The β- Lactam Antibiotics

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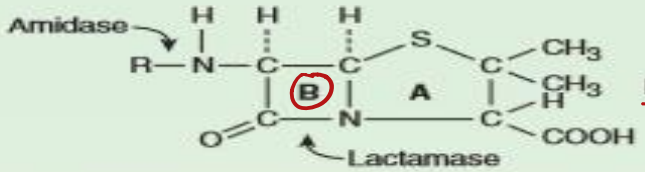
The β- Lactam Antibiotics

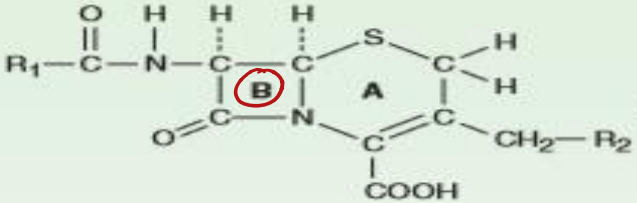
- Penicillins.
- Cephalosporins.
- Carbapenems.
- Monobactams.

have β-lactam ring in structure (chemical classification).



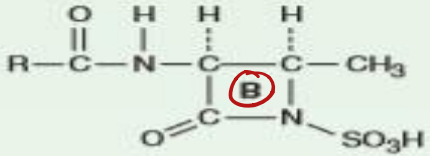
Penicillin

Substituted 6-aminopenicillanic acid



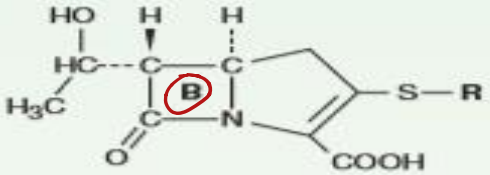
Cephalosporin

Substituted 7-aminocephalosporanic acid

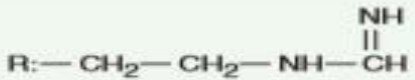


Monobactam

Substituted 3-amino-4-methylmonobactamic acid (aztreonam)



Carbapenem



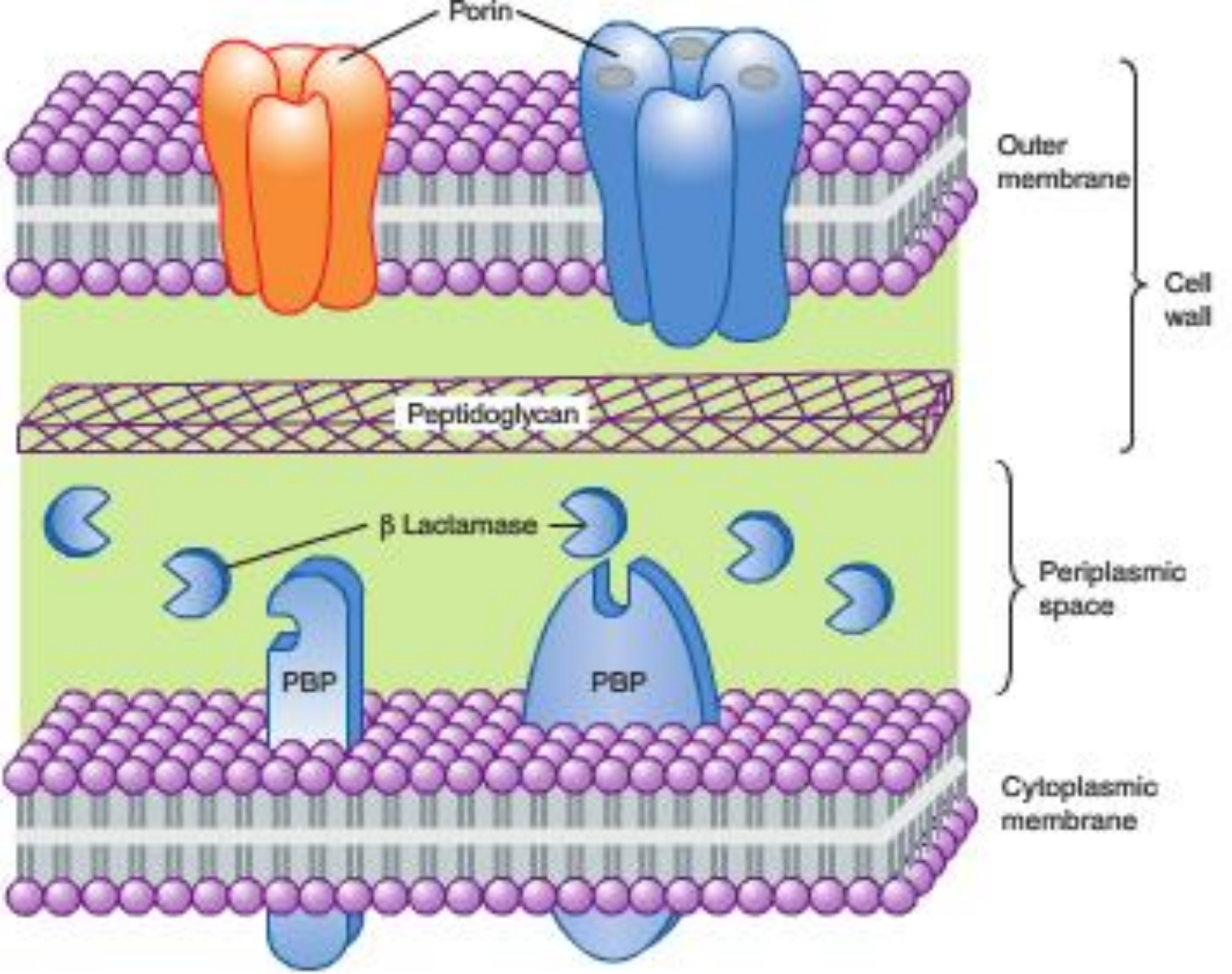
Substituted 3-hydroxyethylcarbapenemic acid (imipenem)

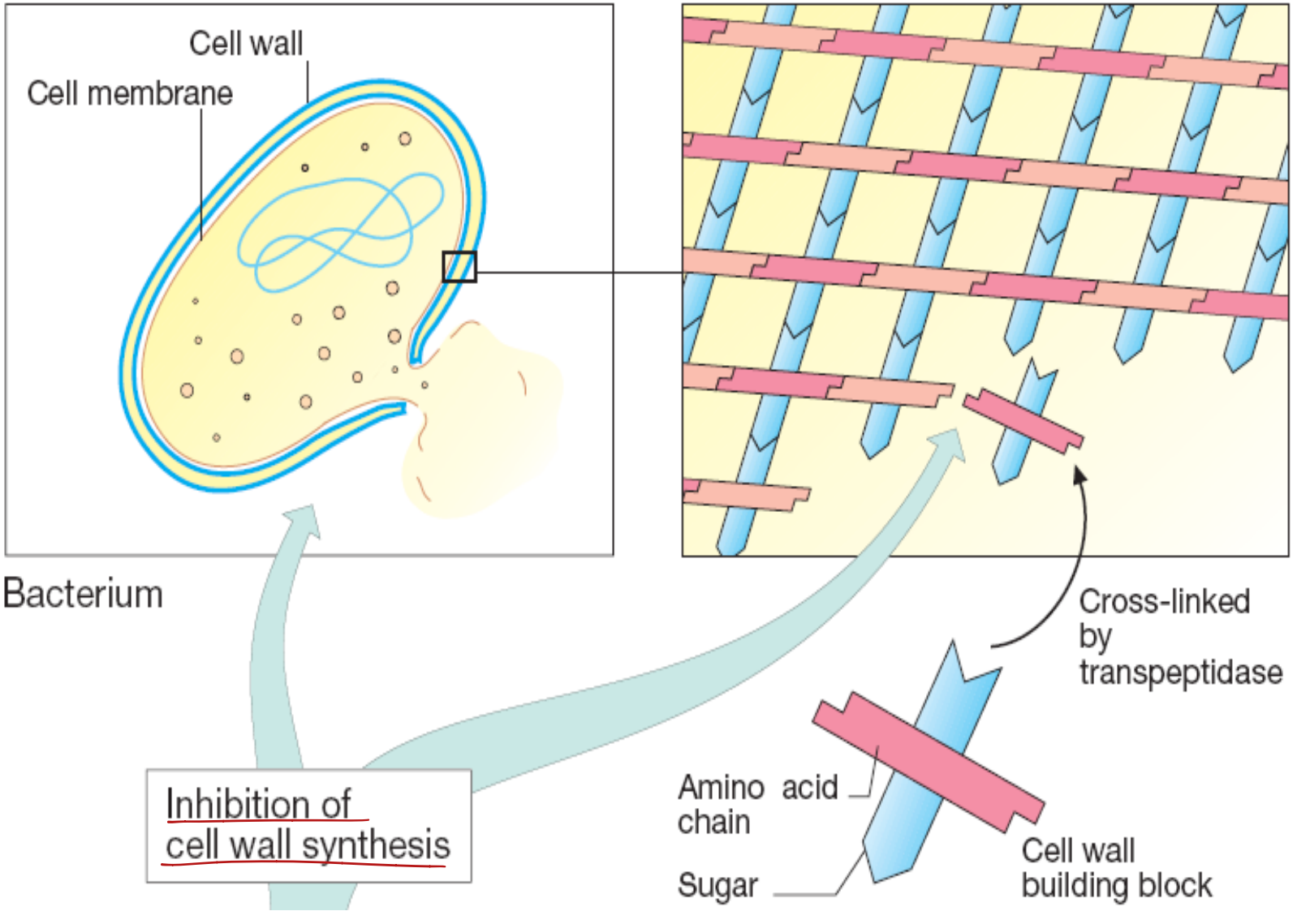
growing multiplying bacteria are affected. mature bacteria are intact.

only work on bacteria with a cell wall.

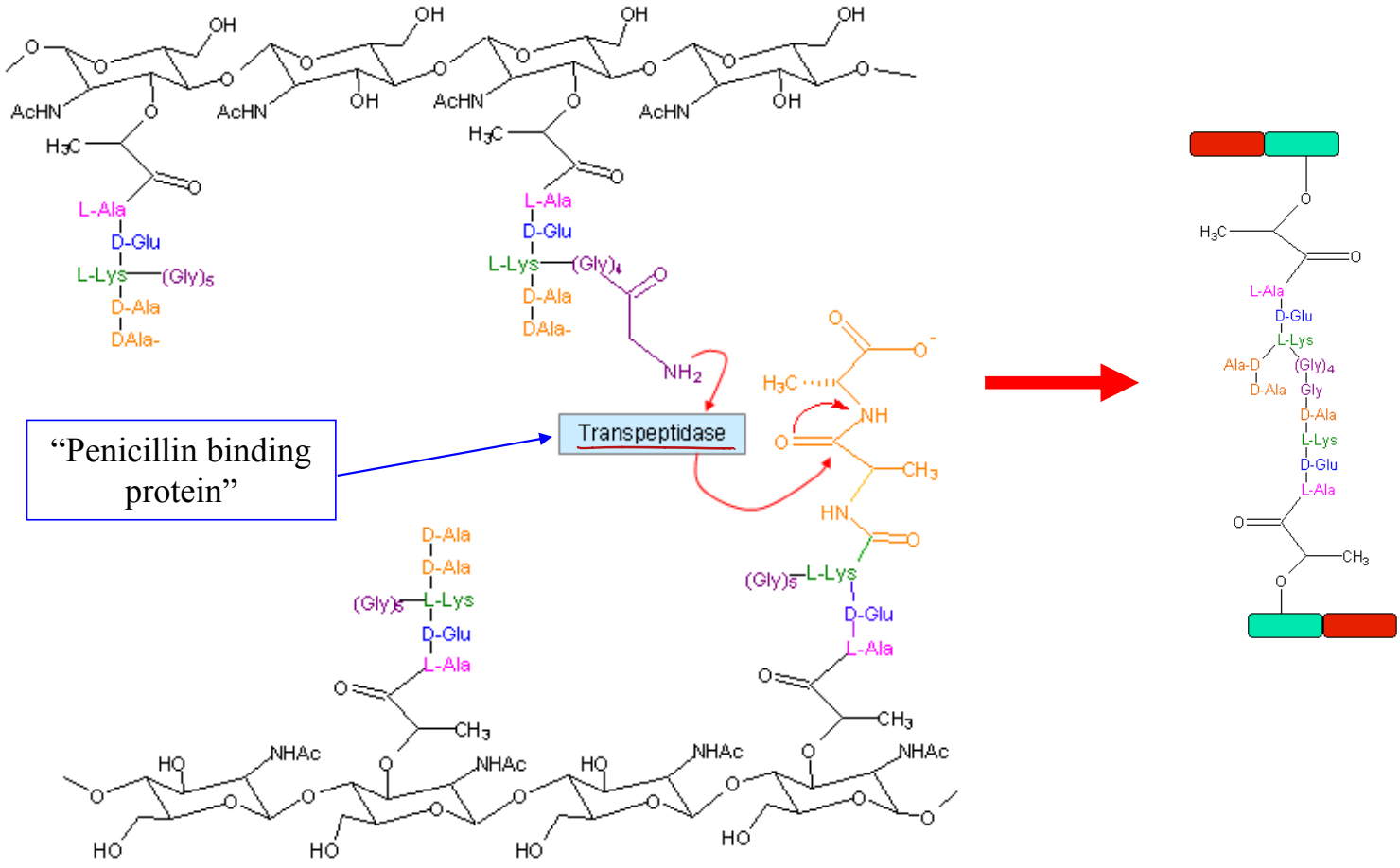
How β- Lactams work?

1. β-lactams bind to Penicillin Binding Protein (PBP).
2. PBP will be unable to crosslink peptidoglycan chains, responsible for the integrity of the cell wall.
3. Multiplying bacteria will not be able to synthesize a stable cell wall.
4. The bacteria will be lyzed by osmotic forces and will die.


Porin
Outer membrane
Cell wall
Peptidoglycan
β Lactamase
Periplasmic space
PBP
PBP
Cytoplasmic membrane


Cell wall
Cell membrane
Bacterium
Cross-linked by transpeptidase
Amino acid chain
Sugar
Cell wall building block
Inhibition of cell wall synthesis

Peptidoglycan Synthesis



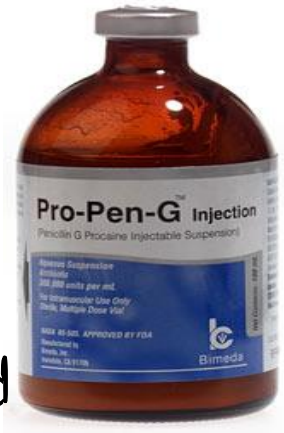
The Penicillins

- **Natural Penicillins:**
  - Penicillin G, → Fleming, 1941.
  - Penicillin V
  - Procaine Penicillin
  - Benzathine Penicillin

  } → long acting forms.
- **Aminopenicillins:**
  - Ampicillin,
  - Amoxicillin
- **Anti-Staph Penicillins:**
  - Oxacillin
  - Dicloxacillin

  effective against staph. at first but then staph. makes β-lactamase (resistance forms)
- **Anti-Pseudomonal Penicillins:**
  - Ticarcillin
  - Piperacillin

Penicillins



- **Penicillin G**
- First natural antibiotic, 1941.
- Used IM, IV. Short acting, rapidly excreted
- **Probencid**: was used when penicillin was very expensive to increase the half life and serum concentration of penicillin.
- **Uses :**
  - Endocarditis (*S. viridans or Streptococcus bovis*)
  - Pharyngitis (group A β-hemolytic streptococci)
  - Cat bite cellulitis (*Pasteurella multocida*)
  - Syphillis (*Treponema pallidum*)
  - Streptococcal meningitis

through renal tubules as urine

3-4 times/day

drug for gout (enhance uric acid secretion), no need anymore.

1st choice for

autoimmune disease

rheumatic fever side effect

S. pyogenes.

acute tonsilitis

S. pneumonia.

IV in hospital.

cant cross BBB except in

inflammed meningies.

Penicillins

- **Penicillin G.**
- **Long-acting forms:** painless injection. (1-2/day)
  - Procaine Pen G , combined with procaine(a local anesthetic), painless and longer acting(12-24 hours).
  - Benzathine Pen (4 weeks), suitable for prophylaxis 1/month. → rheumatic fever patients
- **Phenoxymethyl penicillin G:**
  - Acid-stable, so can be given orally.
  - Uses : Streptococcal infections when oral therapy is preferred, usually in children. & adults if preferred 3-4/day.

Adverse Reactions of Penicillins

- **Allergic reactions:** skin rash**,** serum sickness, drug fever, anaphylaxis(1 in 40,000).
- Very common.
- Cross allergenicity with all beta lactams.
- Hemolytic anemia, pancytopenia, neutropenia. Are rare reactions

severe allergy (anaphylactic shock) ↓ if not treated immediately patient dies. give epinephrine (physiological drug)

deficiency of RBC, WBC & platelets

abnormally low level of neutrophils

we see allergies after 2nd administration.

he talked about thigh abcesses & the use of dirty syringes in 1940s and how sciatic nerve damage causes lower limb paralysis & thats a problem of injections

Aminopenicillins

can work on pseudomonas.

- **Ampicillin (IV, PO), QID:** replaced by: (should be given only IV, if oral is needed use amoxicillin)
- **Amoxicillin (PO),BID** → we dont have IV

Quater/day (4 times/day)

bi/day (twice/day)

- Broad spectrum activity, same as Penicillin G, plus *H. influenzae,* some *E. coli,* and are integral drugs in *H. pylori* regimens. (& gram-ve bacteria; could be serious infection, neonatal meningitis; peptic ulcer disease.)
- **The most useful antibiotics for treating children** (no.1 antibiotic)
- Adverse effects: (most viral diseases are associated with a rash (marker for viral infection not bacterial))
  - Non-allergic rashes (9%) – especially when associated with a viral illness (infectious mononucleosis - EBV)
  - Amoxicillin is better tolerated orally and better absorbed (Ampicillin is partially absorbed and can cause diarrhea and can alter the normal intestinal flora and should be taken on empty stomach, only better because of IV administration)

Anti-Staph Penicillins

- **Methicillin**
- **Oxacillin**
- **Dicloxicillin**

- However, there are Methicillin-resistant *Staphylococcus aureus(MRSA).* → vancomycin used.

Anti-Pseudomonal Penicillins

- **Piperacillin**
- **Ticarcillin**

↳ can cause pneumonia/respiratory infection.

- Most active penicillin against *Pseudomonas.*
- Cover *Pseudomonas*, most *Enterobacteriaceae* (*E. coli, Proteus, Klebsiella, Enterobacter, Serratia, Citrobacter, Salmonella and Shigella*)
- Often used in combination with an Aminoglycoside or a Quinolone.

* tonsilitis → 50% viral & 50% bacterial infection

Forms of Resistance to Penicillins

A. Production of β-lactamases(penicillinases) which hydrolyse the lactam ring:

b-lactamase production is particularly important in staphylococci, but they are not made by streptococci.

sensitive for penicillins bcs they dont make β-lactamases

At least 90% of staphylococcus species in the West now produce b-lactamases.

One strategy to overcome the problem is the use of b-lactamase inhibitors.

B. Reduction in the permeability of the outer membrane in Gram-negative bacteria.

C. Mutations in the penicillin-binding proteins.

"amoclan" ← "augmentine" ampicilin & amoxicilin

β-Lactamase Inhibitors

has β-lactamase inhibitors

- These are the dugs which can inhibit β-lactamases, and so usually combined(in a fixed combination) with few β- lactam antibiotics to prevent resistance.
- Structure resembles the β- lactam antibiotic. → confuses the enzyme (competitive inhibition).
- Some have minor antimicrobial activity by themselves.
- They increase the activity, and may be the spectrum of activity of the β- lactam antibiotic.

Types of β- lactamases

- **Penicillinases**, inhibited by clavulanic acid.

we have both

- **Penicillinases**, *not* inhibited by clavulanic acid.

- **Cephalosporinases,** not inhibited by clavulanic acid.
- **Metallo- β- lactamases**

β-Lactamase Inhibitors

- **Clavulanic Acid** usually combined with Amoxicillin.
- **Sulbactam** usually combined with Ampicillin.
- **Tazobactam** usually combined with Piperacillin.

The Cephalosporins

- Came one decade after the penicillins.
- Rarely the drugs of first choice for any infection.
  (there are better drugs)
- Mainly used for surgical prophylaxis.
- Expensive, especially the newer generations.
- Same toxicity as penicillins.
- Cross allergic with the penicillins.
- Activity and method of administration differ among the generations.

"medical industry." we make sure the drug is original by measuring the bioequivalence of active ingredient. if its equal to the original then its just as effective.

when theres a patient & we dont know the type of bacteria that infected him we use a broad spectrum drug (cephalosporins).

Cephalosporins

the dr. is against memorizing.

- **1st Generation:**
  - Cephalexin
  - Cefazolin

if it has ph → 1st generation

- **2nd Generation:**
  - Cefoxitin
  - Cefuroxime.
- **3rd Generation:**
  - Cefotaxime
  - Ceftriaxone
- **4th Generation:**
  - Cefepime
- **5th Generation:**
  - Ceftaroline

Cephalosporins

- **First generation** : streptococci, methicillin-sensitive *S. aureus,* and a few gram-negative bacilli. (broader spectrum than penicillin G.)
- **Second generation:** greater stability against -lactamase inactivation and possess a broader spectrum of activity to include gram-positive cocci, gram-negative organisms, and anaerobes.

Cephalosporins

- **Third generation**, have high potency and lactamase stability and a broader spectrum of action against many common gram-negative bacteria and anaerobes, while retaining good activity against streptococci.
- Third-generation cephalosporins are less active against staphylococci than the earlier generations.
- **Fourth generation** Cefepime has broad spectrum activity, used in the empirical treatment of meningitis. → crosses BBB

treatment based on experience & practice

The Cephalosporins

*Not effective against Enterococcus or Listeria

differ in distribution throughout the body.

1st Generation (injection.)	Gram (+)
2nd Generation	Decreasing Gram (+) and Increasing Gram (-)
3rd Generation	Gram (-), but also some Gram (+) less effective with Staph. than previous.
4th Generation	Gram (+) and Gram (-) equal

Ceftaroline

5th generation.

- Ceftaroline is a broad-spectrum cephalosporin that has bactericidal activity against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and *S. pneumoniae*, as well as many gram-negative bacteria. It lacks activity against *Pseudomonas aeruginosa*.

Ceftaroline

- Ceftaroline is a fifth-generation cephalosporin administered as a prodrug whose active metabolite has bactericidal activity against MRSA and vancomycin-intermediate *S. aureus* (VISA) as well as some gram-negative pathogens .

- Ceftaroline has in vitro activity against staphylococci with reduced susceptibility to Vancomycin, Daptomycin, or Linezolid.

↳ if this doesnt work, we can use ceftaroline.

Ceftaroline

- The FDA has approved Ceftaroline for the treatment of : restricted to these 2 cases.

1. Complicated skin and skin tissue infection.
2. Community acquired pneumonia.

- For treatment of complicated skin and skin structure infection, Ceftaroline has been found to be non-inferior to Vancomycin plus Aztreonam.

Distribution of Cephalosporins

- Only few(cefepime (4th), cefuroxime (2nd), cefotaxime (3rd), ceftriaxone (3rd), and ceftazidime (new)) achieve therapeutic concentrations in cerebrospinal fluid.
- Cefotaxime and ceftriaxone are antibiotics of first choice for the empirical treatment of brain abscess and meningitis

(google)
ceftazidime:
new cephalosporin,
activity includes
P. aeruginosa

(google)
cefotaxime, ceftriaxone & ceftazidime are approved for community & hospital acquired bacterial meningitis

Adverse Reactions of Cephalosporins

Hypersensitivity reactions including anaphylaxis, bronchospasm, urticaria, skin rash. cross allergenicity w/ pen. G. ↳type of skin rash.

Nephrotoxicity. → unlike pen. which are considered safe.

Thrombophlebitis after i.v administration.

Superinfection.

Diarrhea with oral cephalosporins. → alteration of flora.

Carbapenems

- **Imipenem**
- **Doripenem,**
- **Ertapenem,**
- **Meropenem**

- **The treatment of choice for infections caused by extended-spectrum beta-lactamase–producing gram-negative bacteria.**

mainly for this →

- **Imipenem has a wide spectrum of activity against many gram-negative rods, including *P. aeruginosa,* gram-positive organisms, and anaerobes.**

- **Imipenem is inactivated by dehydropeptidases in renal tubules, so, usually administered together with an inhibitor of renal dehydropeptidase, Cilastatin.**

ineffective in renal infections without cilastatin

Monobactams

- **Aztreonam:**
- Spectrum: ONLY for Gram negative aerobic bacteria
  - Some *P. aruginosa* are resistant,
- Well distributed into tissues, especially inflamed tissues, with renal clearance.
- Resistant to most b-lactamases.
- Adverse reactions include skin rash.
- No cross-reactivity with other **β-** lactam drugs.
- Used in serious infections such as pneumonia, meningitis, and sepsis caused by susceptible gram-negative pathogens.

Cross reactivity of β-Lactam Antibiotics

- Cephalosporin /Penicillin: 1 – 10%. not significant
- Aztreonam/Penicillin or Cephalosporin: 0%. no cross allergenicity
- Carbapenems/Penicillins: 10% .

→ pneumonia
sepsis
meningitis

Diala Abul Haija,
dont hesitate to contact me
for further clarification.
good luck!