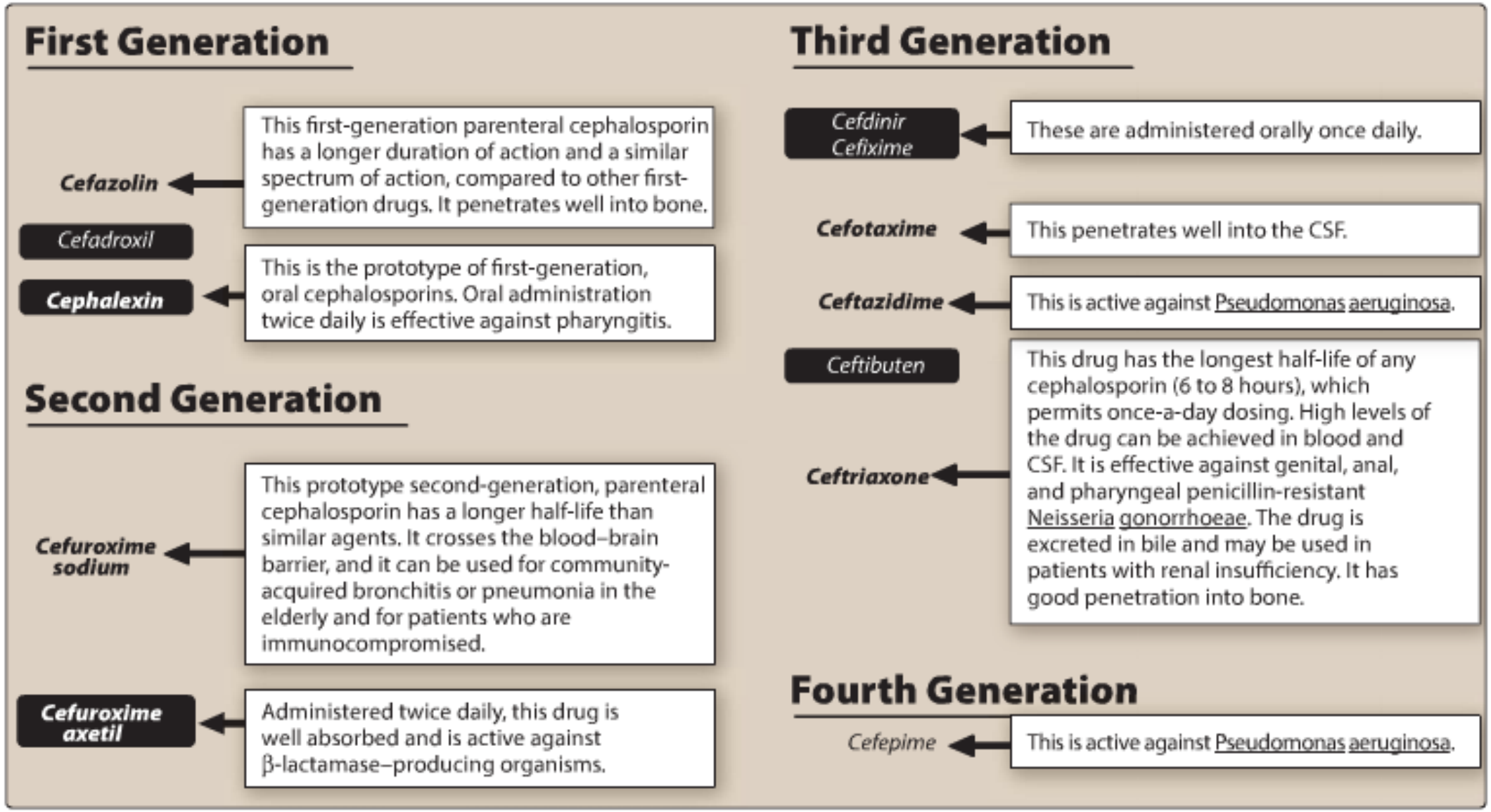


Cephalosporins

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



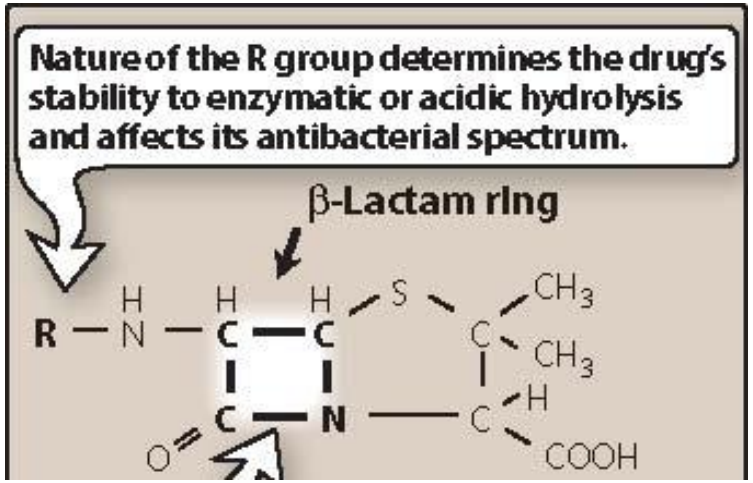


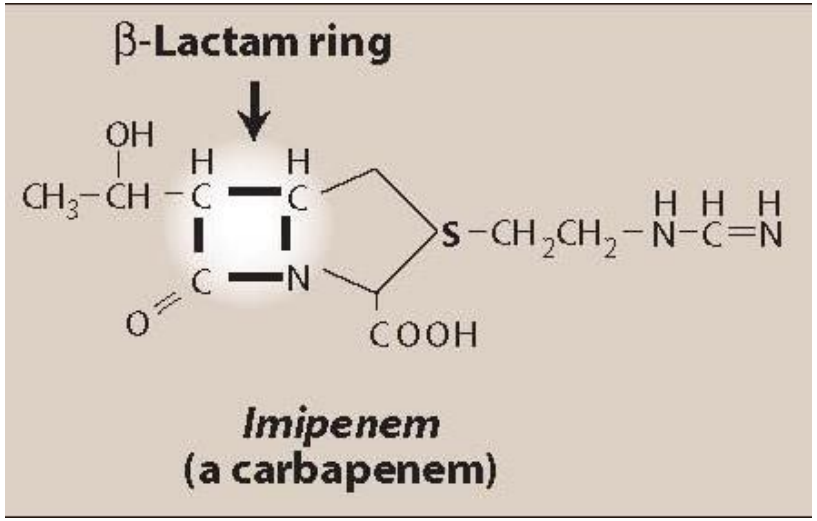
Other β-Lactams

Carbapenems

CARBAPENEMS

Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin PRIMAXIN
Meropenem MERREM

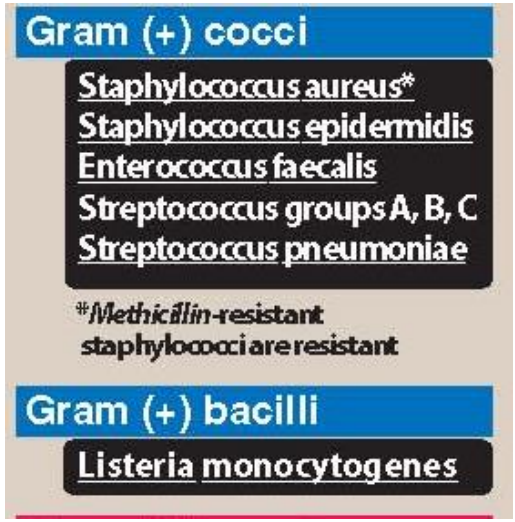




Carbapenems

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

Monobactams

MONOBACTAMS

Aztreonam AZACTAM

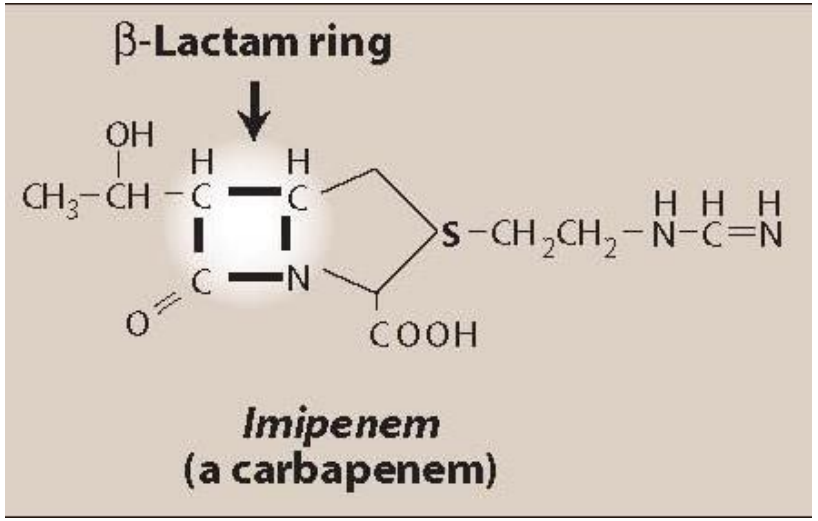
-Effective against gram-negative (including P. aeruginosa)

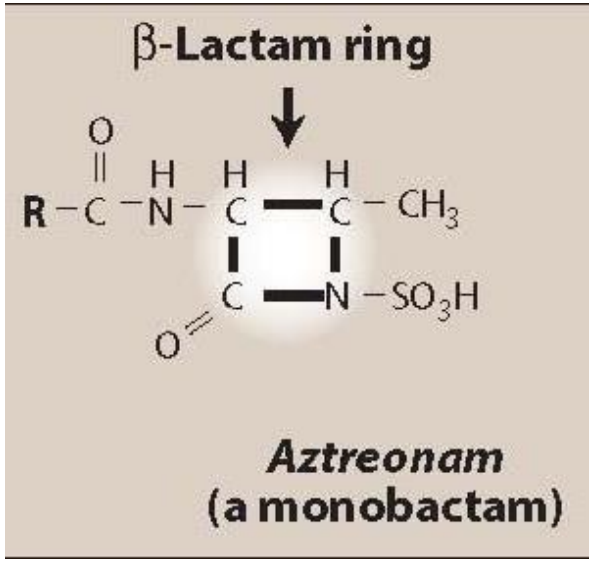
-Lacks activity against gram-positive

-Susceptible to ESBLs

-Relatively non-toxic

-little cross-reactivity with other β-lactams





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

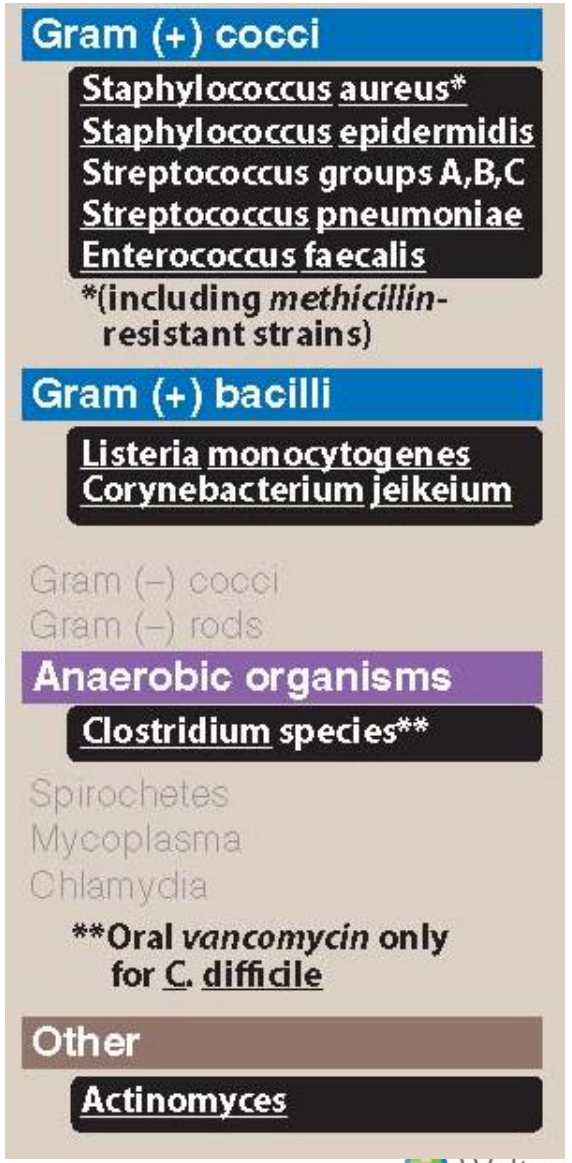
***both indicated for the management of complicated intra-abdominal and urinary tract infections caused by multidrug resistant bacteria

- Meropenem + vaborbactam: used against ESBL-producing bacteria

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

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



Vancomycin

- Bactericidal
- Time- and concentration-dependent

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

Adverse effects

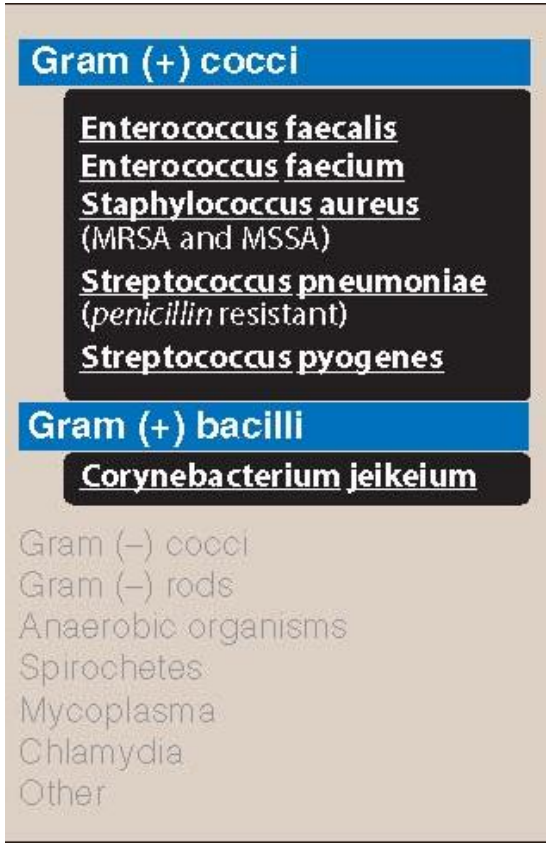
- Nephrotoxicity
- Red man syndrome
- Ototoxicity

Mechanisms of resistance:

- Alteration in binding affinity to peptidoglycan precursors

Daptomycin

- 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	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

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
- Cross-resistance is unlikely

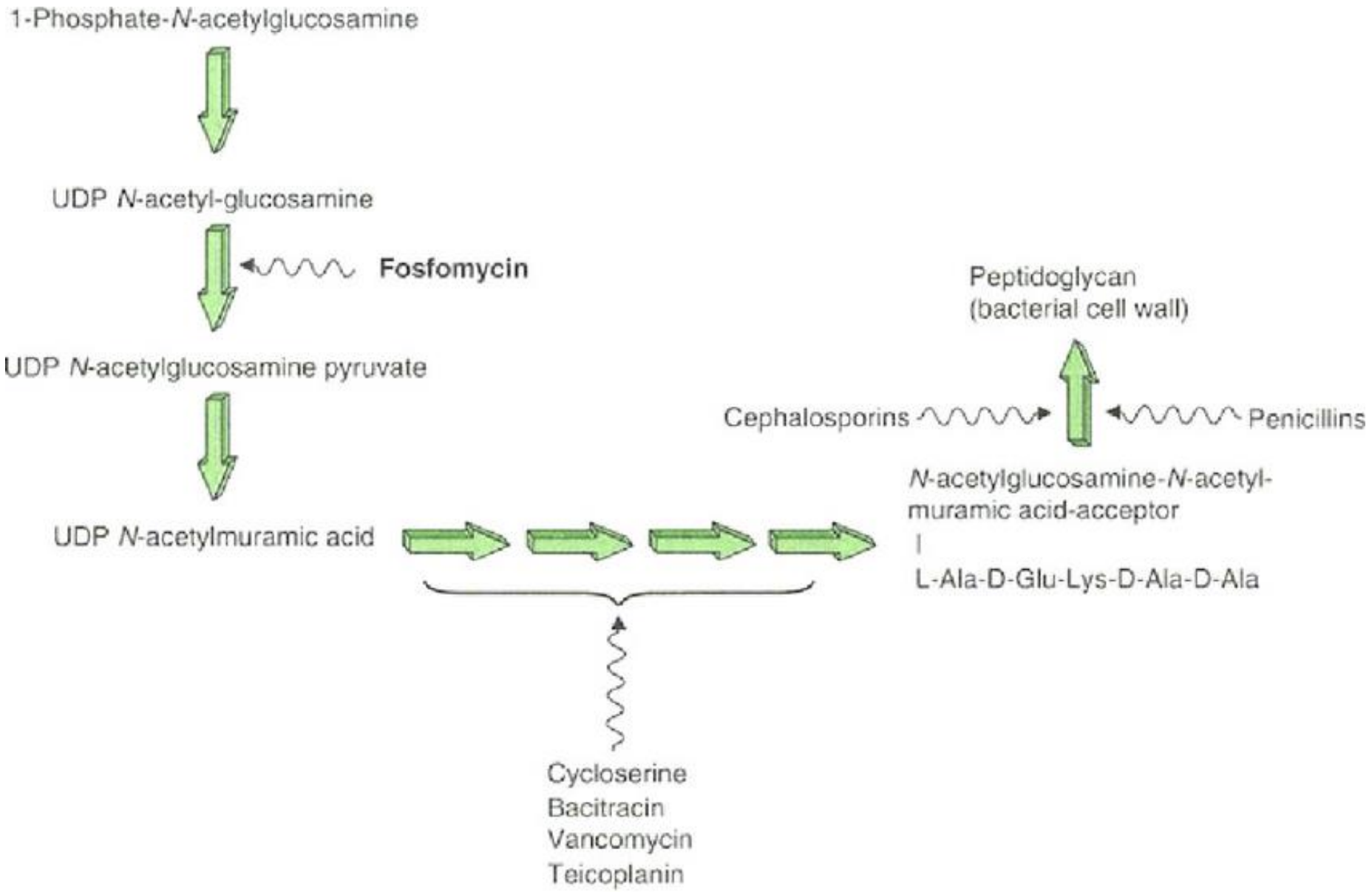
Polymyxin B (Colistin)

- 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
- 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.
- 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

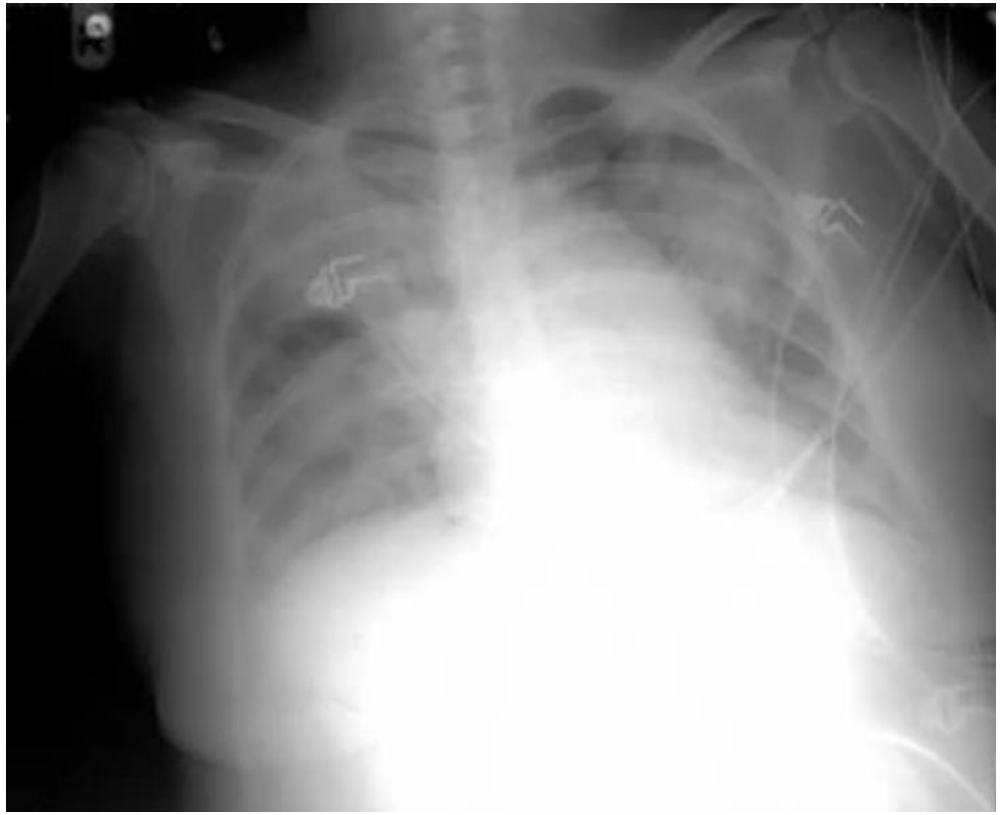


Quick Exercise

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