β-Lactam antibiotics

β-Lactam antibiotics are the most widely produced and used antibacterial drugs in the world, and have been ever since their initial clinical trials in 1941.

β-Lactams are divided into several classes based on their structure and function; and are often named by their origin, but all classes have a common β-lactam ring structure.

Target- Cell Wall Synthesis

The bacterial cell wall is a cross linked polymer called peptidoglycan which allows a bacteria to maintain its shape despite the internal turgor pressure caused by osmotic pressure differences.

If the peptidoglycan fails to crosslink the cell wall will lose its strength which results in cell lysis.

All β-lactams disrupt the synthesis of the bacterial cell wall by interfering with the transpeptidase which catalyzes the cross linking process.

Transpeptidase- PBP

The cross linking reaction is catalyzed by a class of transpeptidases known as penicillin binding proteins

A critical part of the process is the recognition of the D-Ala-D-Ala sequence of the NAMA peptide side chain by the PBP. Interfering with this recognition disrupts the cell wall synthesis.

beta-lactams mimic the structure of the D-Ala-D-Ala link and bind to the active site of PBPs, disrupting the cross-linking process.

BETA LACTAMS - MECHANISMS OF ACTION

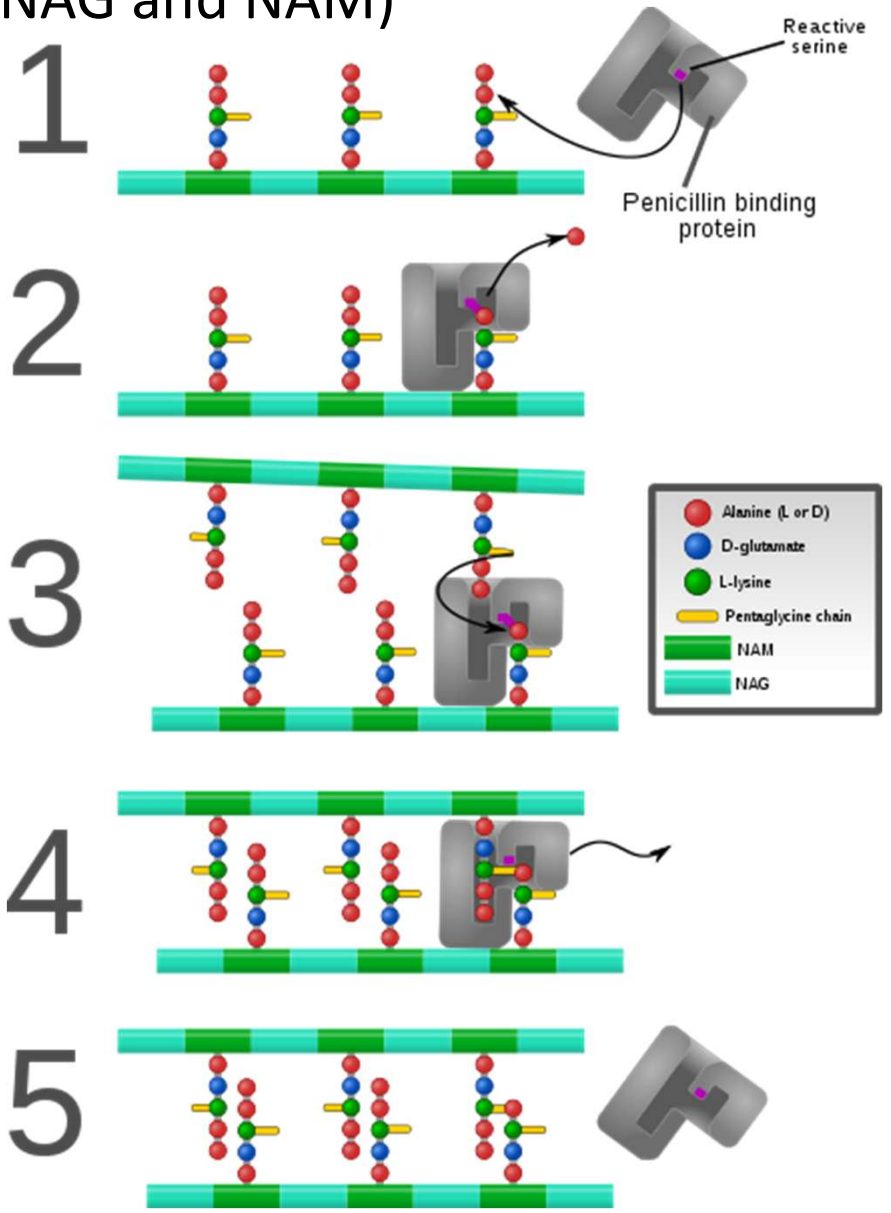
Beta-lactam antibiotics are bactericidal drugs. They act to inhibit cell wall synthesis by the following steps:

(1) Binding of the drug to specific enzymes (penicillin-binding proteins [PBPs] located in the bacterial cytoplasmic membrane;

(2) inhibition of the transpeptidation reaction that cross-links the linear peptidoglycan chain constituents of the cell wall; and

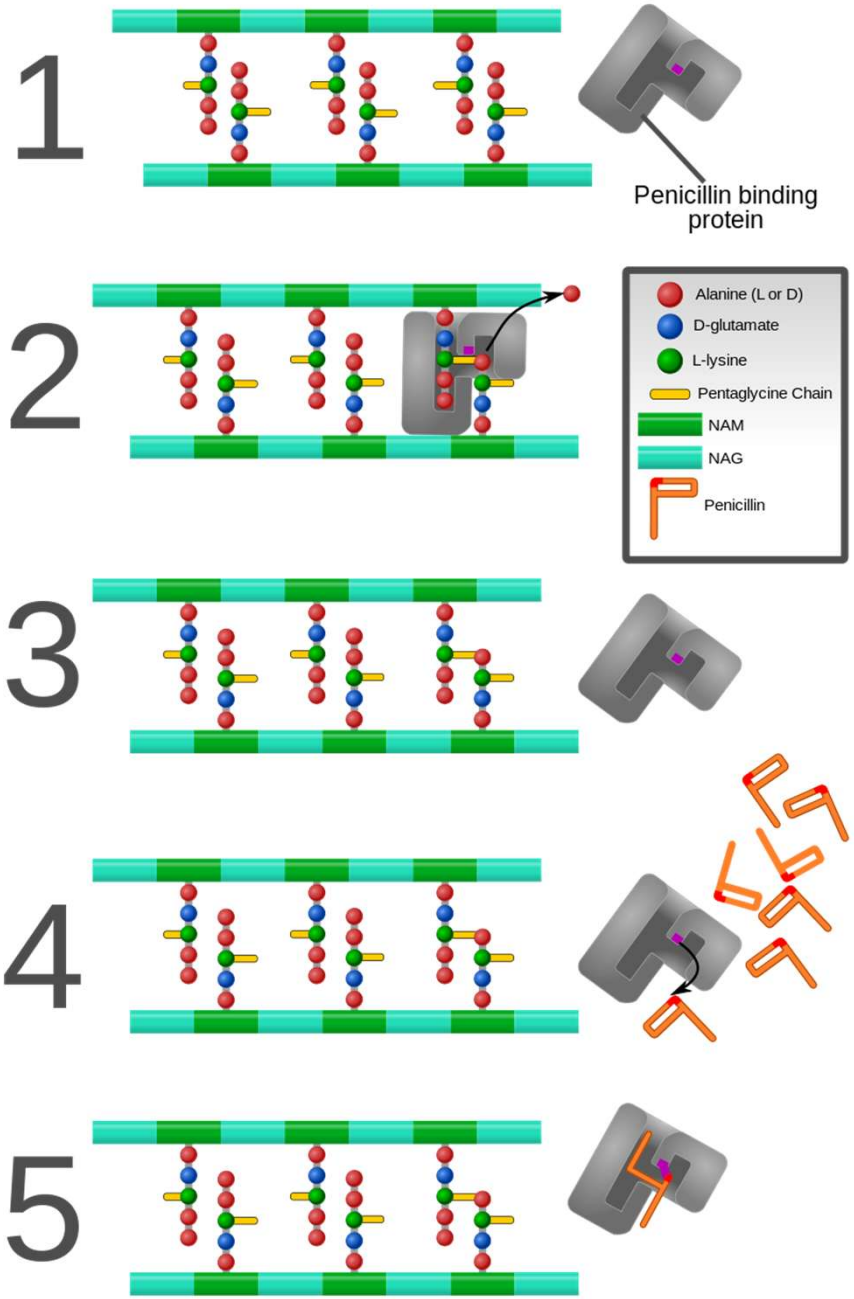
(3) activation of autolytic enzymes that cause lesions in the bacterial cell wall.

Crosslinking of cell wall polymers (NAG and NAM)



https://commons.wikimedia.org/wiki/File:PBP_catalysis.svg

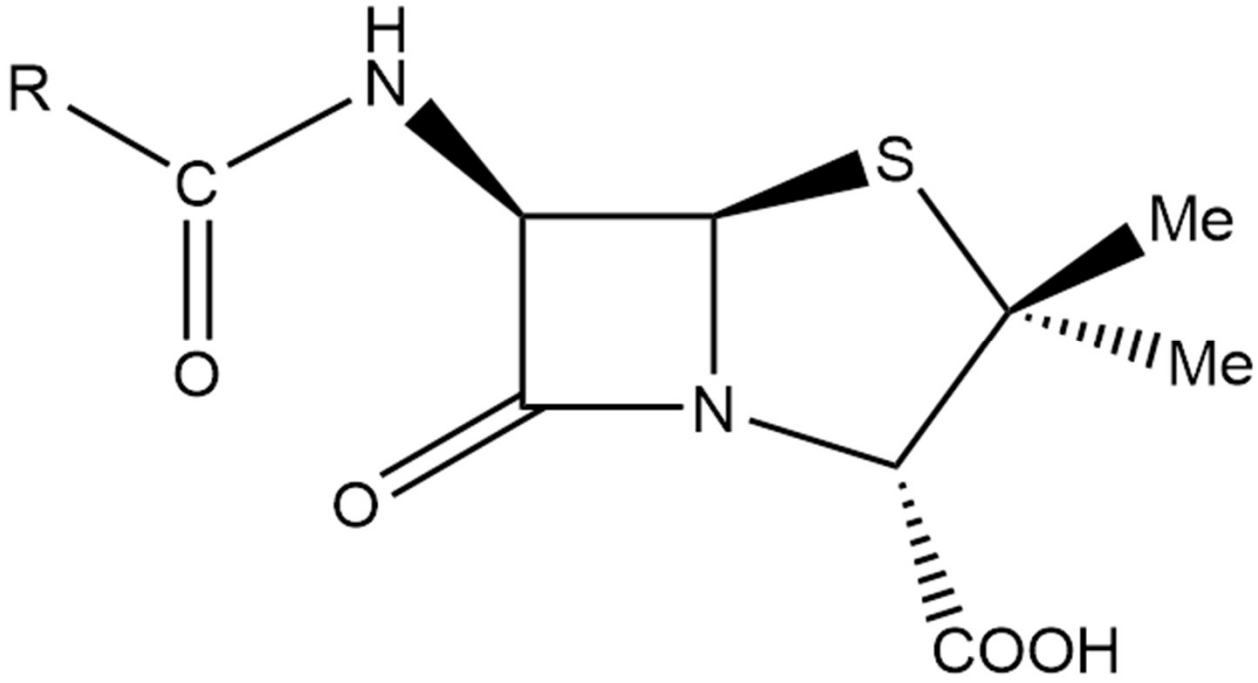
Action of betalactams



Classes of β-Lactams

The classes of β-lactams are distinguished by the variation in the ring adjoining the β-lactam ring and the side chain at the α position.

Penicillin



- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams

Penicillin

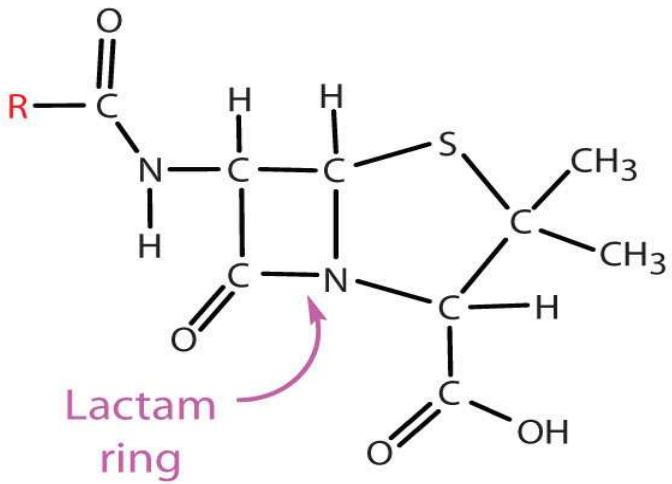
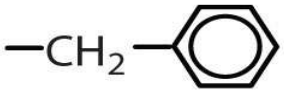
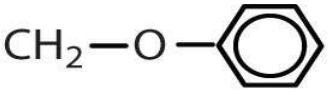
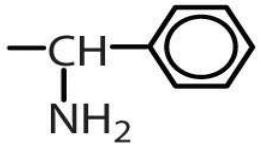
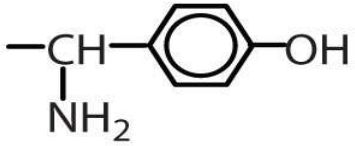
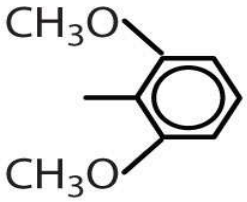
- First antibiotic to be used clinically in 1941

- One of the least toxic antibiotic even today

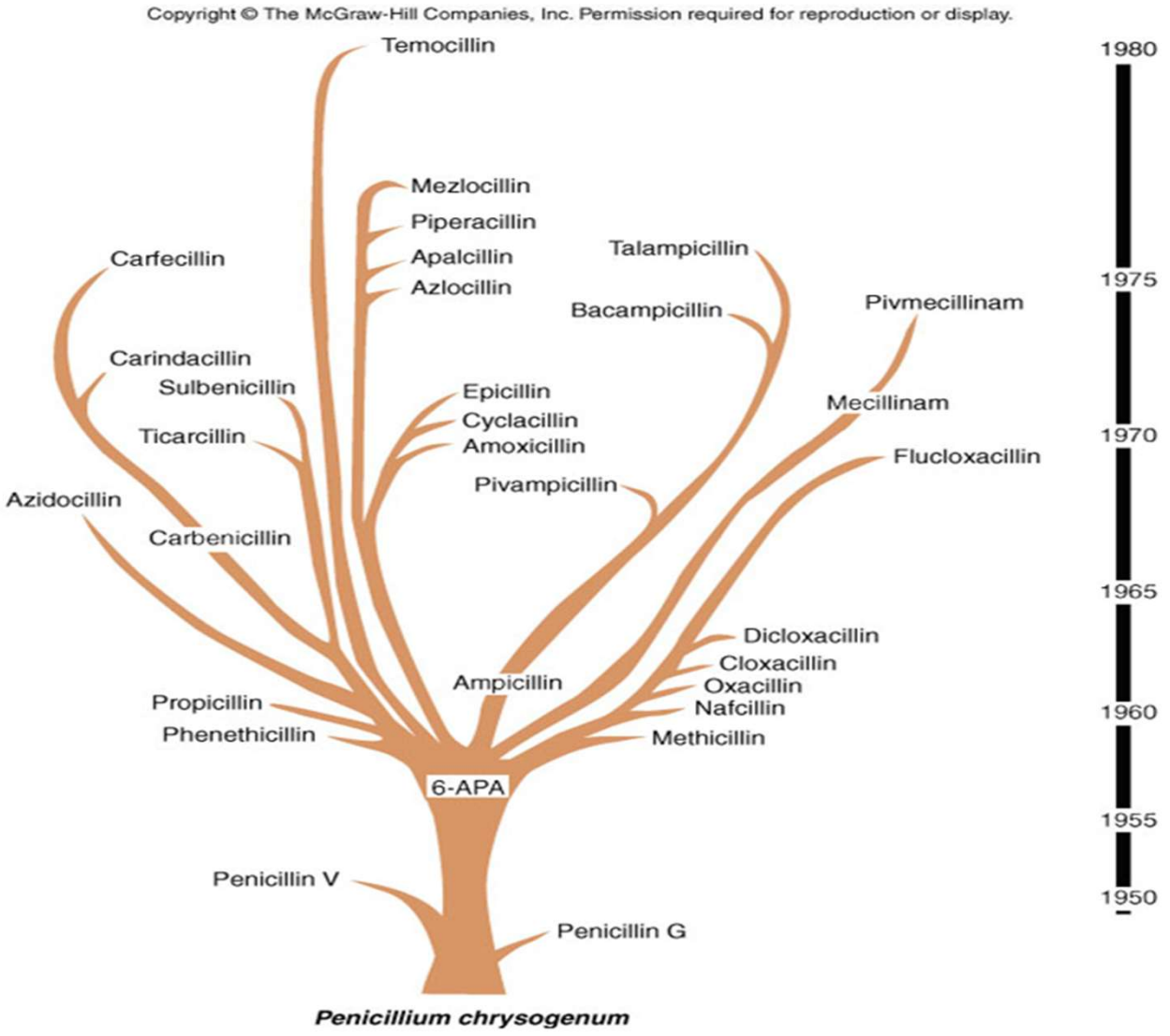
- Obtained from
  - ✓ *Penicillium notatum* (Early)
  - ✓ *Penicillium chrysogenum* (Now, Better Yield)

- Scientists- Fleming – Chain – Florey

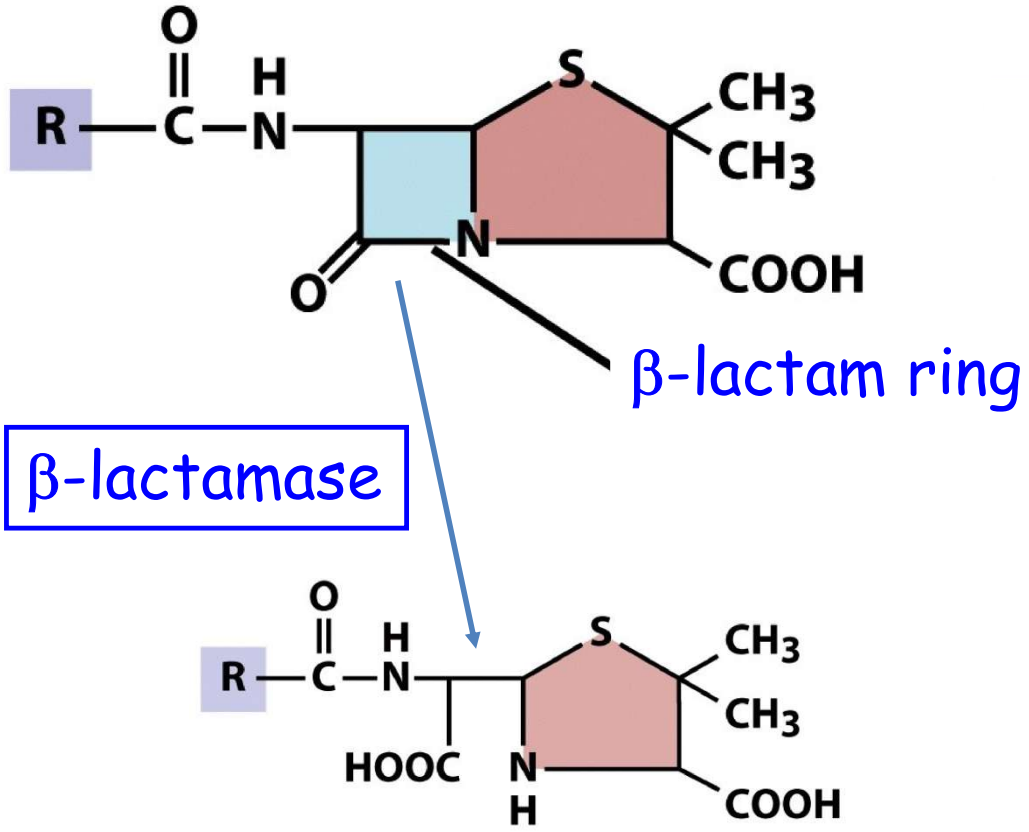
- **Original Penicillins – Penicillin G, Benzyl Penicillin**

Penicillin Structure	R Group	Drug Name
		penicillin G
		penicillin V
		ampicillin
		amoxicillin
		methicillin

History and Classification of Penicillins



Penicillin Resistance



Narrow – spectrum Penicillins – Clinical Uses

Benzylpenicillin (Penicillin G) is the prototype of a subclass of penicillins.

Clinical uses include therapy of infections caused

by common streptococci, meningococci, gram-positive bacilli, and spirochetes.

Many strains of pneumococci (penicillin-resistant *S. pneumoniae* [PRSP] strains). *Staphylococcus aureus* and *Neisseria gonorrhoeae* are resistant via production of beta-lactamases

Penicillin G remains the drug of choice for syphilis. Activity against enterococci is enhanced by coadministration of aminoglycosides. Penicillin V is an oral drug used mainly in oropharyngeal infections...

Very-narrow-spectrum penicillinase-resistant drugs

This subclass of penicillins includes methicillin, nafcillin, and oxacillin….

They are stable to staphylococcal beta lactamase, penicillinase

Their primary use is in the treatment of known or suspected different types staphylococcal infections.

Methicillin-resistant (MR) staphylococci (*S. aureus* [MRSA] and *S. epidermidis* [MRSE]) are resistant to all penicillins and are often resistant to multiple antimicrobial drugs).

Wider-spectrum penicillinase-susceptible drugs

Ampicillin and amoxicillin—has a wider spectrum of antibacterial activity than penicillin G.

Their clinical uses include indications similar to penicillin G as well as infections resulting from *enterococci, Listeria monocytogenes,*

***Escherichia coli, Proteus mirabilis, Haemophilus influenzae, and Moraxella catarrhalis*, although resistant strains occur.**

When used in combination with inhibitors of penicillinases (clavulanic acid, sulbactam, tazobactam), their antibacterial activity is often enhanced. In enterococcal and listerial infections, ampicillin is synergistic with aminoglycosides.

Ureidopenicillin – broad spectrum of activity

Piperacillin

These drugs have broad spectrum activity against several gram-negative rods, including *Pseudomonas, Enterobacter,* and in some cases *Klebsiella species*, also streptococci, enterococci, anaerobes

Piperacillin is susceptible

to penicillinases and are often used in combination with penicillinase inhibitors (eg, tazobactam and clavulanic acid) to enhance their activity.

It is used for the treatment of serious nosocomial infections (pneumonia, sepsis, complicated urinary tract infections, wound infections, abdominal infections) ...)

Penicillins – toxicity, side effects

1. Allergy—Allergic reactions include urticaria, severe pruritus, fever, joint swelling, hemolytic anemia, nephritis, and anaphylaxis.

Complete cross-allergenicity between different penicillins should be assumed.

2. Gastrointestinal disturbances— Nausea and diarrhea may occur with oral penicillins, especially with ampicillin.

Gastrointestinal upsets may be caused by direct irritation or by overgrowth of gram-positive organisms or yeasts.

Cephalosporins

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins.

Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to *7-aminocephalosporanic acid*.

Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms.

However, they tend to be more resistant/stable than the penicillins to certain β-lactamases.

Mechanisms of Action and Resistance

Cephalosporins bind to PBPs on bacterial cell membranes to inhibit bacterial cell wall synthesis by mechanisms similar to those of the penicillins. Cephalosporins are bactericidal against susceptible organisms.

Cephalosporins less susceptible to penicillinases produced by staphylococci, but many bacteria are resistant through the production of other betalactamases that can inactivate cephalosporins.

Resistance can also result from decreases in membrane permeability to cephalosporins and from changes in PBPs.

Methicillin-resistant staphylococci (MRSA) are also resistant to cephalosporins.

Classification of cephalosporins

- **Spectrum of antimicrobial activity**
- **Stability to the effect of beta lactamases**
- **The higher the generation (1-4) - the wider the spectrum of activity and the higher the stability**

First generation

First-generation drugs—cefazolin (parenteral) and cephalexin (oral) are examples of this subgroup.

They are active against gram-positive cocci, including staphylococci and common streptococci. Many strains of *E. coli* and *K. pneumoniae* are also sensitive.

Clinical uses include treatment of infections caused by these organisms and surgical prophylaxis in selected conditions.

Second generation

Cefuroxim, cefprozil

Have slightly less activity against gram-positive organisms than the first-generation drugs but have an extended gram-negative coverage.

Examples of clinical uses include infections sinus,

ear, and respiratory infections caused by *H. influenzae* or *M. catarrhalis*

Urinary tract infections caused by *E. coli, Proteus spp...*

.. surgical prophylaxis in selected conditions

Third-generation

Ceftazidime, cefotaxime, ceftraixone

include increased activity against gram-negative organisms resistant to other beta-lactam drugs and ability to penetrate the blood-brain barrier. Most are active against *Providencia, Serratia marcescens*, and beta-lactamase producing strains of

H. influenzae* and *Neisseria

Ceftriaxone and cefotaxime are currently the most active cephalosporins against penicillin-resistant pneumococci (PRSP strains)

- **Also have activity against *Pseudomonas* (cefoperazone, ceftazidime)**
- **Ceftriaxone (parenteral) and cefixime (oral), currently drugs of choice in gonorrhea.**

Fourth-generation

Cefepime is more *resistant to beta-lactamases* produced by gram-negative organisms, including *Enterobacter, Haemophilus, Neisseria*, and some *penicillin resistant pneumococci*…

Cefepime combines the gram-positive activity of first-generation agents with the wider gram-negative spectrum of third-generation cephalosporins.

Fifth generation ?

Ceftaroline has activity in infections caused by methicillin-resistant staphylococci

The only registered beta lactam antibiotic with an effect on MRSA

The spectrum of action corresponds to the 3rd generation (Gramnegative b. but not *P.aeruginosa*)

Side effects, toxicity

Allergy—Cephalosporins cause a range of allergic reactions from skin rashes to anaphylactic shock. These reactions occur *less frequently with cephalosporins than with penicillins*.

Complete cross-hypersensitivity between different cephalosporins should be assumed. Cross-reactivity between penicillins and cephalosporins is incomplete (5–10%).

They may increase the nephrotoxicity of aminoglycosides when the two are administered together.

Carbapenems - Imipenem, Meropenem and Ertapenem

- **Chemically different from penicillins but retaining the beta-lactam ring structure**
- **Reserve antibiotics - Now used to treat gram negative infections due to so called ESBL producing organisms e.g,**
- ***E. coli, Klebsiella***
- **They are administered intravenously**
- **They have wide activity against gram-positive cocci (including some penicillin-resistant pneumococci), gram-negative rods, and anaerobes.**
- **For pseudomonal infections, they are often used in combination with an aminoglycoside.**

Beta-Lactamase Inhibitors

Clavulanic acid, sulbactam, and tazobactam are used in fixed combinations with certain hydrolyzable penicillins.

- amoxicilin/clavulanic acid, ampicilin/sulbactam, piperacilin/tazobactam

They are most active against plasmid-encoded beta lactamases such as those produced by *gonococci, staphylococci, E coli*, and *H influenzae…*

- **They are not good inhibitors of inducible chromosomal beta-lactamases (AmpC..) formed by *Enterobacter, Pseudomonas, and Serratia*.**

Beta-Lactamase Inhibitors

β-lactamase inhibitors with a diazabicyclooctane core:

Avibactam, approved in combination with ceftazidime (Avycaz, Zavicefta), currently undergoing clinical trials for combination with ceftaroline

Durlobactam, approved in combination with sulbactam (Xacduro) to treat hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) pneumonia caused by Acinetobacter baumannii-calcoaceticus complex

Relebactam, used in combination with imipenem/cilastatin (Recarbrio).

β-lactamase inhibitors with other types of non β-lactam cores:

Vaborbactam, used in combination with meropenem (Vabomere). Has a boronic acid core.

BETA LACTAMS - MECHANISM OF RESISTANCE

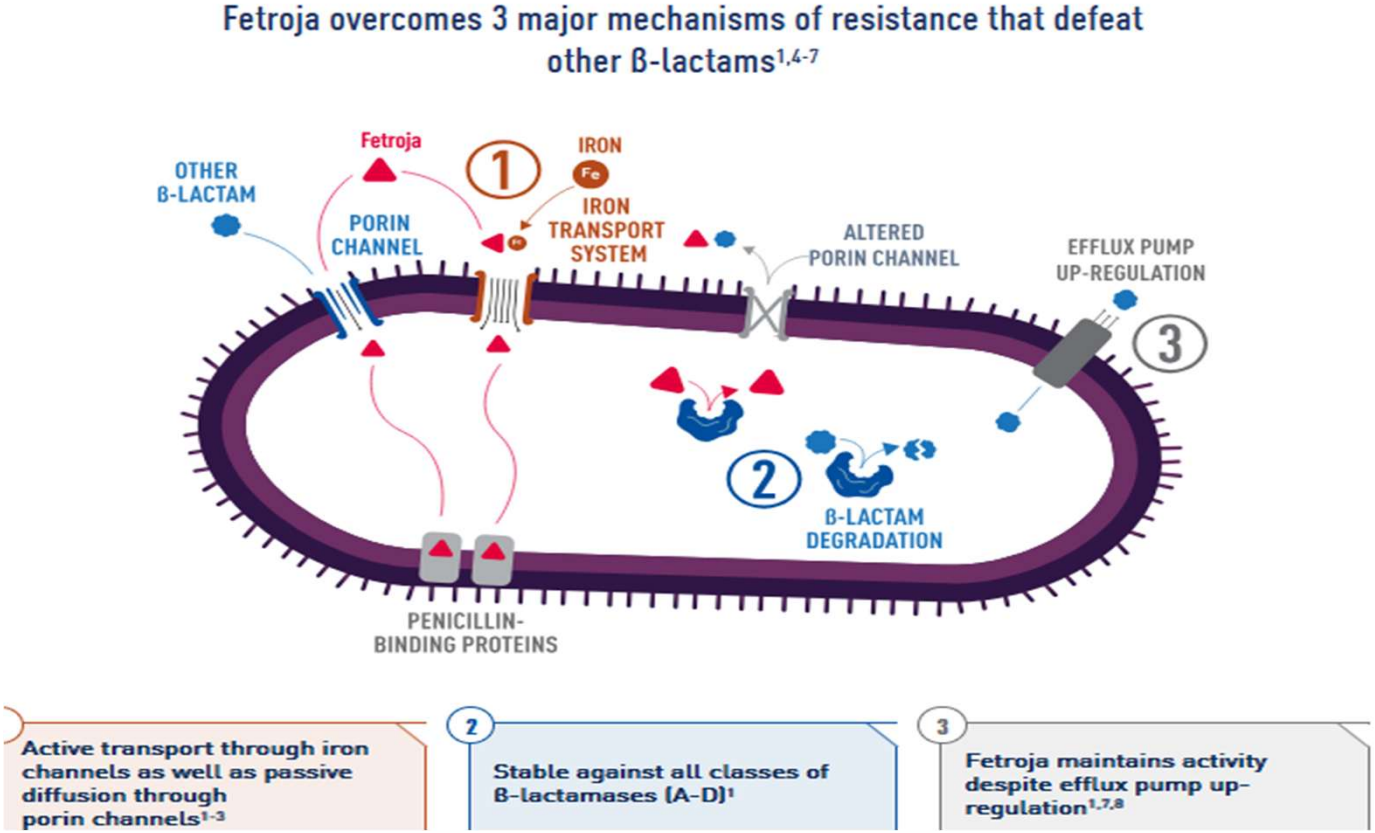
- **The formation of beta-lactamases**

  by most staphylococci and many gram-negative organisms.

- ✓ **Inhibitors of these bacterial enzymes (e.g., clavulanic acid, sulbactam, tazobactam) are often used in combination with penicillins to prevent their inactivation.**
- **Structural change in target PBPs is responsible for methicillin resistance in staphylococci and for resistance to penicillin G in pneumococci (eg, PRSP, penicillin resistant *Streptococcus pneumoniae*) and enterococci.**
- **In some gram-negative rods (eg, *Pseudomonas aeruginosa*), changes in the porin structures in the outer cell wall membrane may contribute to resistance by impeding access of penicillins to PBPs.**

Cefiderocol

- Cefiderocol is a first-in-class siderophore cephalosporin antibiotic that acts as a "Trojan horse" to combat multidrug-resistant (MDR) Gram-negative bacteria. It binds to extracellular iron, exploiting bacterial iron-transport systems to actively enter the periplasmic space, where it binds to penicillin-binding proteins (PBPs)—primarily PBP3—inhibiting cell wall synthesis.



Monobactams - Aztreonam

Aztreonam is a synthetic, bactericidal monobactam antibiotic used primarily to treat severe aerobic Gram-negative bacterial infections, including *Pseudomonas aeruginosa*. It works by inhibiting bacterial cell wall synthesis and is uniquely resistant to many beta-lactamases, making it a crucial option for patients allergic to penicillin.