Cell Wall Inhibitors
Lec.14 sheet

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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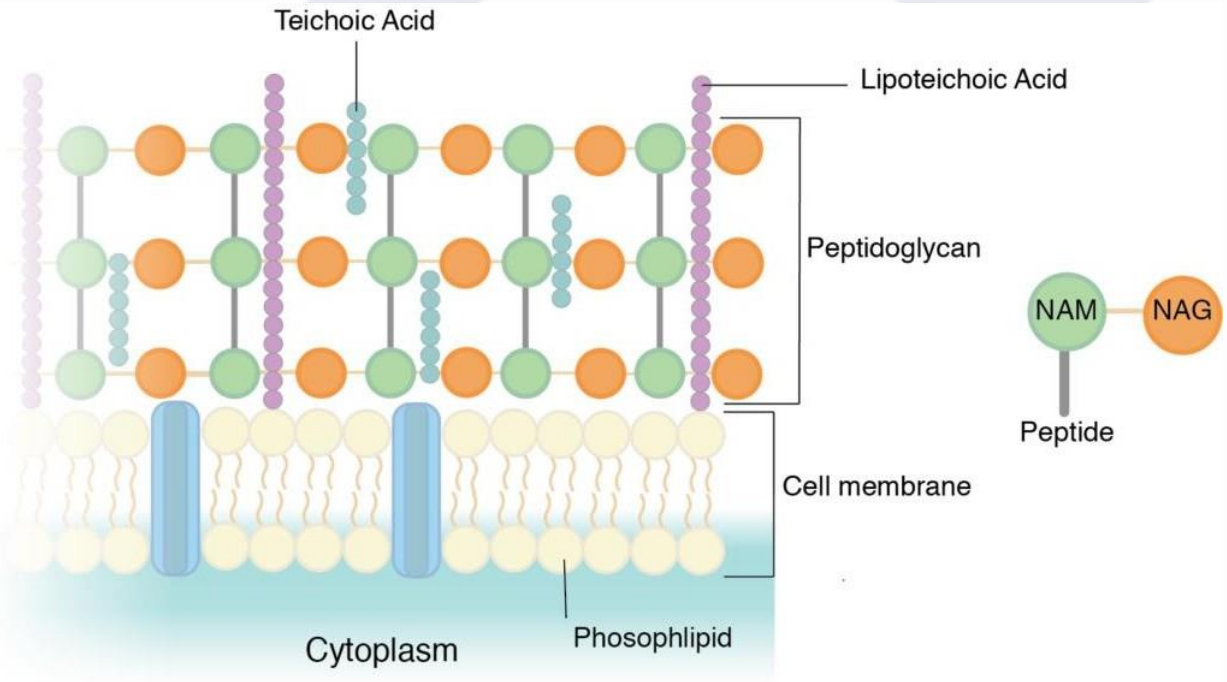
Faculty of Medicine

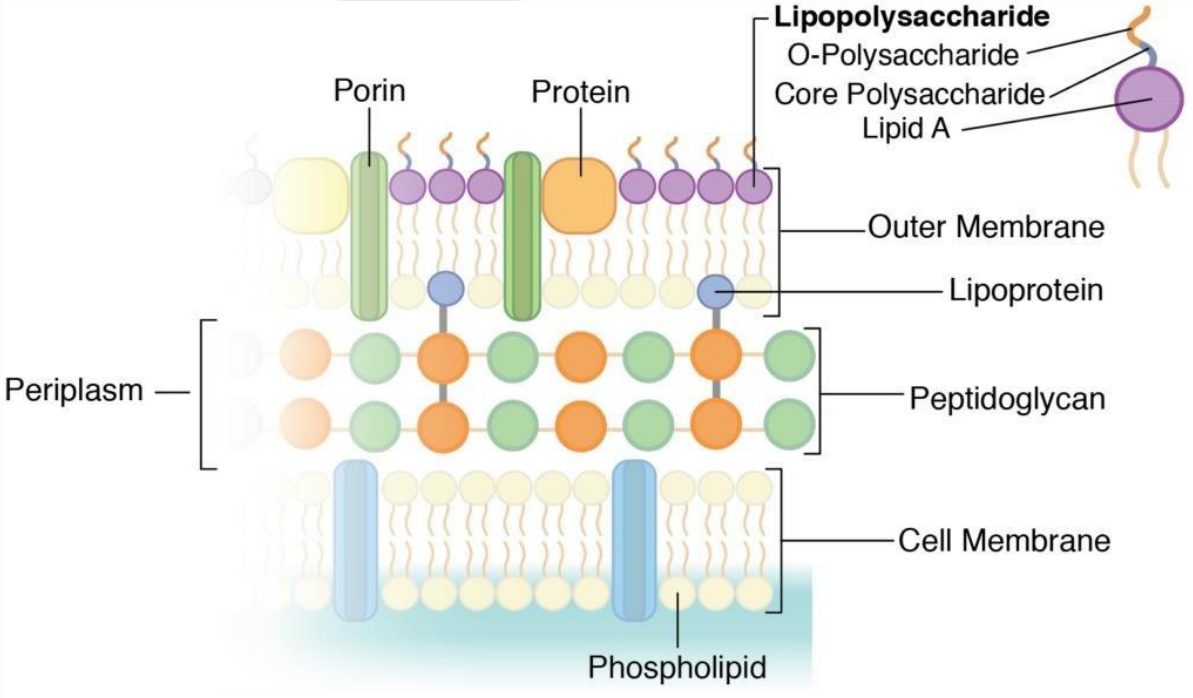
The Hashemite University

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:

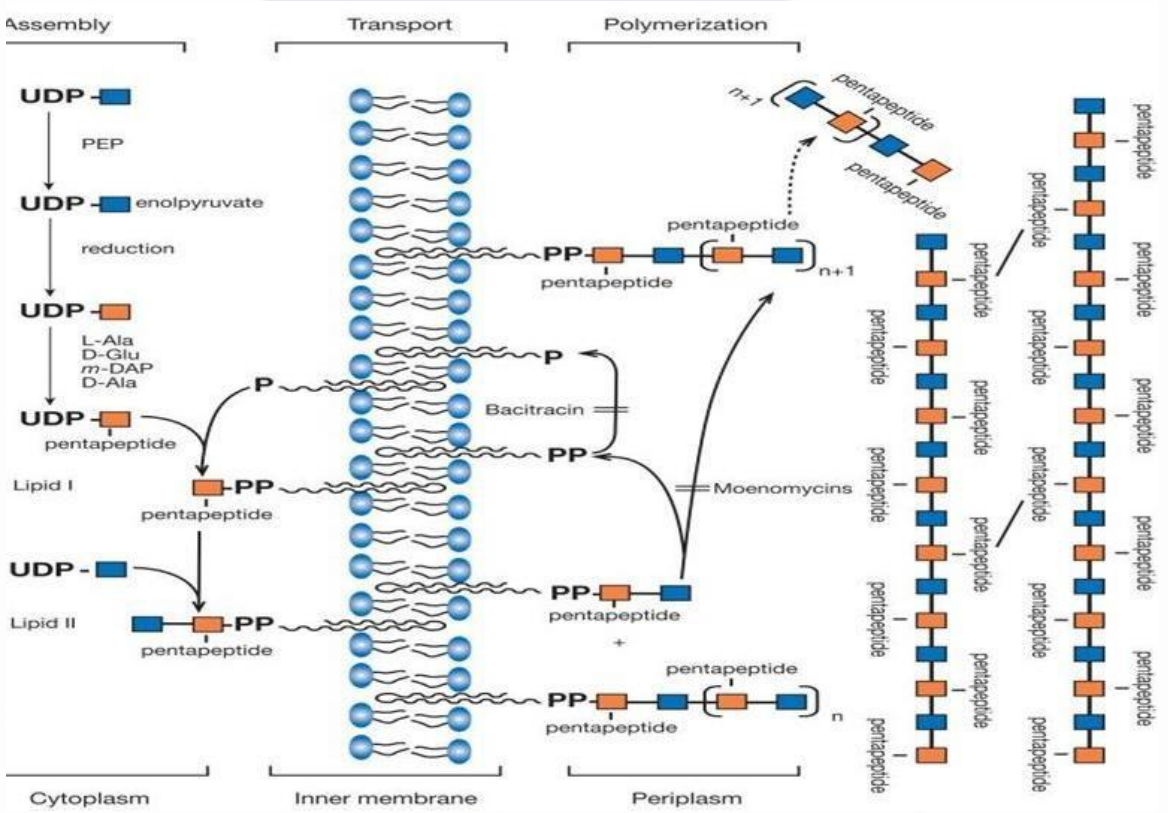
- Synthesis of glycan precursors: UDP-MurNAc-pentapeptide, UDP-GlcNAc

2. Cytoplasmic membrane Stage:

- Transfer to membrane receptors

3. Extracellular membrane stage:

- Transpeptidation via PBP

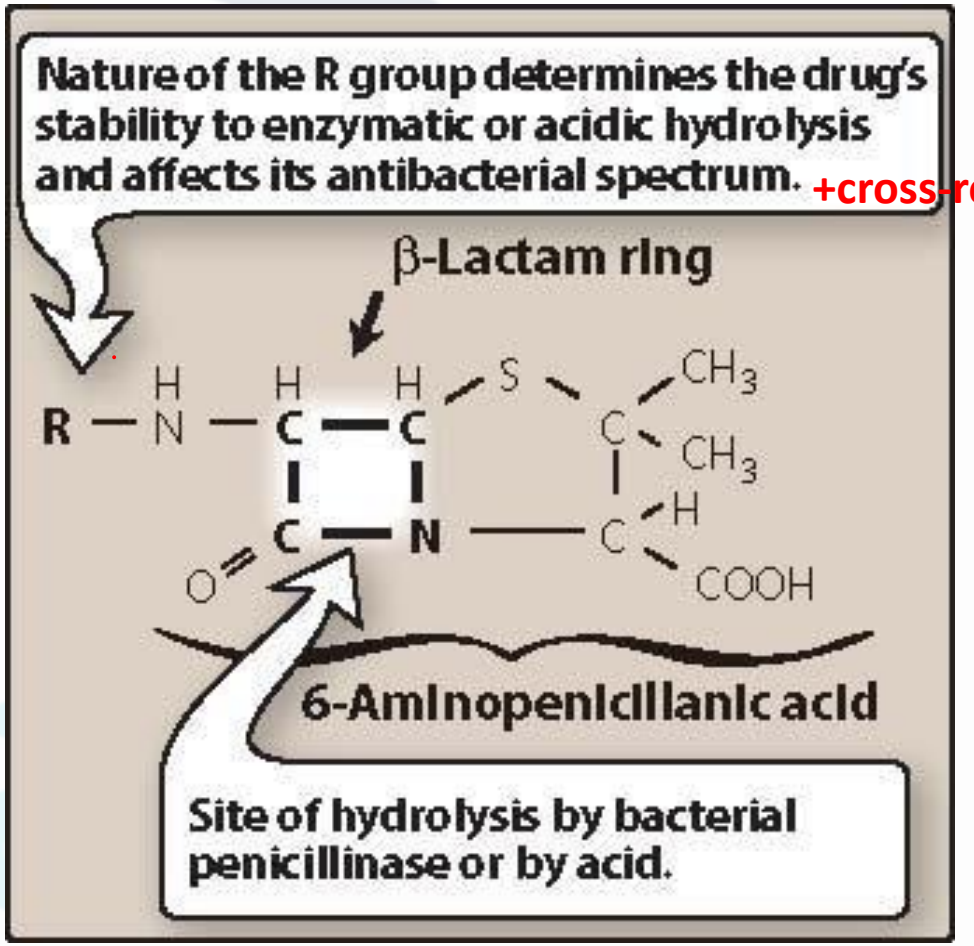


Penicillins

Penicillins

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

All these penicillins have similar mechanism of action and chemical structure

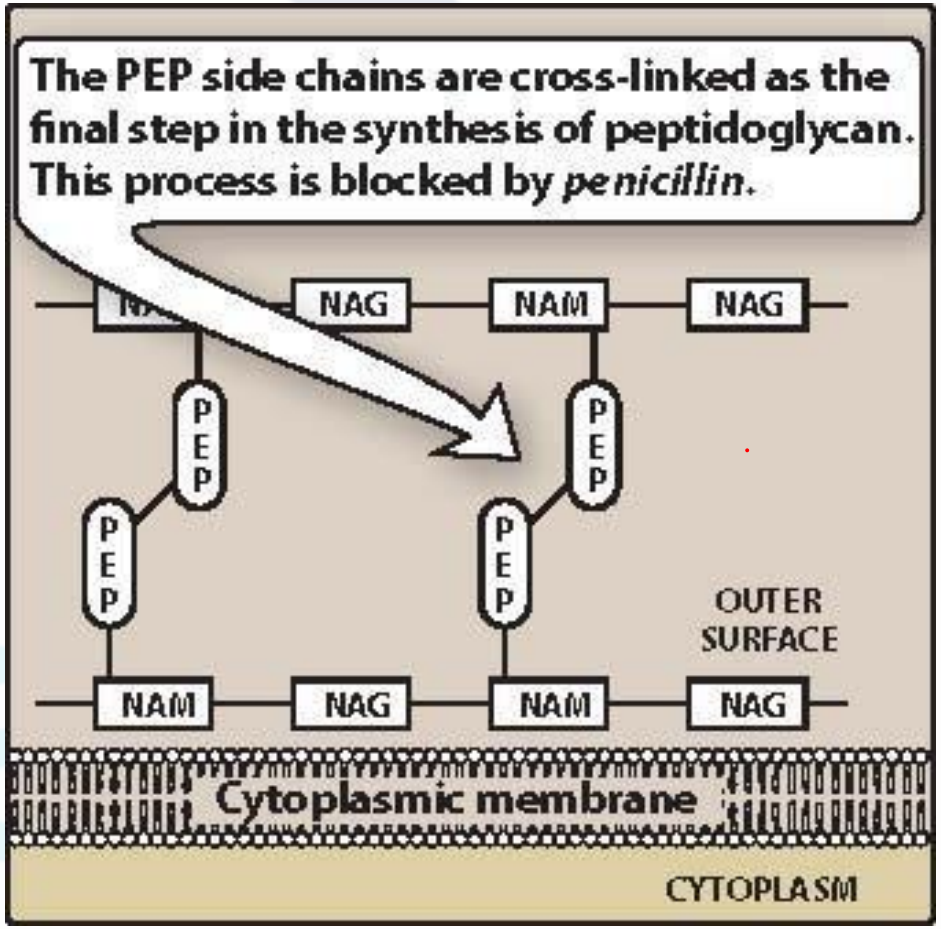


+cross-resistance

Quick Microbiology Reminder

Penicillin-binding proteins:

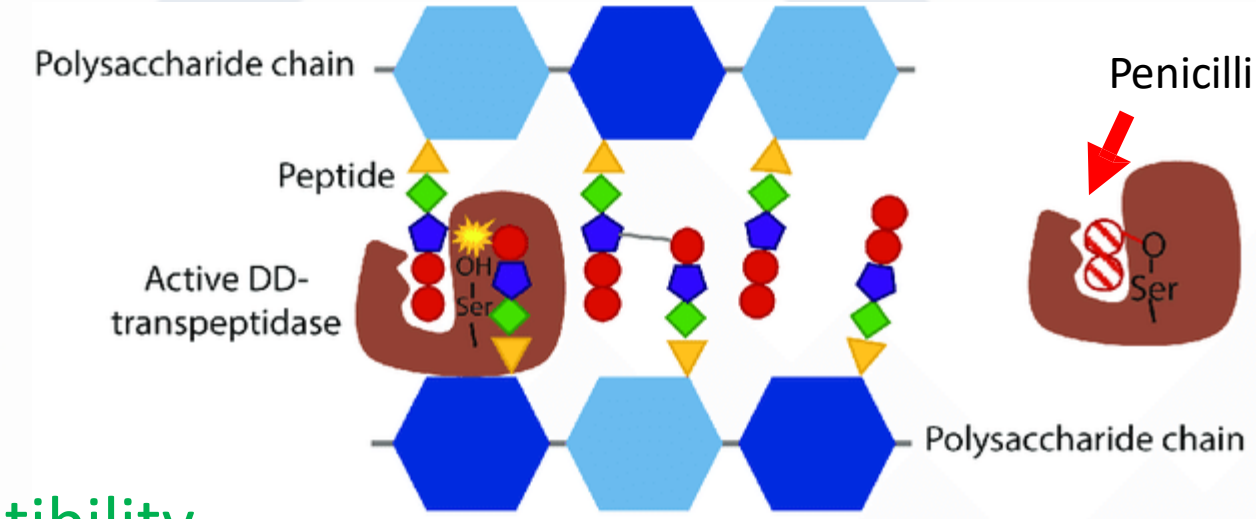
- Penicillins bind and inactivate bacterial cell membrane proteins called: penicillin-binding proteins (PBPs).
- Bacterial enzymes involved in cell wall synthesis
- Variable among different species
- Involved in resistance



Penicillins

Mechanism of action(very important)

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



- Factors determining PBP susceptibility to these antibiotics include size, charge, and hydrophobicity

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(because dividing bacteria is actively synthesizing and transpeptiding their cell wall whereas non-dividing bacteria have their cell wall already synthesized)

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

In general, gram-positive microorganisms have cell walls that are easily traversed by penicillins, and, therefore, in the absence of resistance, they are susceptible to these drugs.

Gram-negative microorganisms have an outer lipopolysaccharide membrane 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-filled channels (called porins) to permit transmembrane entry.


Gram (+) resistant
Gram (-) resistant
Pseudomonas
1) Methicillin - Sensitive
Staph aureus
produces
Penicillinase
(lactamase)
2) Methicillin - Resistant
Staph aureus
altered
PBP

Penicillins' journey

1) Natural Penicillins (Penicillin V & G) ⟹ Used to be effective against lots of Gram(+), now effective against limited species
   - very limited Gram(-) activity

2) extended-spectrum (ampicillin, amoxicillin) ⟹ effective against Gram(+).
   S. aureus Produce Penicillinase Produce against them
   - Good gram(-) activity, but some Penicillins Produce like Pseudomonas

3) Antistaphylococcal Penicillins
(methicillin, nafcillin, oxacillin, dicloxacillin)

⇒ effective against MSSA, if is resistant to Penicillinase (lactamase)

* Not effective against MRSA

4) AntiPseudomonal Penicillins
(Piperacillin, ticarcillin)

⇒ effective against Pseudomo and other gram-ve

Penicillins

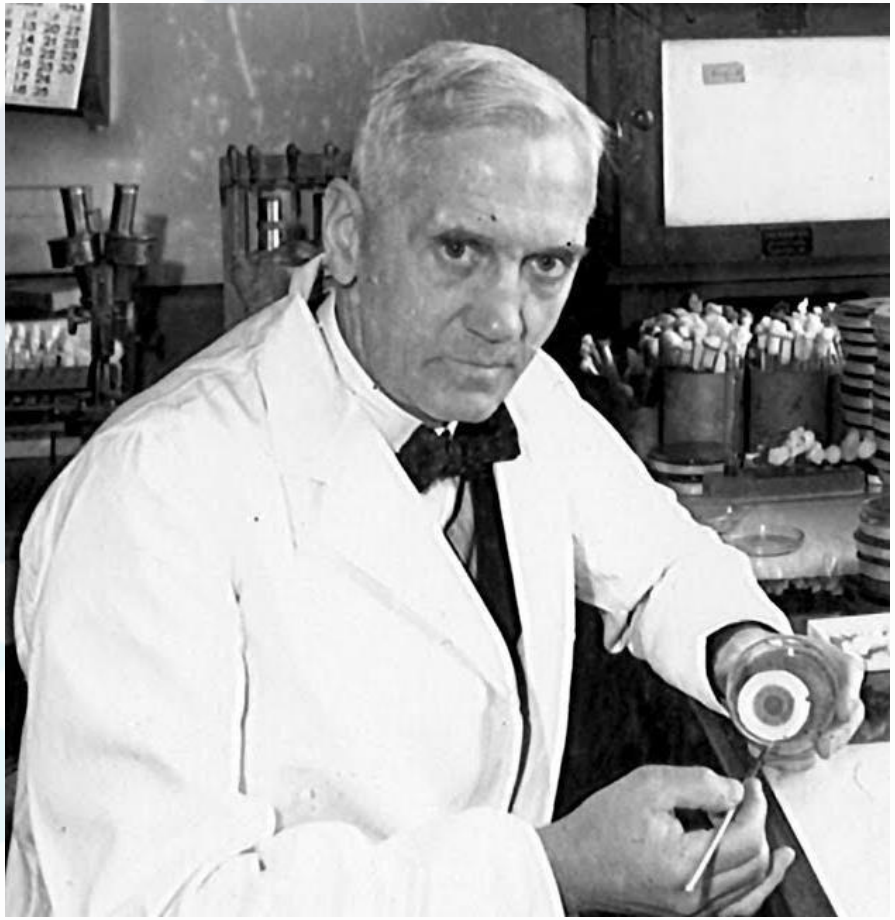
Antibacterial spectrum

1. Natural penicillins:

- Penicillin G, Penicillin V: *Penicillium chrysogenum*

- Drugs of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum). A single injection is enough

- Penicillin V is the oral acid stable form of penicillin(but still has limited GI absorption). Penicillin G is not acid stable and so given as IM injection

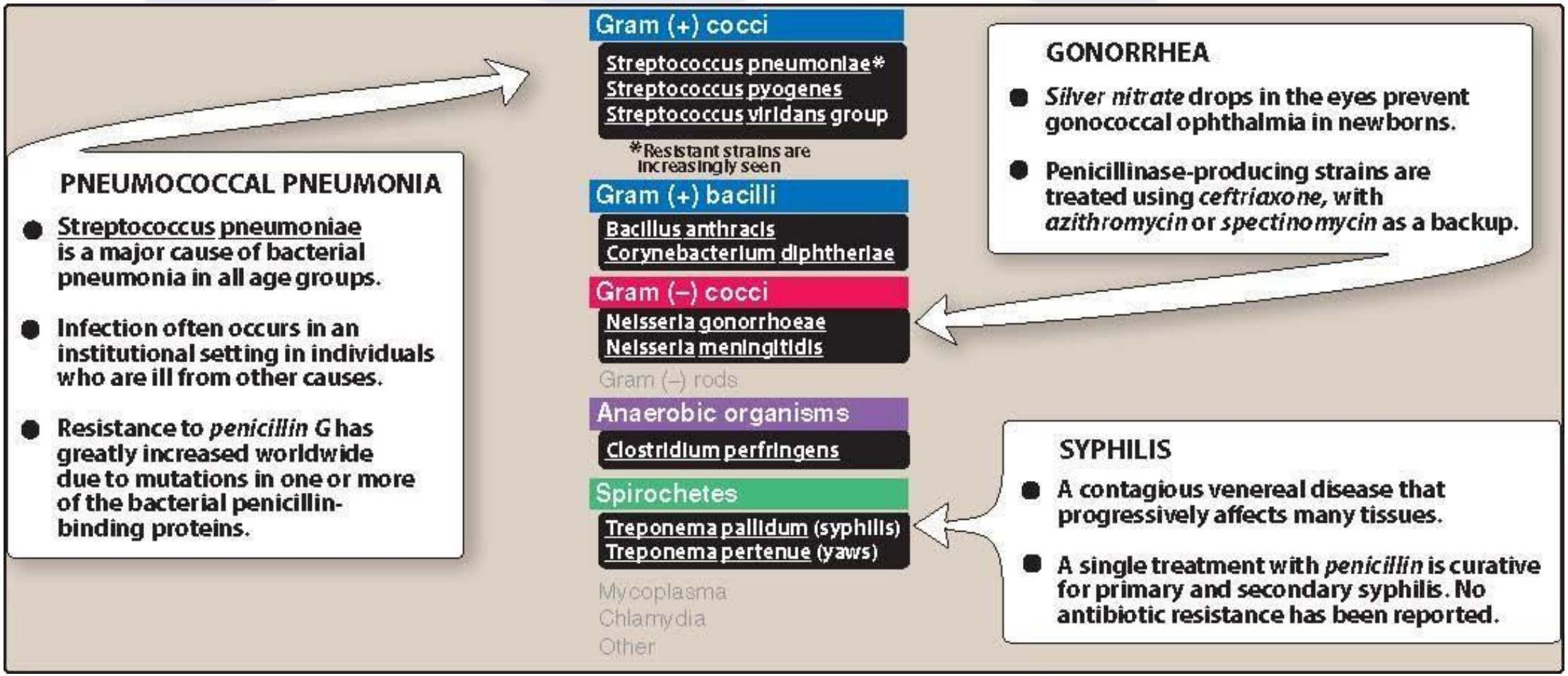


Penicillins

If a question tells you that strep pneumonia resistance is due to beta lactamase enzyme, **NO!!**

The **potency** of **penicillin G** is five to ten times greater than that of **penicillin V** against both **Neisseria spp. and certain anaerobes**

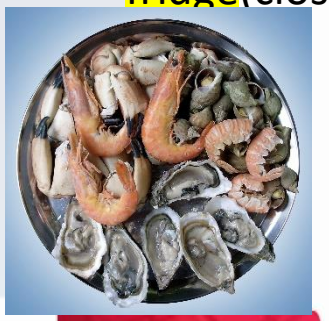
Antibacterial spectrum

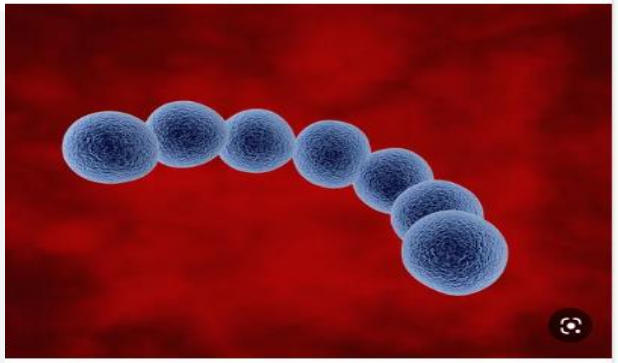


Penicillin structure mnemonics

Two pennies(penicillin)

The two pennies will buy a sea food(syphilis) **pie** with a chain of purple berries(strep **pyo**genes), The rest is kept in the fridge(clostridium perfringens)





Wolters Kluwer

If a question comes in the exam and says that a patient has pneumococcal(strep pneumoniae) pneumonia and penicillin was one of the choices, don’t go for it! The majority of pneumococci are resistant.

Penicillins

Antibacterial spectrum:

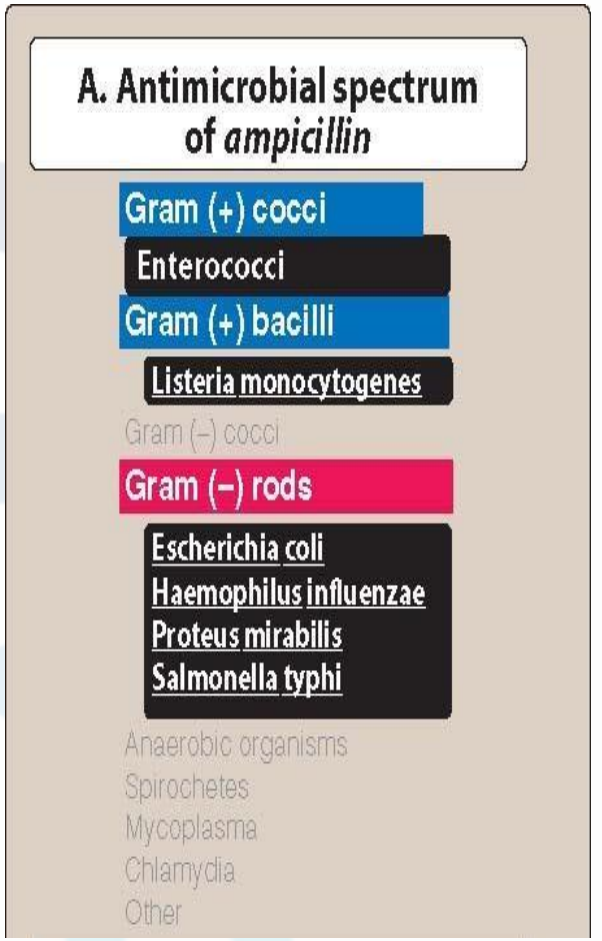
2. Extended-spectrum penicillins(also called aminopencillins):

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

❑Ampicillin(usually given by IV): **drug of choice** for gram-positive bacillus ***L. monocytogenes(causes neonatal meningitis), enterococci(a normal flora of gut → causes infective endocarditis and septicemia, H.influenze →resp infections***

❑Amoxicillin(Usually given by mouth):

1. Upper respiratory infections(like sinusitis إلتهاب جيوب أنفية
2. dental prophylaxis against endocarditis



Mnemonic

Listeria(list) affects the brain(meningitis) and is treated by ampicillin

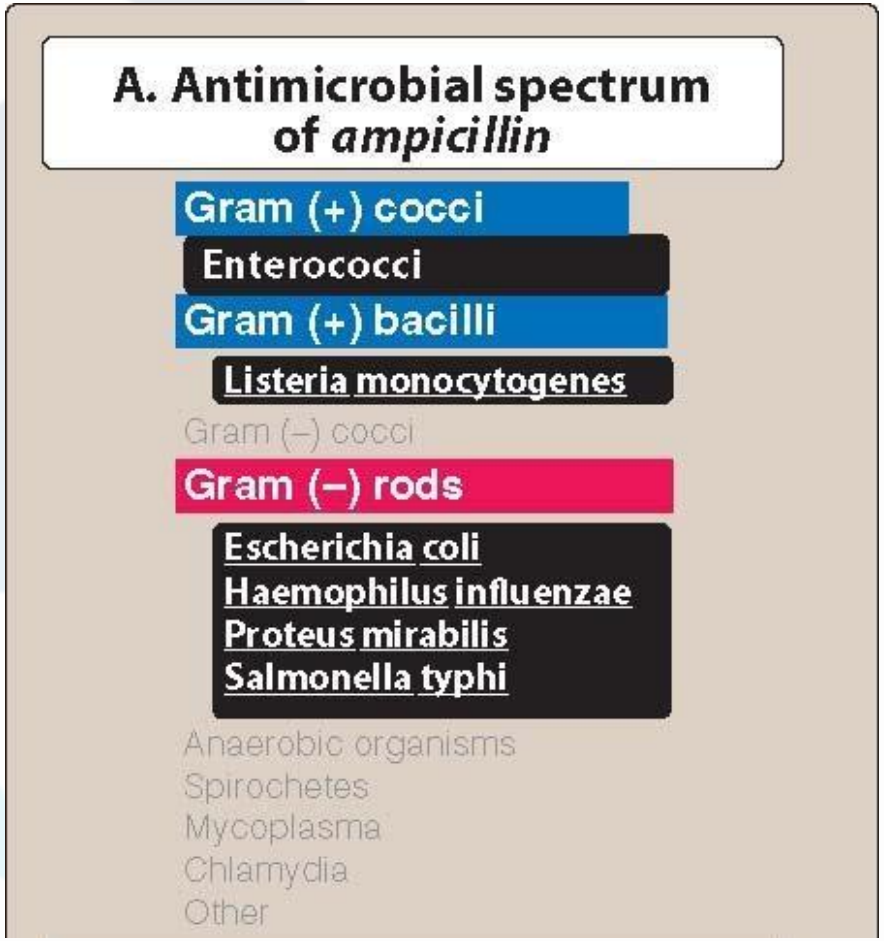
Penicillins

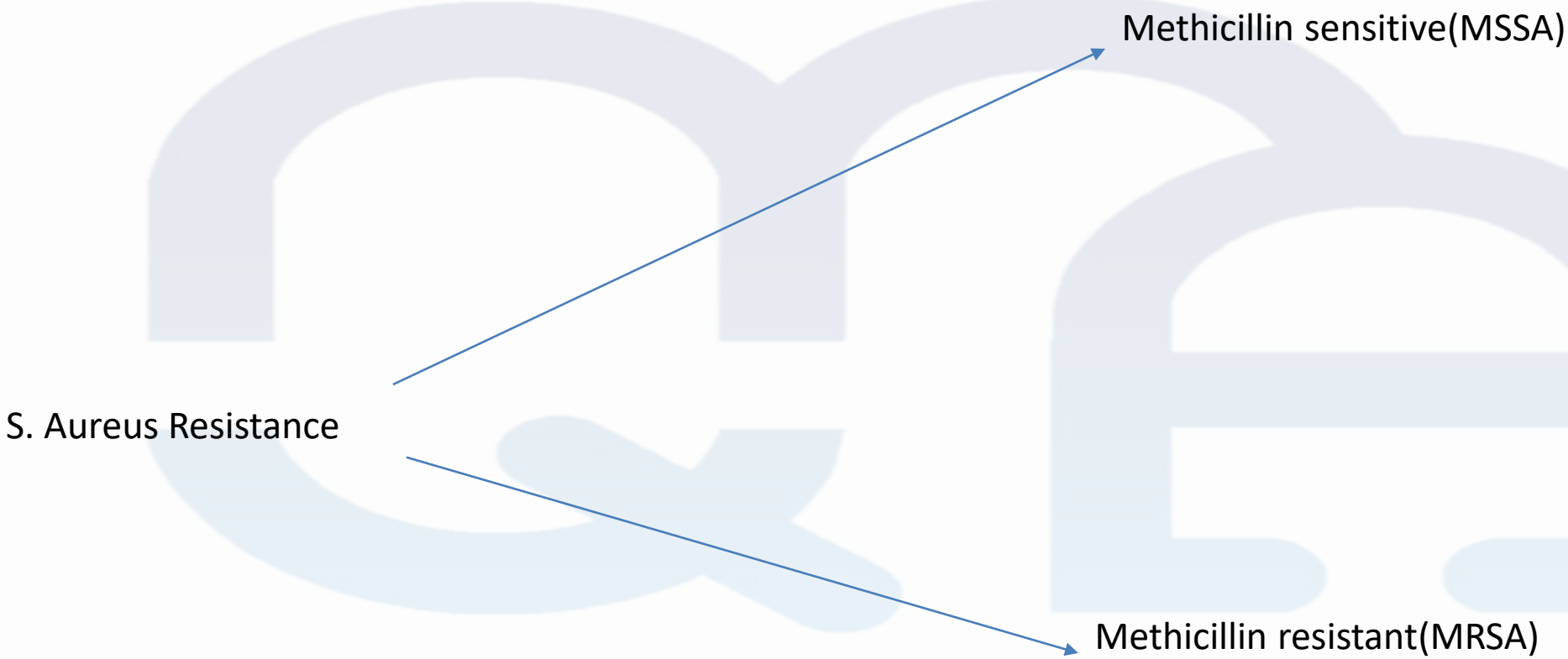
Antibacterial spectrum:

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




Methicillin sensitive(MSSA)
S. Aureus Resistance
Methicillin resistant(MRSA)

Penicillins

Antibacterial spectrum

3. Antistaphylococcal penicillins(penicillinase-resistant penicillins):

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

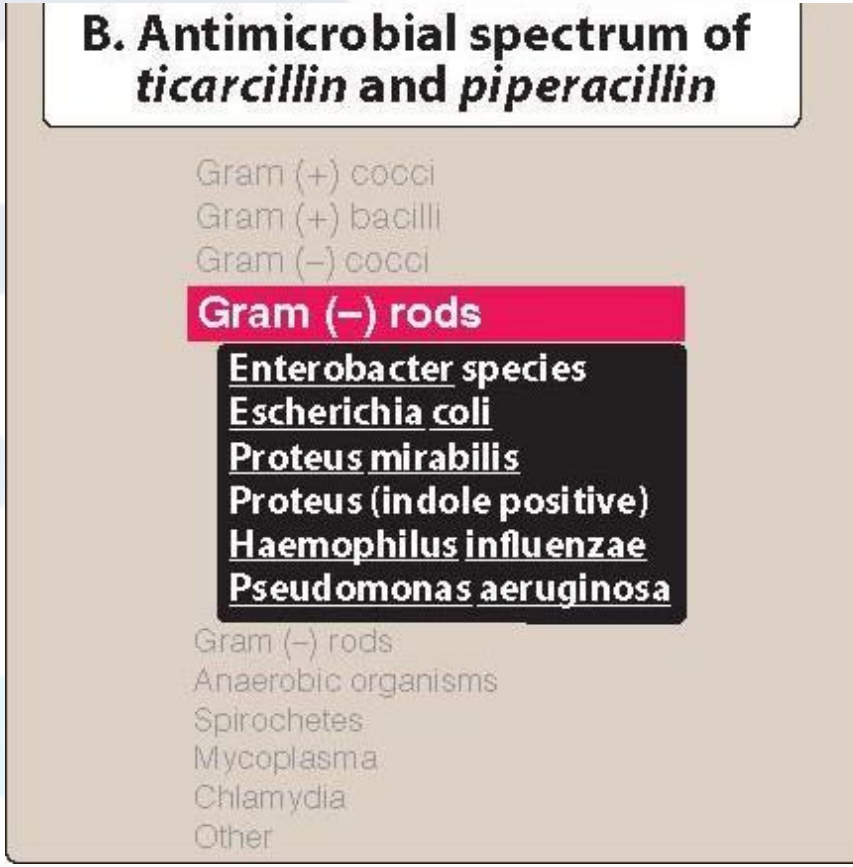
Penicillins

Antibacterial spectrum:

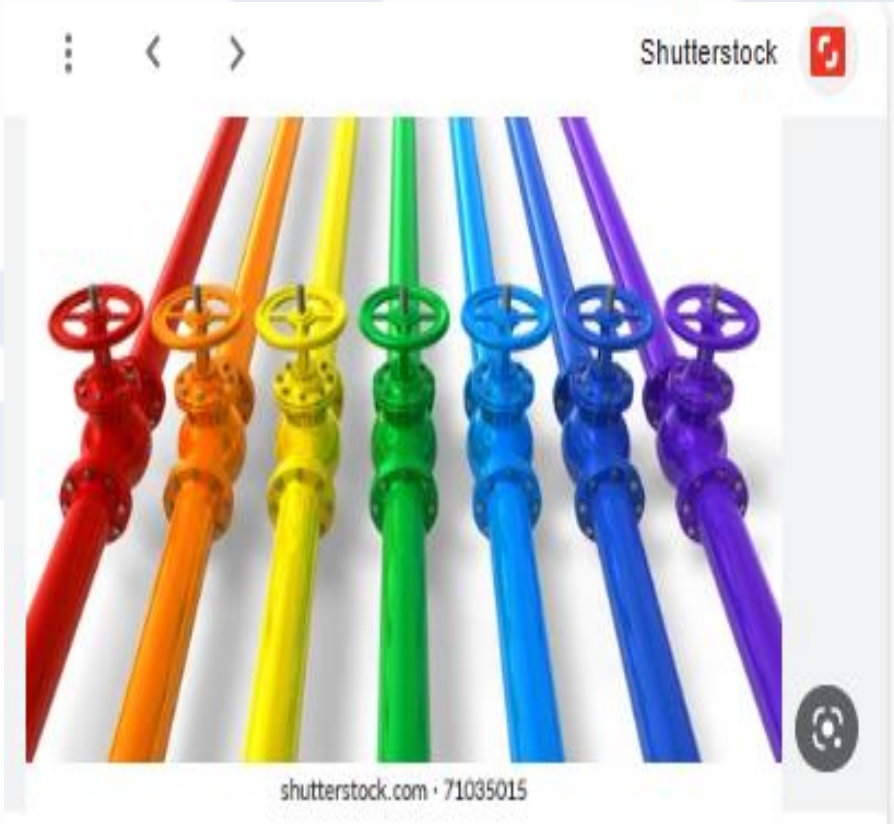
4. Antipseudomonal penicillins:

- Piperacillin
- Effective against gram-negative bacilli
- Common combinations: Piperacillin + tazobactam (penicillinase inhibitors)→effective against most Enterobacteriaceae and Bacteroides species(but not against *Klebsiella*)

They are not effective against gram positive



Antipseudomonas mnemonics



Colored pipes→
anti**pseudomonal** piperacillin

Colored cars→
anti**pseudomonal**
Ticarcillin

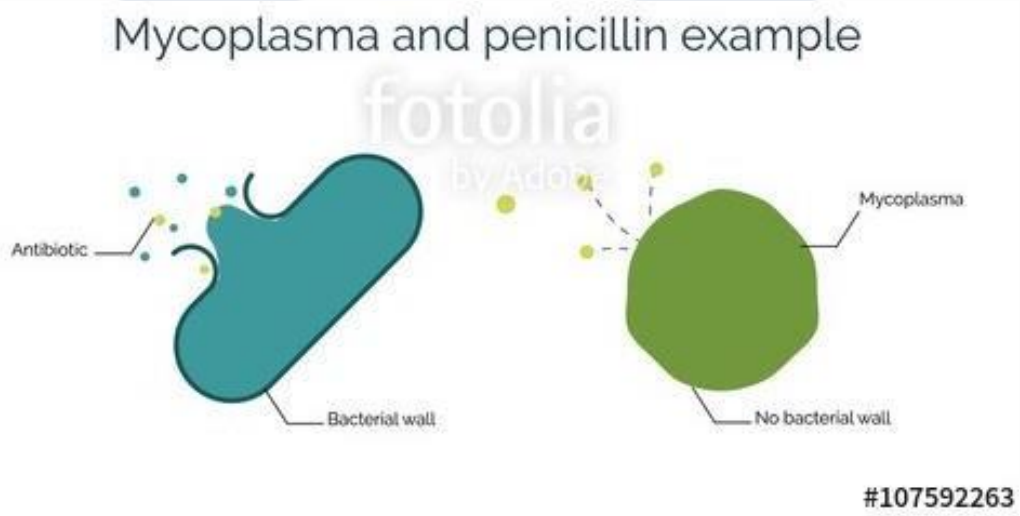
Tazobactam+piperacillin

Penicillins

Mechanisms of resistance

- **Intrinsic Resistance:**

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



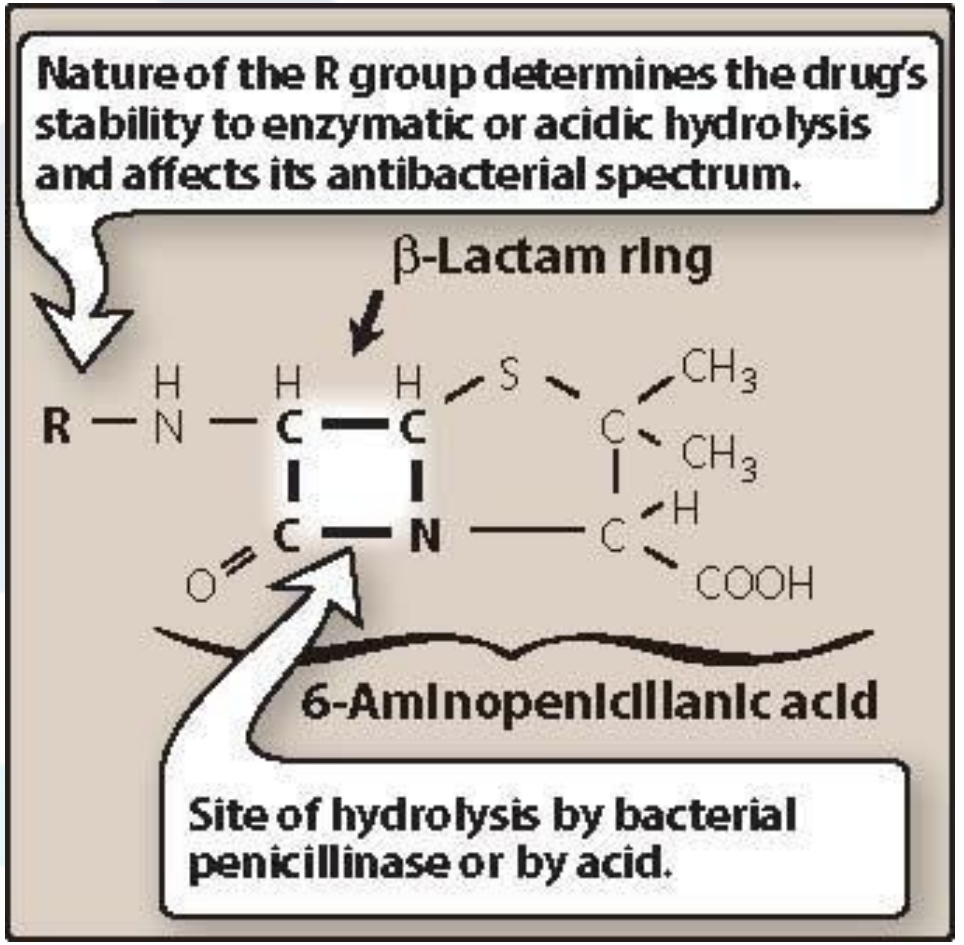
Penicillins

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.

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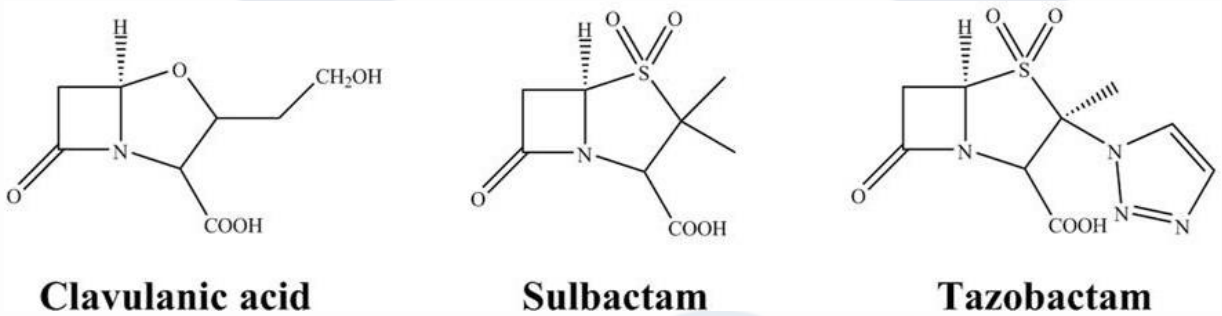
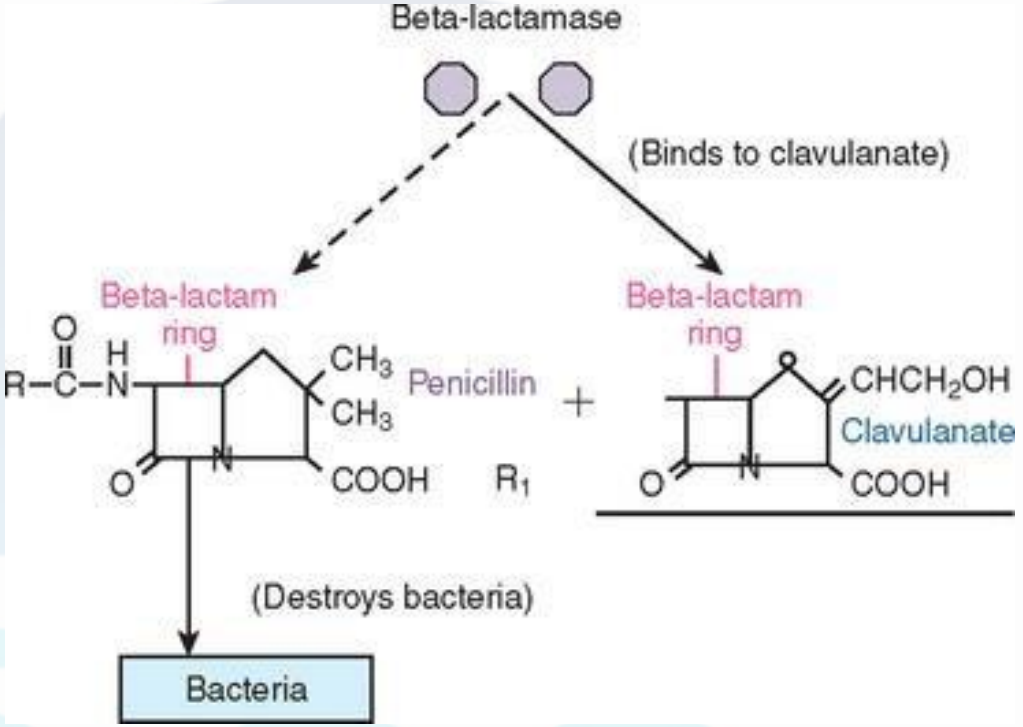
How is this problem solved?

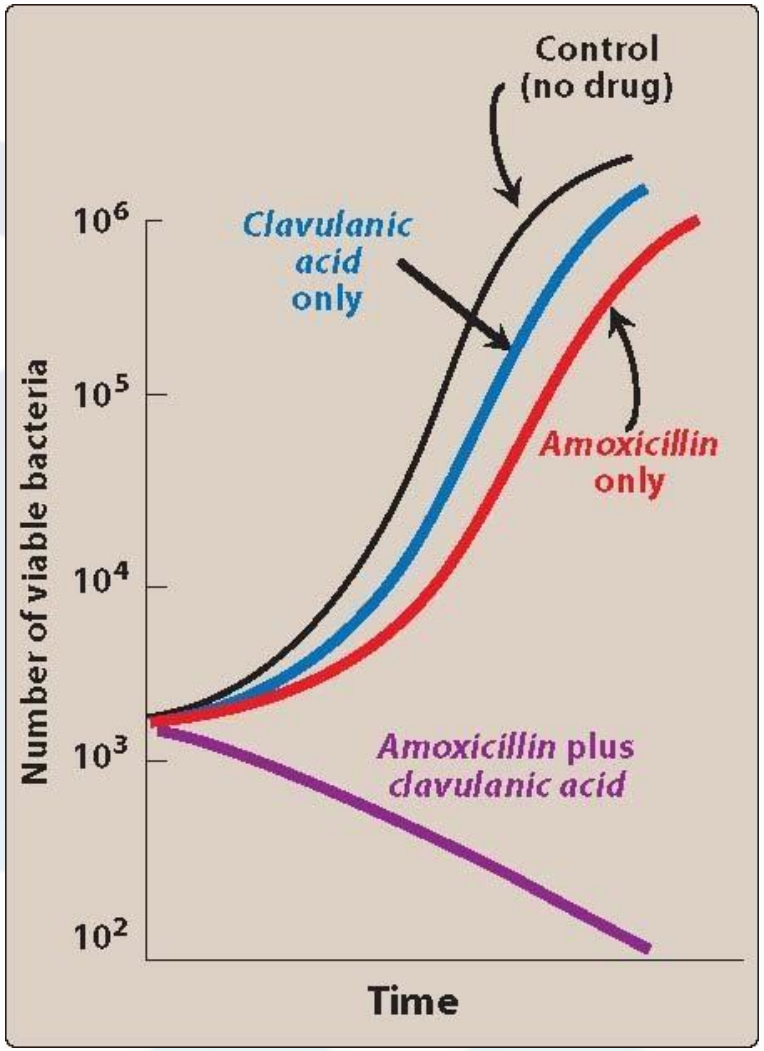
β-Lactamase Inhibitors





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(usually be gram(-ve)):

- Reduced permeability e.g., *Pseudomonas aeruginosa*
- *Pseudomonas عندها سد*
- Efflux pump e.g., *Klebsiella pneumoniae(that's why antipseudomonal drugs can't target klebsiella!)*
- *Klebsiella بتسيل الدوا برا ال club*

3. Altered PBPs:

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

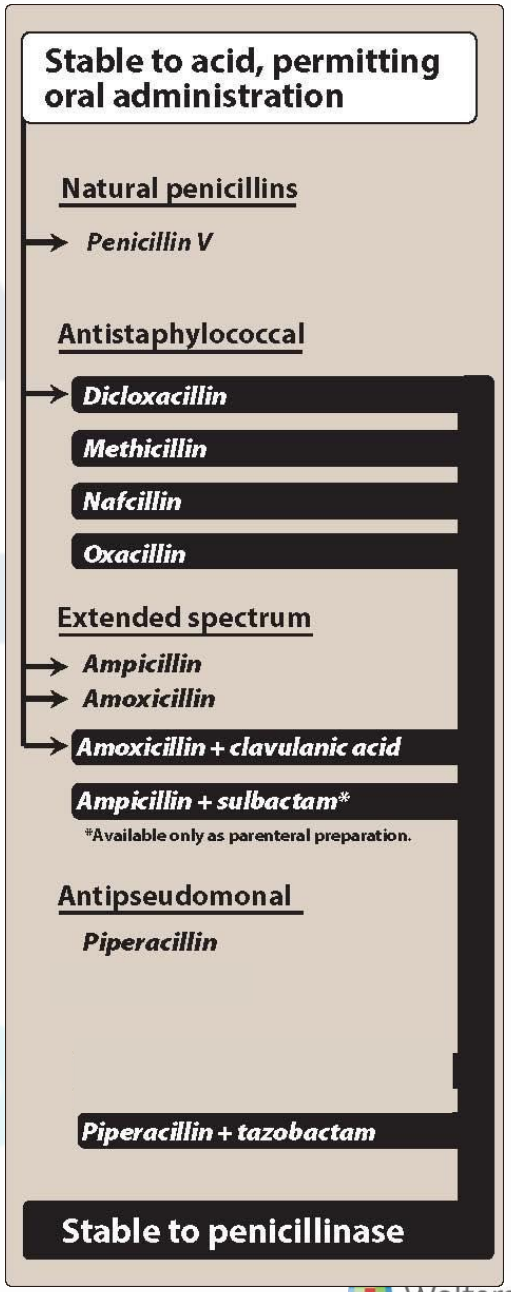
Penicillins

Pharmacokinetics

- **Routes of administration**

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

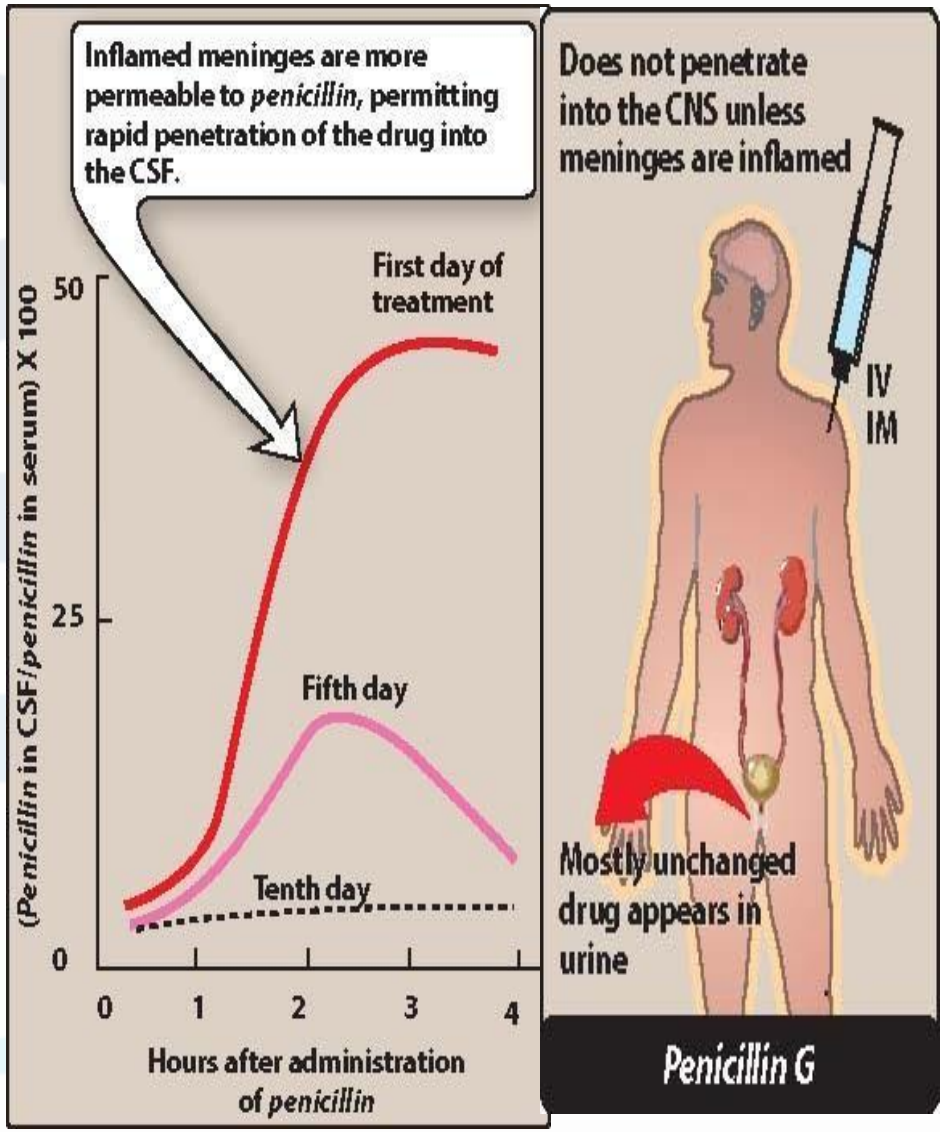
They are **slowly absorbed** into the **circulation** and **persist at low levels** over a **long time period. Used for S. pyogenes rheumatic fever prophylaxis.**



Pharmacokinetics

Penicillins

- **Absorption**
  - Most penicillins are incompletely absorbed after oral administration
  - Empty stomach? More absorption because a stomach full of food means less emptying of contents(including drug) into intestines so that stomach can digest food. So full stomach exposes penicillins to acids for longer time. An example is **dicloxacillin. Amoxicillin is acid stable and not affected.**
- **Distribution**
  - Good distribution e.g., cross placenta (but no teratogenic effect, it is a class B drug)
  - Insufficient penetration to prostate, bone, CSF (unless inflamed)

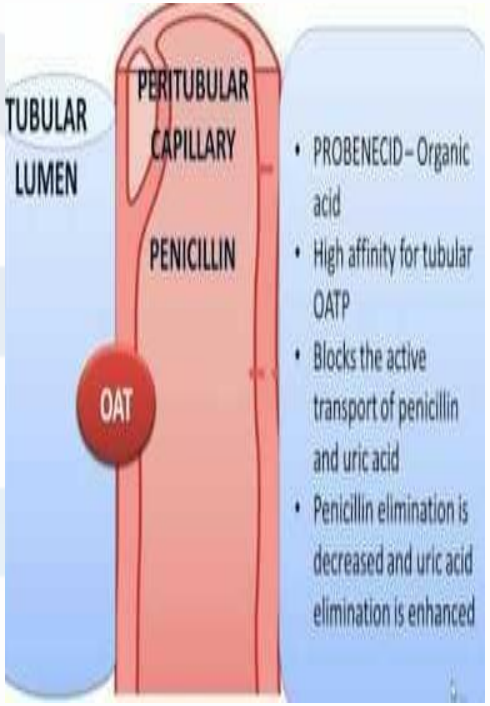


Penicillins

Pharmacokinetics

- **Metabolism**

- Insignificant metabolism(An advantage in people with hepatic impairment, no need to reduce dose)
- Some metabolism of penicillin G may occur in renal failure
- Exceptions?(Nafcillin, oxacillin, and methicillin, they are metabolized in liver and excreted in bile)→advantage in renal failure because of no need for dose reduction
- **Excretion:**
- Renal: (Main)tubular secretory system through organic acid carrier,
- glomerular filtration
- *Probenecid* is an inhibitor of renal tubular excretion of penicillin. So give lower penicillin dose with probenecid



Slide reminder

glomerular pores). e.g. mannitol

Factors affecting glomerular filtration

- Glomerular filtration rate (GFR)
- Plasma protein binding (PPB) → prevents filtration

2. **Active tubular secretion**: through special transport system (carrier) → saturable & site for competition.

- Acid carrier e.g. for penicillins, probenecid, frusemide, uric acid
  - Probenecid →↓ tubular secretion of penicillin→↑ duration of action of penicillin
  - frusemide →↓ tubular secretion of uric acid →hyperuricemia as an adverse effect.
- basic carrier e.g. for digoxin, quinidine.

3. **Active tubular reabsorption**:

- Unionized form of drug (lipophilic) → tubular reabsorption

Penicillins

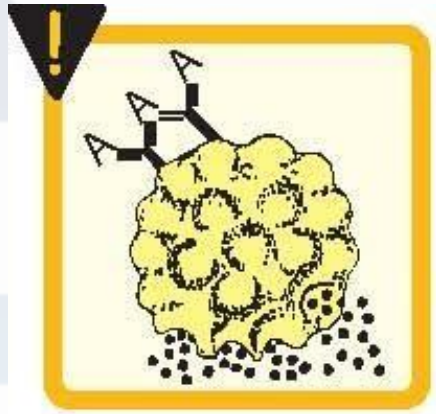
Adverse effects

1. Hypersensitivity:

- 5-10% percent of patients (simple rash to angioedema to anaphylaxis)
- Cross-allergy among different beta lactam antibiotics
- **Always inquire** about penicillin allergy in history taking

2. Diarrhea:

- Caused by intestinal flora imbalance
- More with **extended-spectrum agents**
- May be due to **C.difficile pseudomembranous colitis**



Hypersensitivity

Diarrhea

Penicillins

Adverse effects

3. Nephritis:

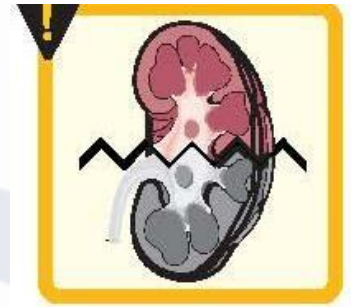
- Methicillin: no longer used because of this

4. Neurotoxicity:

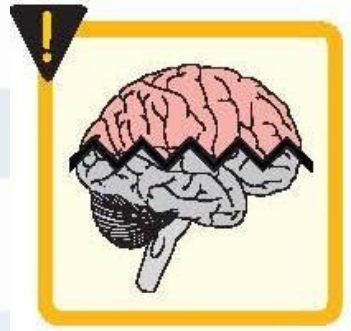
- If injected intrathecally or very high plasma levels are reached. Epileptic patients are particularly at risk due to the ability of penicillins to cause **GABAergic inhibition.**

5. Hematological toxicities

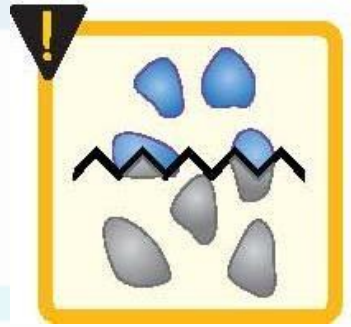
- Decreased coagulation
- Cytopenias in therapy for more than 2 weeks , blood counts should be monitored weekly for such patients.



Nephritis



Neurotoxicity



Hematologic toxicities

penicillin's in general, are very safe drugs. They are considered from pregnancy class B drugs→Can be given during pregnancy.

They are very commonly prescribed in outpatient clinics for treatment of infections

Quick Revision

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

1. Antistaphylococcal penicillins: methicillin., nafcillin,oxacillin and dicloxacillin
2. Extended spectrum penicillins WITH beta-lactamase inhibitor: ampicillin+Sulbactam/ amoxicillin+clavulanic acid

- Name a penicillin that is effective against penicillinase-producing S. aureus (MRSA)? None

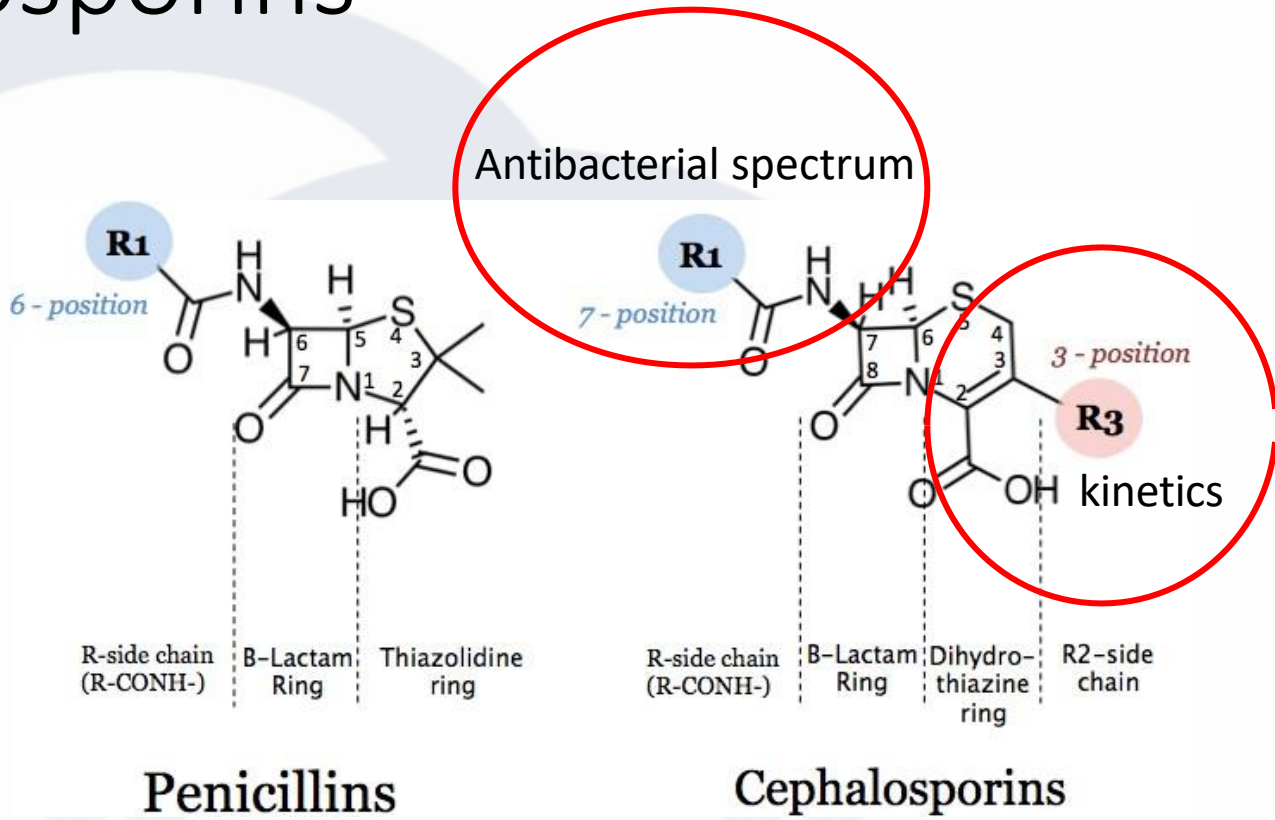
Cephalosporins

Cephalosporins journey

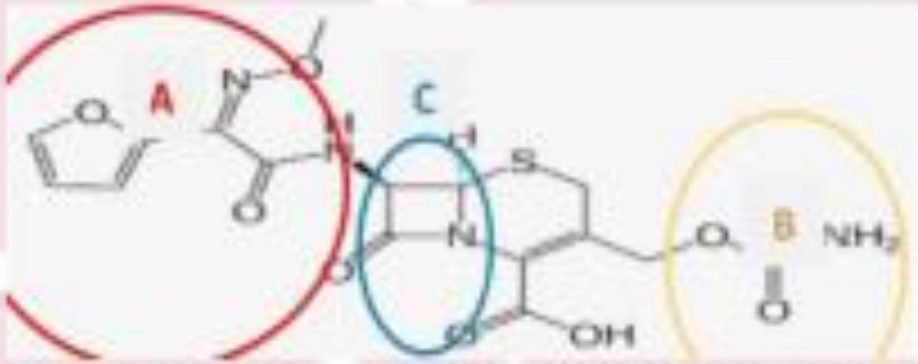
* 1st gen → Similar to natural Penicillin
  Past spectrum
  - Gram(+ve), including MSSA! and a few gram(-ve)
* 2nd gen → Similar to extended Penicillin
  - Gram(-ve) with more gram(+ve) extension
* 3rd gen → Greater gram(-ve) coverage
  So wide gram(-ve) and gram(+ve) coverage
* 4th gen → Anti Pseudomonal
* 5th gen → MRSA!!

Cephalosporins

- β-lactams
- Structurally/functionally related to penicillins
- Semisynthetic :by chemical attachment of side chains to 7-aminocephalosporanic acid
- More resistant to certain β-lactamases



5. **The following diagram depicts the chemical structure of cefuroxime, based on your understanding of the structure pharmacology relationship of cephalosporin, which of the following statement is CORRECT?**



A. Group A is responsible for the pharmacokinetic properties of cefuroxime.
B. Group C is responsible for the activity of cefuroxime against MRSA.
C. Group B is responsible for the susceptibility of cefuroxime to beta-lactamases.
D. Group A is responsible for determining the antibacterial spectrum of cefuroxime.
E. Group C is responsible for the extent of hepatic metabolism of cefuroxime.

Answer: D

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

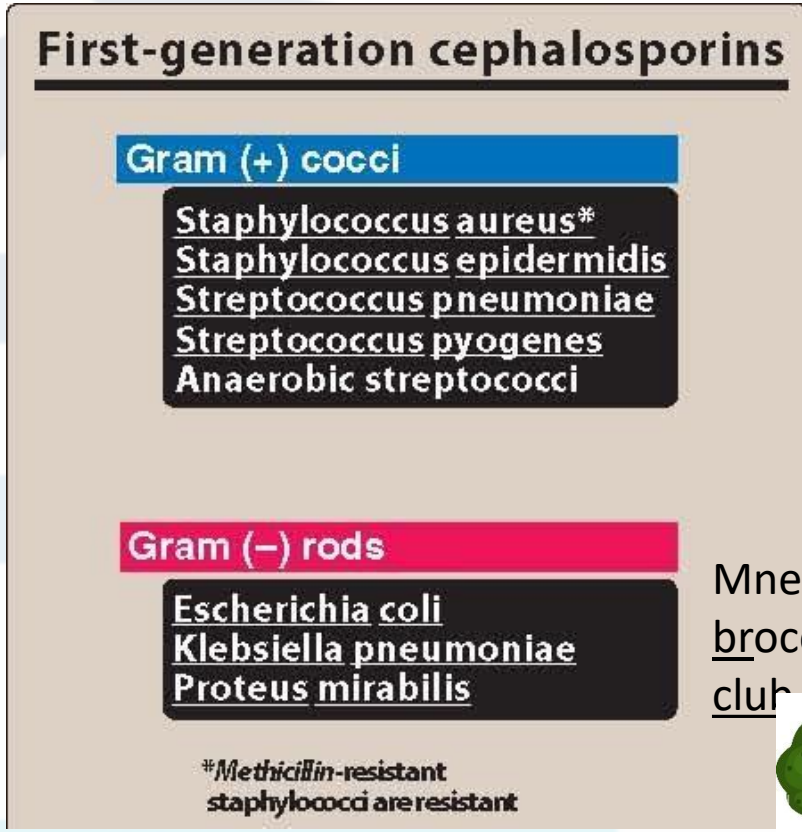
- Isolates of .S.. pneumoniae resistant to penicillins are also resistant to first-generation cephalosporins

- Bacteroides fragilis is resistant

Cefazolin

Cephalexin

cefadroxil



Mnemonic: broccoli sport club

*Not MRSA

Mnemonic:1st generation cephalosporins

1st generation= very young child

The young child Alex(cephalexin) draws(cefadroxil) a zoo(cefazolin)

Cephalosporins

Antibacterial spectrum

- **Second-generation cephalosporins:**

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

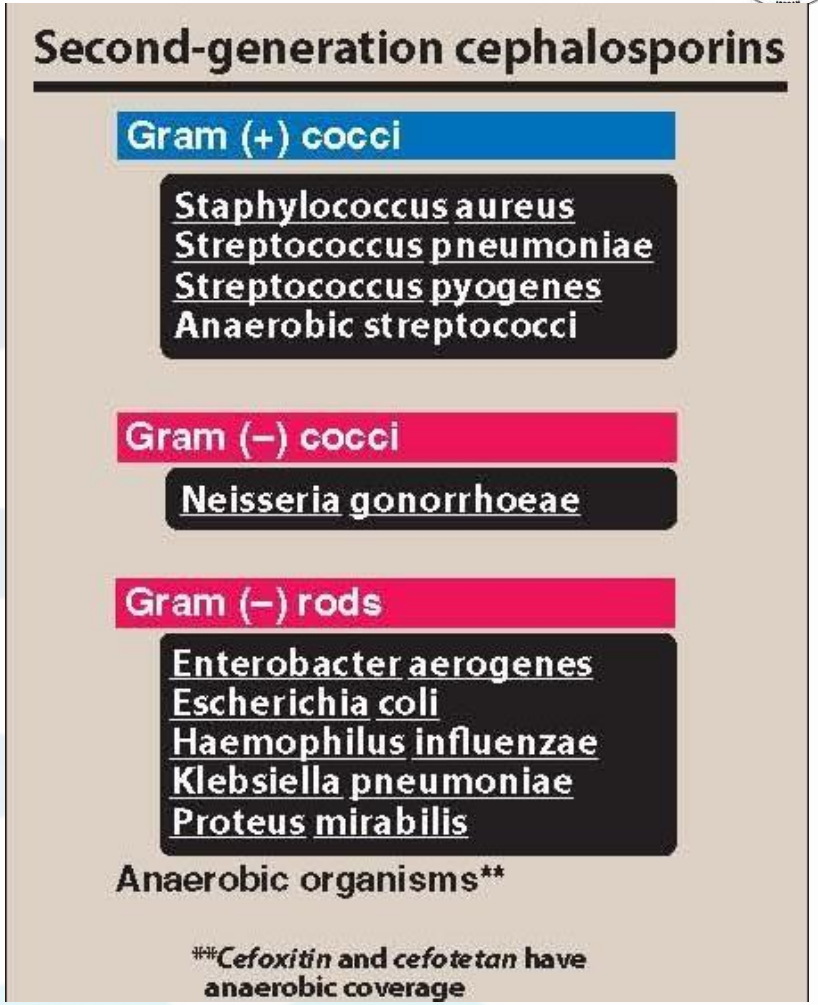
-Slightly weaker gram(+) activity

Cefotetan

Cefuroxime

Cefoxitin

Cefprozil



Cephamycins(cefoxitin and cefotetan) have activity against anaerobis(e.g. B. fragilis) but are not first line because of resistance

2nd generation cephalosporin mnemonics

2nd generation cephalosporins: older children who watch cartoons

Fox(Cefoxitin)

Cefuroxime Furفرو

Titan(cefotetan)

Bro
(Cefprozil)

Antibacterial spectrum

- **Third-generation cephalosporins:**

- Greater activity against gram-negative bacilli (broad-spectrum)
  -Less potent than 1st generation against MSSA

  Active against beta-lactamase producing strains **of H. influenzae and Neisseria gonorrhoeae**

- **Drugs of choice** for the treatment of meningitis(usually caused by S.pneumonia and Meningitides) and gonorrhea
- Must be used with caution "collateral damage"→normal flora disruption and C. difficile infection

Ceftriaxone

Cefotaxime

Ceftazidime

Cefdinir

*only ceftazidime

Mnemonic

What do teenagers(3rd generation) do?
They go out in taxi(cefotaxime) to have dinner(cefdinir), play trix(ceftriaxone) +ceftazidime?

An axe in head→ceftriaxone is used in meningitis

فاس مع لحمة نية
neisseria

Cephalosporins

Antibacterial spectrum

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

Cefepime

Antibacterial spectrum

- **Advanced-generation(5th generation) cephalosporins:** Ceftaroline
- Broad-spectrum: unique structure allows ceftaroline to **bind to PBPs** found in **MRSA and penicillin-resistant Streptococcus pneumoniae**
- <u>Only</u> β-lactam that is active against MRSA
  - Indicated for complicated skin MRSA infections and pneumonia
  - How about pseudomonas? ESBL? Ceftaroline is <u>susceptible</u> to them and so there are gaps in covering these gram negative organisms
  - *What are the limitations for using ceftaroline?*

The twice-daily dosing regimen also limits use outside of an institutional setting is a major limitation for ceftaroline usage outside of an institutional setting

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*

- ceftriaxone causes biliary jaundice(إصفرار) in neonates and so

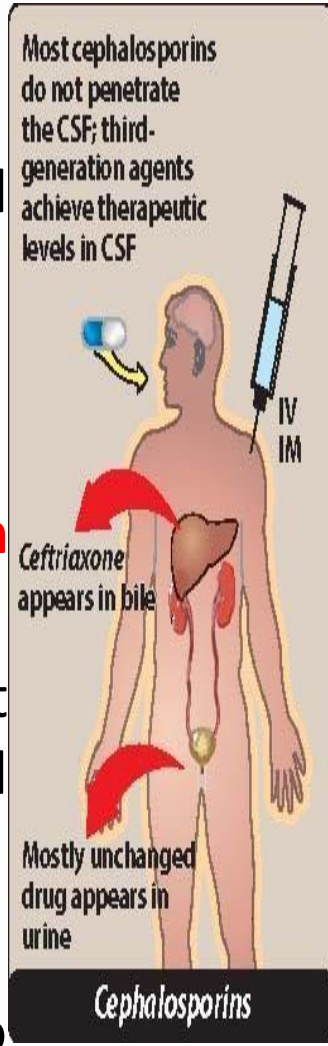
cefotaxime is preferred in neonates

-cefazolin can penetrate bone→ used in **osteomyelitis(usually caused by staph aureus)**

Cefazolin is also commonly used for surgical prophylaxis due to its activity against **penicillinase-producing .S.. aureus,** along with its good tissue and fluid penetration.

- **Elimination:**

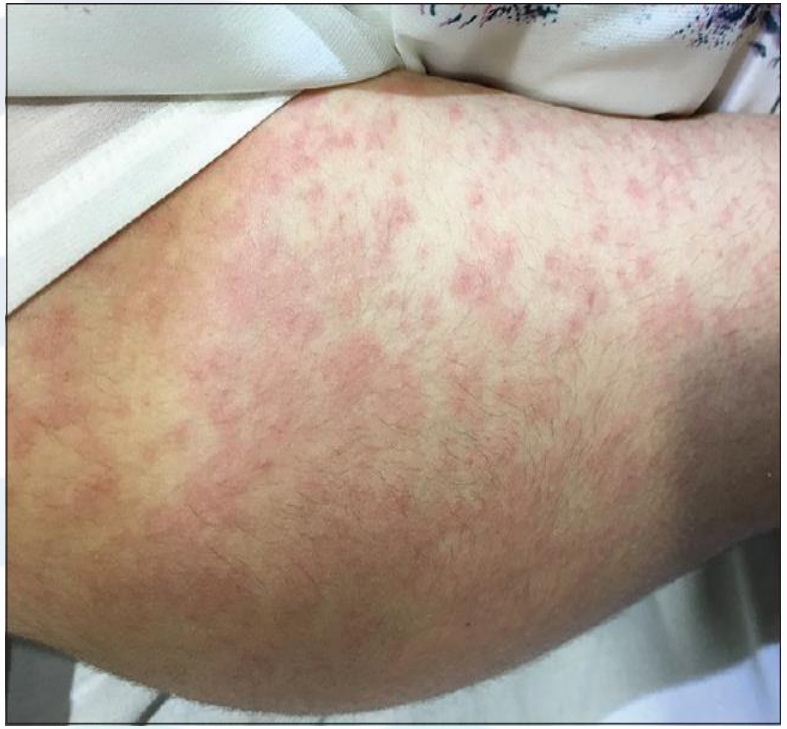
-Renal tubular secretion and filtration (except ceftriaxone, eliminated in bile so preferred in renal failure with no need for dose reduction)

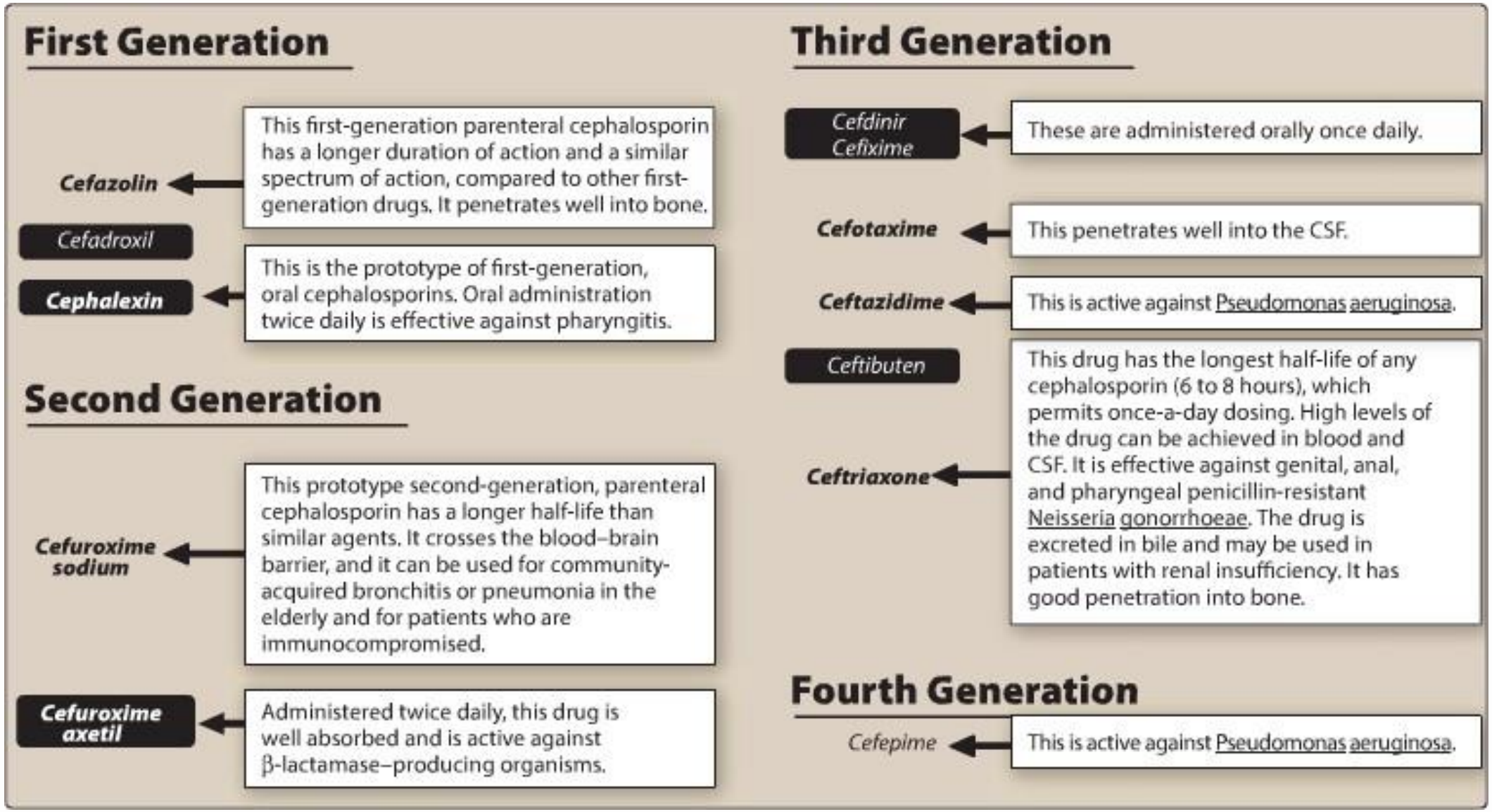


Cephalosporins

Adverse effects

- Hypersensitivity (cross-reactivity with penicillin(in about 3-5% of people with penicillin allergy)
- Highest rate of allergic cross- sensitivity occurs with cephalosporins with **similar side chains to penicillins**→1st generation
- People who had anaphylaxis or steven johnson from penicillins SHOULD NOT receive cephalosporins
- Remember: broad-spectrum antibiotics are associated with superinfections





Cephazolin→osteomyelitis(limb pain,swelling, redness, inability to move limb)

Natural penicillins
Amoxicillin → sore throat/ pharyngitis
1st gen cephalo(cefalexin)
2nd gen cephalo(cefuroxime)

Amoxicillin → respiratory infections(dyspneaضيقة نفس , cough, sputum, chest pain)
Cefuroxime(2nd)

Ceftriaxone(3rd) →meningits(headache, photophobiaضو بيتحملش, Neisseria gonorrhea
Cefotaxime(3rd)

Cefepime(4th) or antipseudomonal pencillins→ pseudomonas
Ceftaroline(5th)→MRSA

(Amoxicillin/ampicillin)+lactamase inhibitors
Antistaphylococcal pencillins -→MSSA
1st gen cephalo
2nd gen cephalo

Listeria,enterococci→**Don't** use cephalosporins, **use ampicillin**

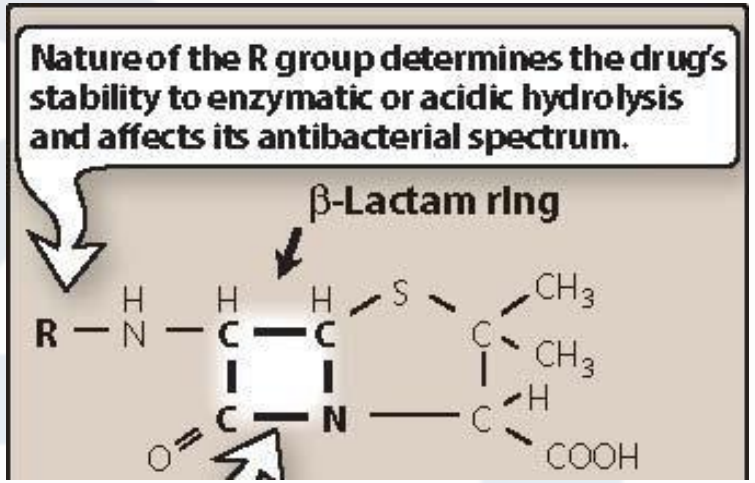
Empiric therapy for neonatal(1 month old) meningitis→Ampicillin(covers listeria)+ 3rd gen cefotaxime(covers other microbes)

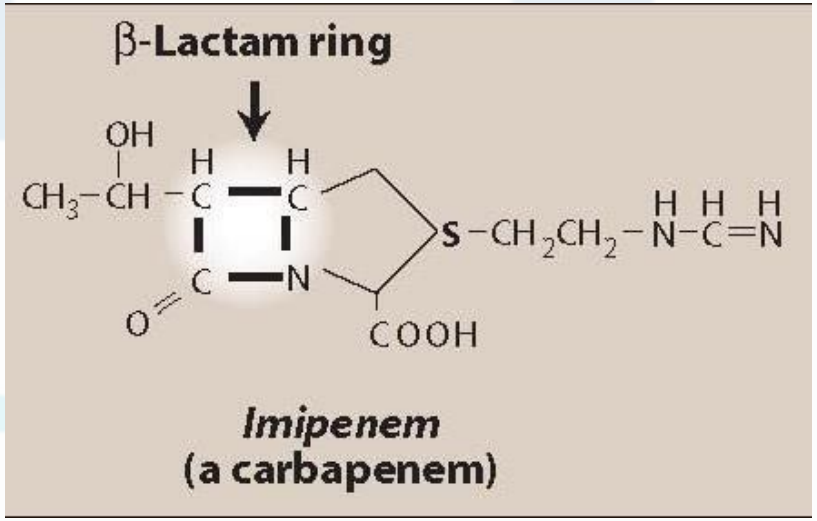
Other β-Lactams

Carbapenems

CARBAPENEMS

Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin PRIMAXIN
Meropenem MERREM





Carbapenems are synthertic
Carbapenems are In same manner has β- lactam ring, but the different is in sulfur group , this sulfur is externalized in carbapenem as side chain and has been replaced by a carbon atom .

Carbapenems

Antibacterial spectrum

- Broad-spectrum empiric(used for therapy)
- Resist β-lactamases
- (Except for metalolactamase)
- Effective against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa
- **Not effective against MRSA**

*Not MRSA

Mnemonic:
No carbapenem or penicillin is effective against MRSA

Unlike other carbapenems, ertapenem lacks coverage against P aeruginosa, Enterococcus species, and Acinetobacter species.
Ertapenem is administered IV once daily

Carbapenems

Pharmacokinetics:

Imipenem, meropenem, and doripenem are administered IV and penetrate well into body tissues and fluids.

Meropenem is known to reach therapeutic levels in bacterial meningitis even without inflammation.

imipenem(the prototype) is given with cilastatin because cilastatin inhibits renal dehydropeptidase in proximal renal tubules, renal dehydropeptidase breaks down imipenem. So cilastatin will increase half-life of imipenem and so you don't have to give large frequent doses.

Other carbapenems don't need cilastatin.

In general Carbapenem is relatively safe , they can cause gastrointestinal adverse affect which is nausea , vomiting and diarrhea also they have hematologic adverse effects similar to penicillins , so they can cause neutropenia and eosinophilia ز High concentration of carbapenem can provoke seizures in patient who susceptible or have epilepsy.

Carbapenems and penicllins share a common bicyclic core→Risk of penicillin cross-allergy is <1%

Carbapenems are last resort drugs.

Monobactams

MONOBACTAMS

Aztreonam AZACTAM

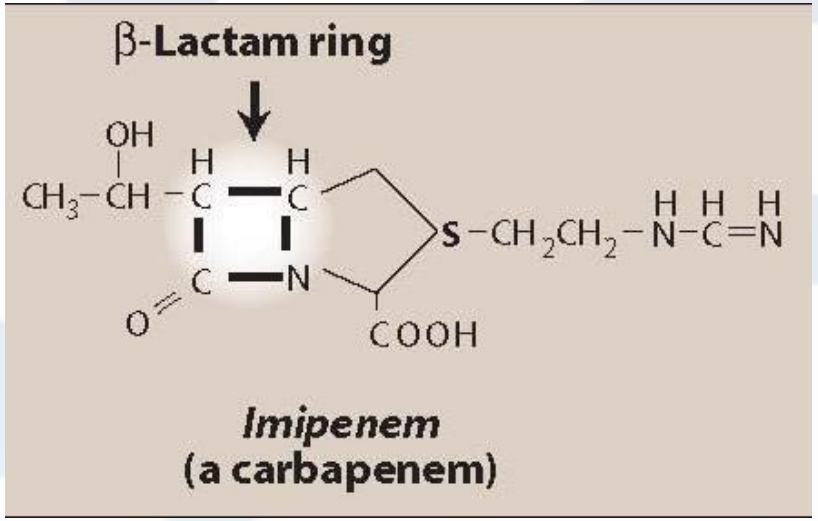
-Effective against gram-negative (including P. aeruginosa)

-Lacks activity against gram-positive and anaerobs

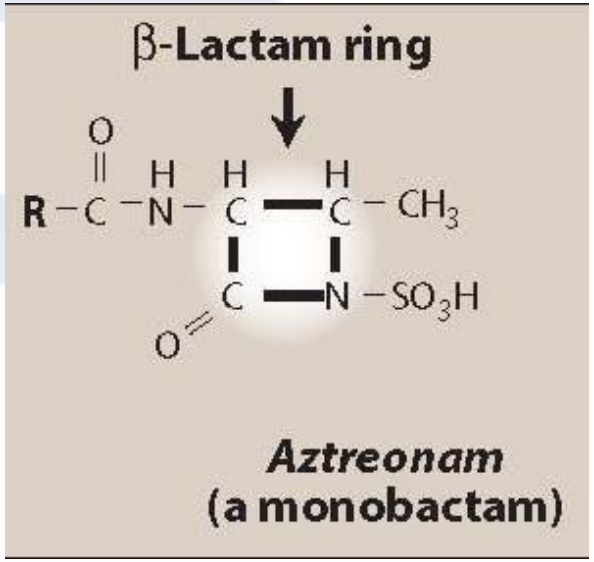
--Susceptible to ESBLs

-Relatively non-toxic

-little cross-reactivity with other β-lactams→safe alternative for penicillin allergy



Imipenem
(a carbapenem)



Aztreonam
(a monobactam)

administered either IV or IM and can accumulate in patients with renal failure

Aztreonam mnemonic

Pink=gram negative coverage only

Colors=resemble pseudomonas

Never, ever make the mistake of thinking that sulbactam and tazobactam are monobactams!!
These are beta-lactamase inhibitors

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

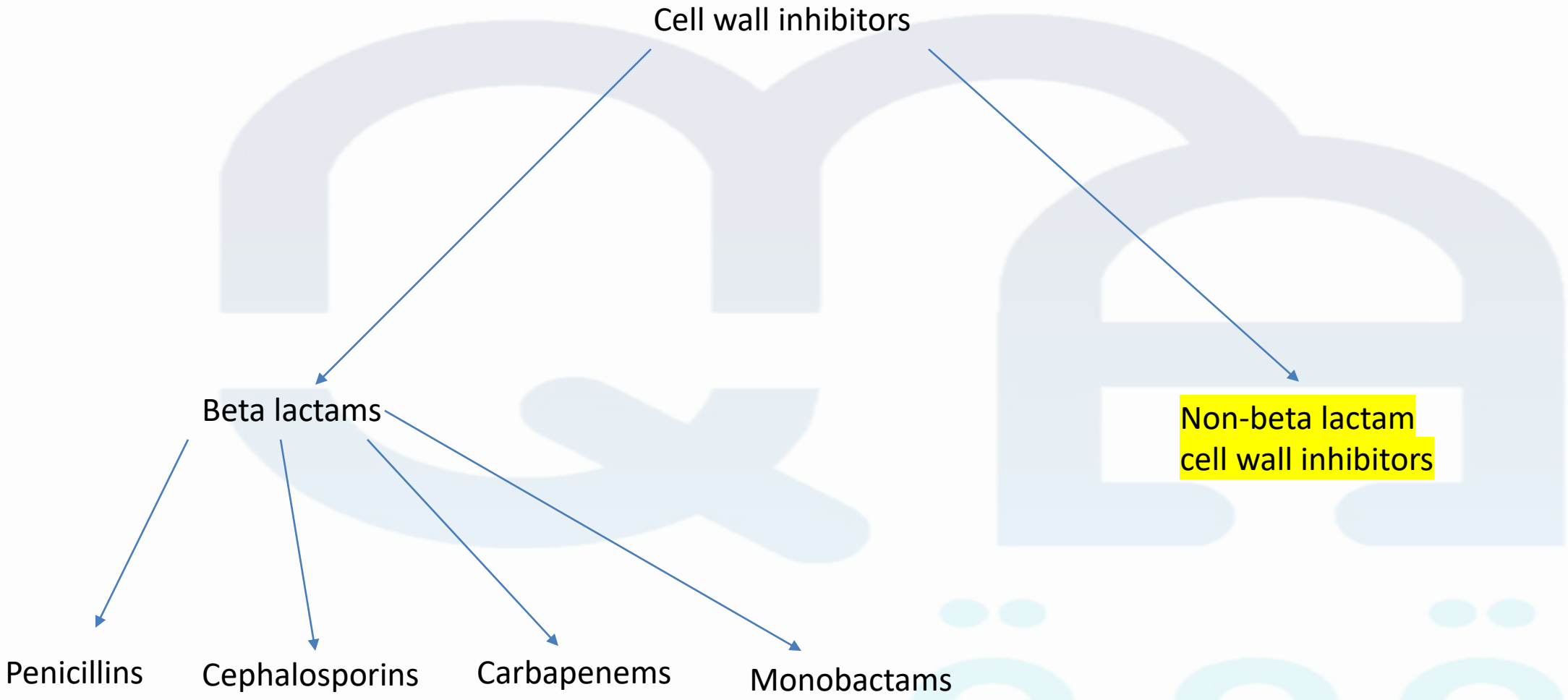
- Ceftolozane + tazobactam: used for **multidrug resistant P. aeruginosa** and some ESBLs-producing bacteria
- Ceftazidime + avibactam: used against ESBL-producing bacteria+pseudomonas

***both indicated for the management of complicated intra-abdominal and urinary tract infections caused by multidrug resistant bacteria. But are **susceptible to metallo-lactamases.**

- Meropenem + vaborbactam: used against ESBL-producing bacteria

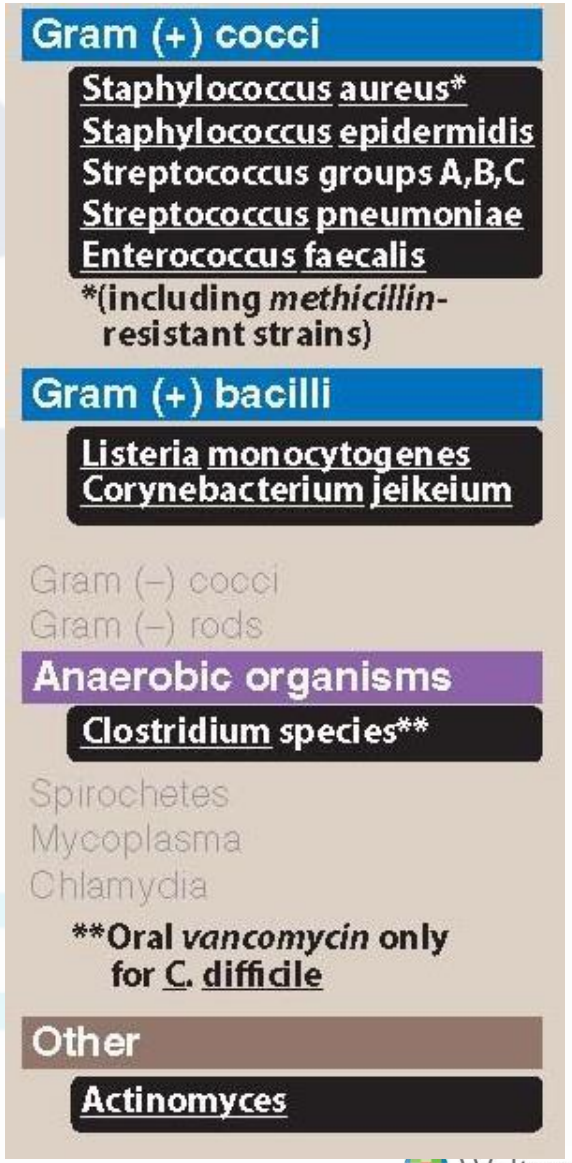
Mnemonic: the carbapenem(carbonفحم) results in vaborبخار

***indicated for the management of complicated urinary tract infections. **But is susceptible to metallo-lactamases.**

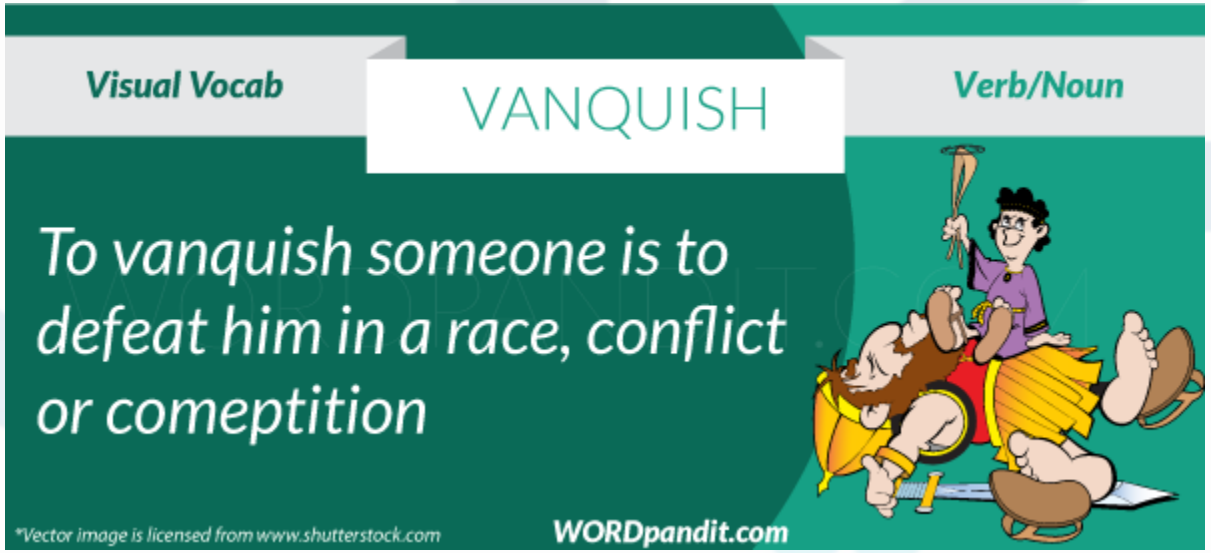


Vancomycin

- Firstly, Vancomycin is **NOT** a beta-lactam
- tricyclic glycopeptide
- **What is the mechanism of action of vanco?**
- Effective against gram-positive bacteria INCLUDING MRSA and MRSE(**main** drug for MRSA)
- Oral and IV
- Vanco has poor absorption, so it is not absorbed after oral administration
- IV vanco used in patients with **MRSA skin infections, infective endocarditis**, **MRSA nosocomial pneumonia** ….
- Oral vanco used for severe antibiotic associated **pseudomembranous colitis**

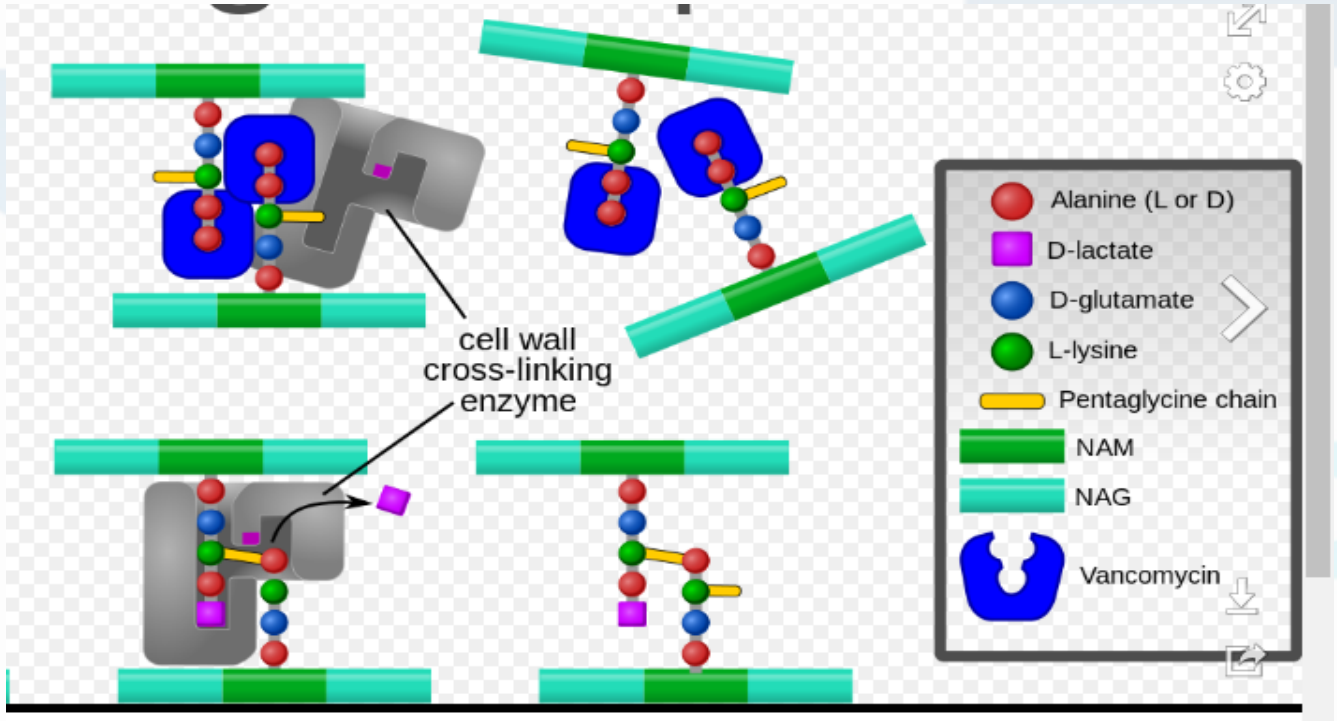


Vancomycin spectrum mnemonic
Vancomycin was named because it vanquishes gram positive



Vancomycin mechanism

Binds to ala-D peptidoglycan precursors, preventing cross-linking enzyme from binding to them and initiating cross-linkages(so vancomycin works on 3rd last step of cell wall synthesis



Vancomycin

- Bactericidal
- Time- and concentration-dependent

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

Adverse effects

- Nephrotoxicity
- Infusion related:Red man syndrome and phlebitis(vein inflammation)
- Ototoxicity

Mechanisms of resistance:

Resistance against vancomycin is rare. but is mostly seen in Enterococcus faecium

- Mechanism involves Alteration in binding affinity to peptidoglycan precursors

Frequency of administration is dependent on renal function and serum ;evels. Therefore, monitoring of creatinine clearance is required to optimize exposure and minimize toxicity.

Optimal cure rates are observed when trough concentrations are maintained between 10 and 20 mcg/ml.

Initial trough concentrations are attained prior to the fourth or fifth vancomycin dose to ensure appropriate dosing.

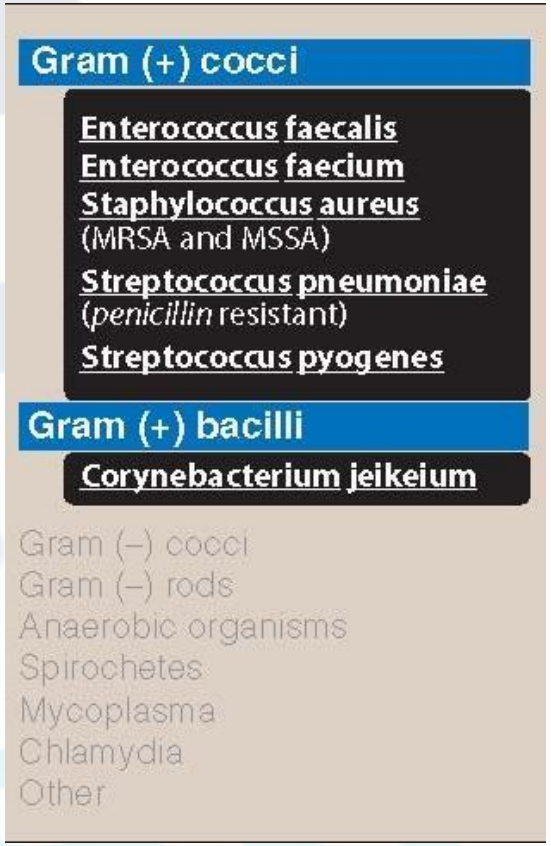
[Note: The area under the curve/minimum inhibitory concentration ratio (AUC24/ MIC) is the best predictor of vancomycin activity against .S. aureus, with an AUC/MIC of greater than or equal to 400 associated with treatment success.]


MRSA
10
20
Summary

Daptomycin

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

Because it is inactivated by pulmonary surfactant!!



Daptomycin mnemonic

Gram positive only

Arm covers lungs, **don’t use for pneumonia!**

Avocado=**lipo**peptide

Lipoglycopeptides

Telavancin

- Semisynthetic
- Bactericidal
- Concentration-dependent
- The lipid tail is essential in anchoring the drug to the cell walls to improve target site binding. Additionally, telavancin and oritavancin disrupt membrane potential
- 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(QT prolongation)+fetal harm and teratogencity, foamy urine and interference with coagulation lab studies (so don't use with heparin)

Prior to initiation, assessment of renal function, pregnancy status, and current medications is needed to ensure safe administration.

In contrast to telavancin, oritavancin and dalbavancin have prolonged half-lives (245 and 187 hours, respectively), allowing for single-dose administration for the management of ABSSSI.

Stable patients with ABSSSI may be treated as outpatients, eliminating the need for inpatient admission, central catheter placement, and/or daily outpatient parenteral antibiotic therapy.

29.2 Which of the following adverse effects is associated with daptomycin?

A. Ototoxicity

B. Red man syndrome

C. QT_c prolongation

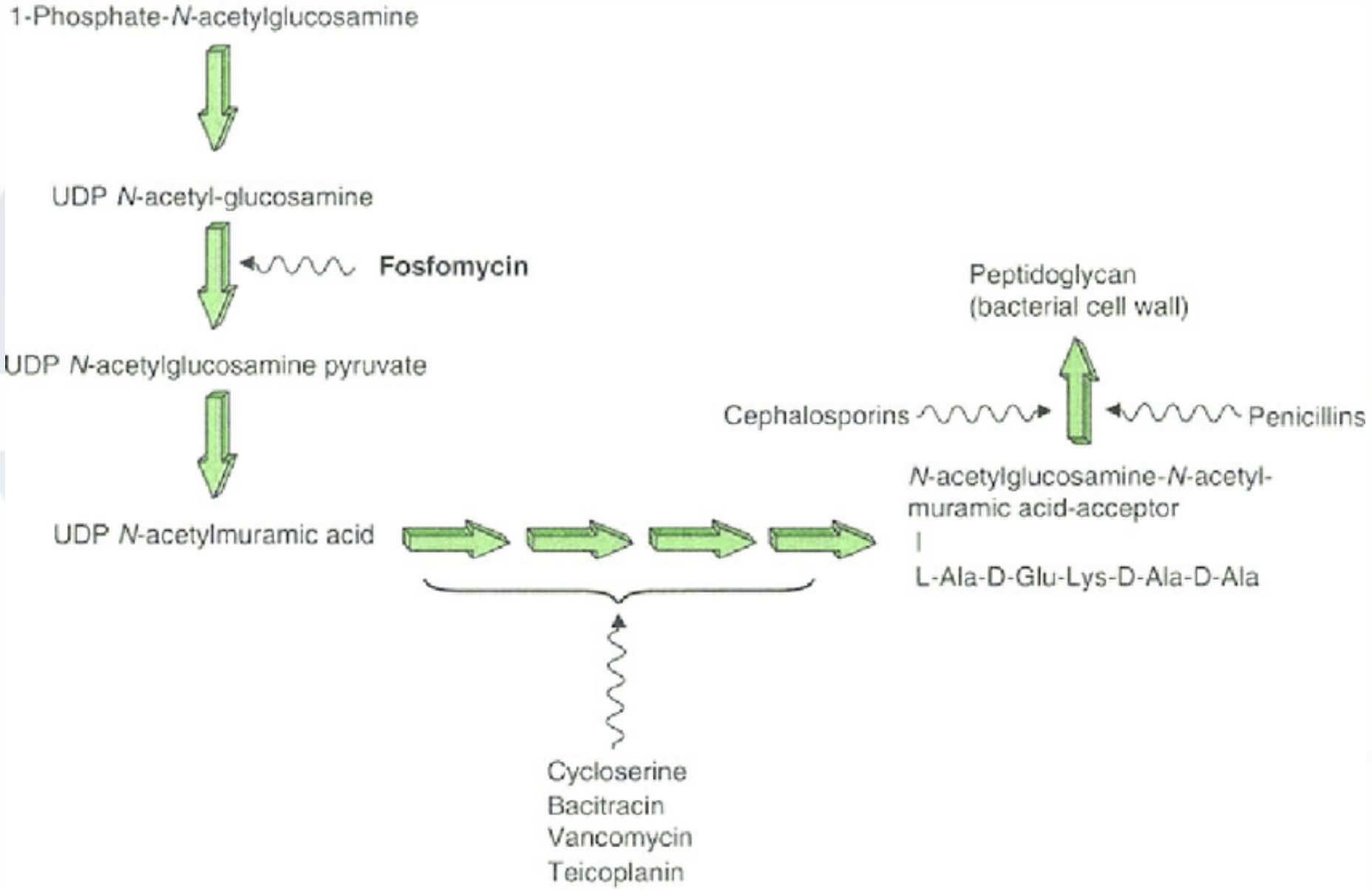
D. Rhabdomyolysis

Correct answer = D. Ototoxicity and red man syndrome are associated with vancomycin. QTc prolongation is associated with telavancin. Myalgias and rhabdomyolysis have been reported with daptomycin therapy and require patient education and monitoring.

	VANCOMYCIN	DAPTOMYCIN	TELAVANCIN
Mechanism of Action	Inhibits bacterial cell wall synthesis	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein	Inhibits bacterial cell wall synthesis; disrupts cell membrane
Pharmacodynamics	Combination of time and concentration-dependent Bactericidal	Concentration-dependent Bactericidal	Concentration-dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: Staphylococcus aureus (including MRSA), Streptococcus pyogenes, S. agalactiae, *penicillin*-resistant S. pneumoniae, Corynebacterium jeikeium, *vancomycin*-susceptible Enterococcus faecalis, and E. faecium		
Unique Antibacterial Spectrum	Clostridium difficile (oral only)	*Vancomycin*-resistant E. faecalis and E. faecium (VRE)	Some isolates of *vancomycin*-resistant enterococci (VRE)
Route	IV/PO	IV	IV
Administration Time	60- to 90-min IV infusion	2-min IV push 30-min IV infusion	60-min IV infusion
Pharmacokinetics	Renal elimination Half-life: 6–10 h Dose is adjusted based on renal function and serum trough levels	Renal elimination Half-life: 7–8 h Dose is adjusted based on renal function	Renal elimination Half-life: 7–9 h 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	Elevated hepatic transaminases and creatine phosphokinase (check weekly), myalgias and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while receiving 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 C. difficile infection; monitor serum trough concentrations for safety and efficacy	*Daptomycin* 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 *telavancin* dose to avoid interaction

Fosfomycin

- Synthetic 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**إلتهاب المثانة
- Acute cystitis signs/symptoms: Dysuriaألم أثناء التبول, lower abdominal pain, frequencyالشعور بحاجة للتبول بكثرة, urgency شعور بأنه لازم يروح حالا ومش قادر يستنى
- Cross-resistance is unlikely



Polymyxin B

- Cation polypeptides
- **MOA**: bind phospholipids on the bacterial cell membrane of gram-negative bacteria (disrupt cell membrane by acting on the lipopolysaccharides and not cell wall)
- Active against most gram-negative bacteria including P. aeruginosa
- **However,alterations in the cell membrane lipid polysaccharides allow many species of Proteus and Serratia to be intrinsically resistant**
- Bactericidal
- Concentration-dependent
- Available through many routes, but has Limited use because of **nephrotoxicity/neurotoxicity**
- Spared for multi-drug resistant infections(salvage therapy)

Colistin(polymyxin E) is only available as a prodrug, colistimethate sodium, which is administered IV or inhaled via a nebulizer.

Quick Exercise

Name five cell wall synthesis inhibitors that have antipseudomonal activity.

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

THANK YOU