Pharmacology - 2

DR. YOUSEF ABUSAMRA. PH.D.

Assistant professor of pharmacology and pharmacognosy

Faculty of Pharmacy

Philadelphia University – Amman - Jordan

yabusamra@philadelphia.edu.com

Beta-Lactam & Other Cell Wall- & Membrane-Active Antibiotics

Pharmacology-2/ Beta-lactam and other cell-wall active antibiotics/
Dr. Y. Abusamra
Faculty of Pharmacy
Philadelphia University

LEARNING OUTCOMES

After competing studying this chapter, the student should be able to:

- Classify the drugs into subgroups such as penicillins, cephalosporins, carbapenems, and categorize cephalosporins into the 5-categories currently recognized.
- Recognize the bacterial spectrum of all these antibiotic subgroups.
- Summarize the most remarkable pharmacokinetic features of these drugs.
- Numerate the most important side effects associated with these agents.
- Select the antibiotic of choice to be used in certain infections, as associated with the patient status including comorbidity, the species of bacteria causing the infection and concurrently prescribed drugs.

Beta-lactam and other cell-wall inhibitors

- Some antimicrobial drugs selectively interfere with synthesis of the bacterial **cell wall**, a structure that mammalian cells do not possess.
- The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links. {See the figure}
- To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms.

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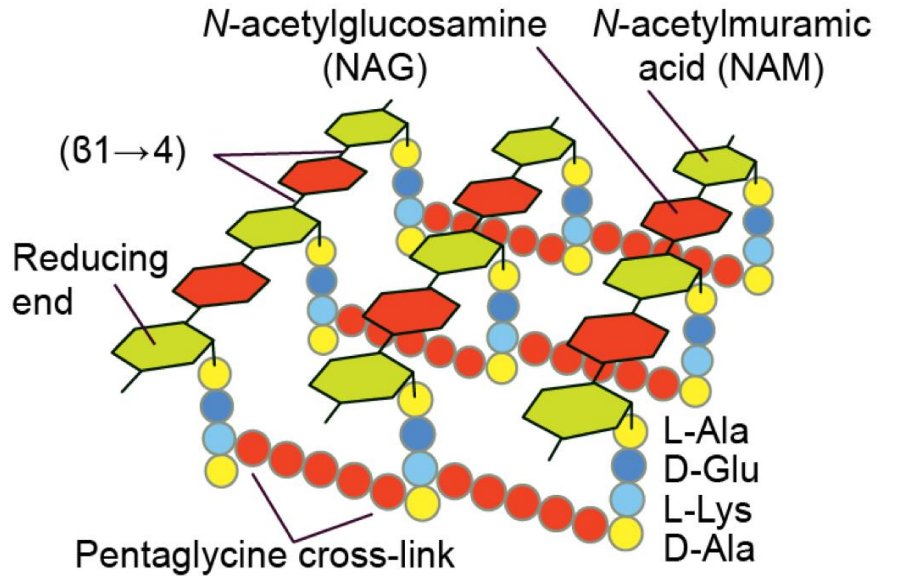
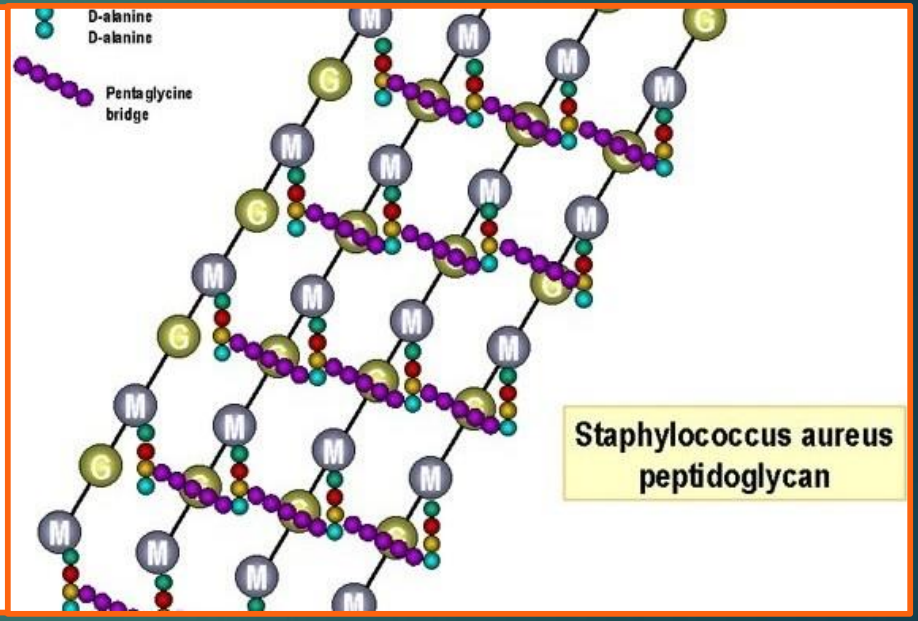
PENICILLINS:

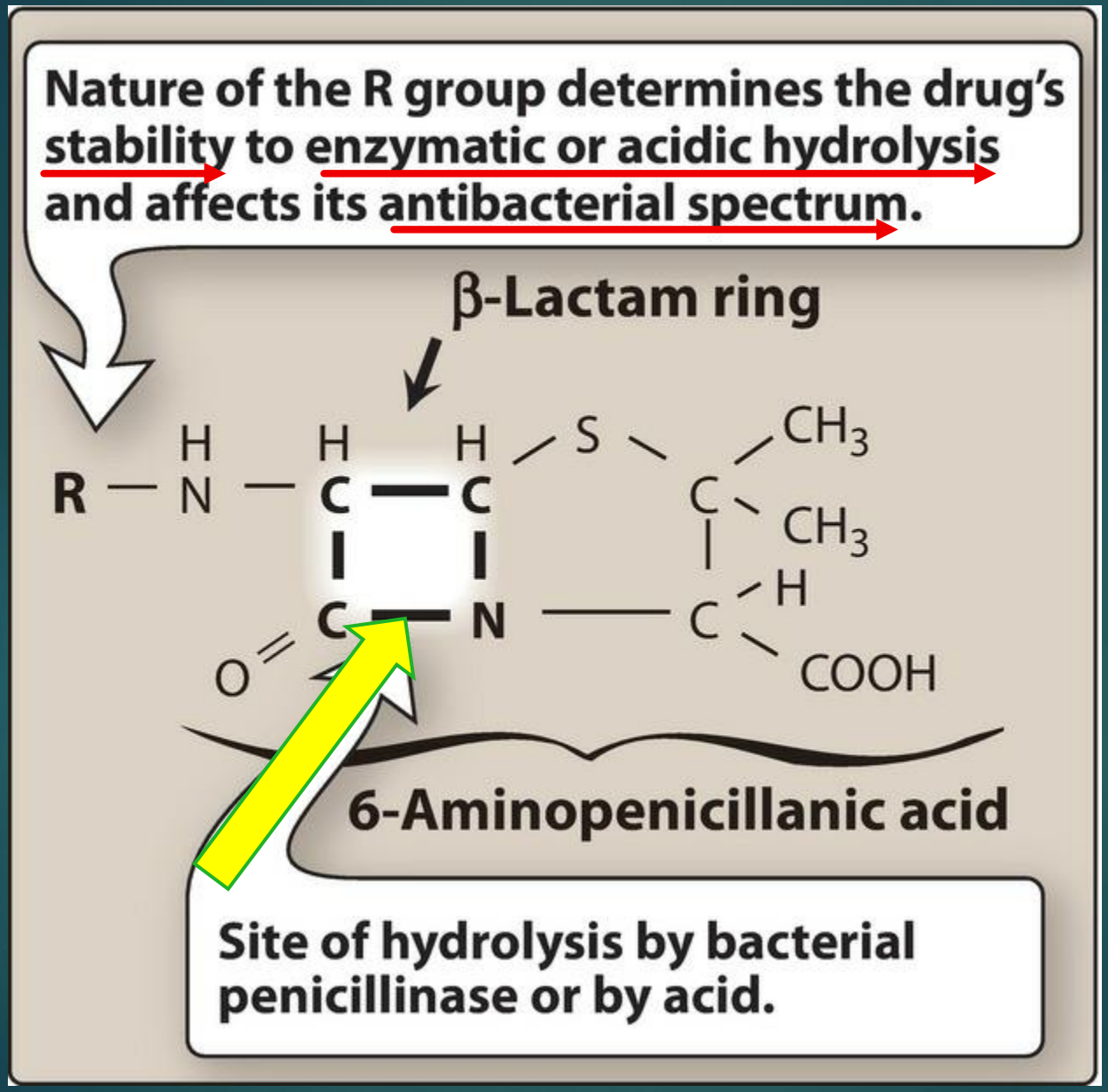
- The basic structure of penicillins consists of a core four-membered β-lactam ring, which is attached to a thiazolidine ring and an R side chain.
- Members of this family differ from one another in the R substituent attached to the 6- aminopenicillanic acid residue.

Bacterial cell wall
peptidoglycans



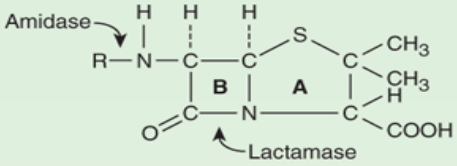


Beta-lactam and other cell-wall inhibitors

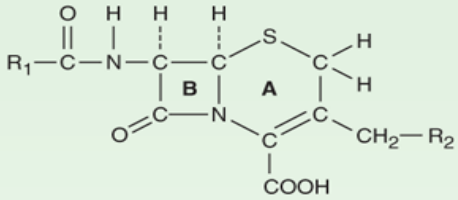


Core structures of four β-lactam antibiotic families.

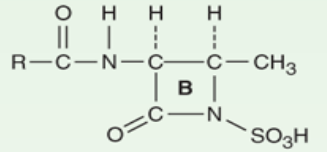
- The ring marked B in each structure is the **β-lactam** ring.
- The penicillins are susceptible to inactivation by **amidases** and **lactamases** at the points shown.
- The carbapenems have a **different stereochemical** configuration in the lactam ring that imparts **resistance to most common β-lactamases.**



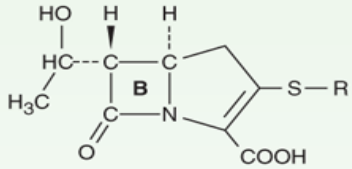
Substituted 6-aminopenicillanic acid

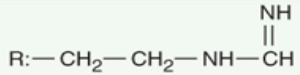


Substituted 7-aminocephalosporanic acid



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





Substituted 3-hydroxyethylcarbapenemic acid (imipenem)

Mechanism of action of penicillins:

1. Penicillin-binding proteins:

- Penicillins inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium.

2. Inhibition of transpeptidase:

- Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of **CROSS-LINKS** essential for cell wall integrity.

3. Production of autolysins:

- Many bacteria, particularly the gram-positive cocci, produce degradative enzymes (autolysins) that *participate in the normal remodeling of the bacterial cell wall.*

ANTIBACTERIAL SPECTRUM:

- The antibacterial spectrum of the various penicillins is determined by their ability to cross the bacterial peptidoglycan cell wall to **reach the PBPs** in the periplasmic space.
- Factors determining PBP susceptibility to these antibiotics include **size**, **charge**, and **hydrophobicity** of the particular β-lactam antibiotic.
- 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.

1. NATURAL PENICILLINS:

- Penicillin G and penicillin V are obtained from fermentations of the fungus *Penicillium chrysogenum*.
- These have greatest activity against Gram-positive organisms, Gram-negative cocci, and non-β-lactamase-producing anaerobes.
- They have little activity against **GRAM-NEGATIVE RODS**, and they are susceptible to hydrolysis by β-lactamases.
- The potency of penicillin G is five to ten times greater than that of penicillin V against both *Neisseria* spp. and certain anaerobes.
- Most *streptococci* are very sensitive to penicillin G, except *Streptococcus pneumoniae* and about 90% of *Staphylococcus aureus* are resistant.
- Penicillin remains the **DRUG OF CHOICE** for the treatment of **gas gangrene** (*Clostridium perfringens*) and **syphilis** (*Treponema pallidum*).

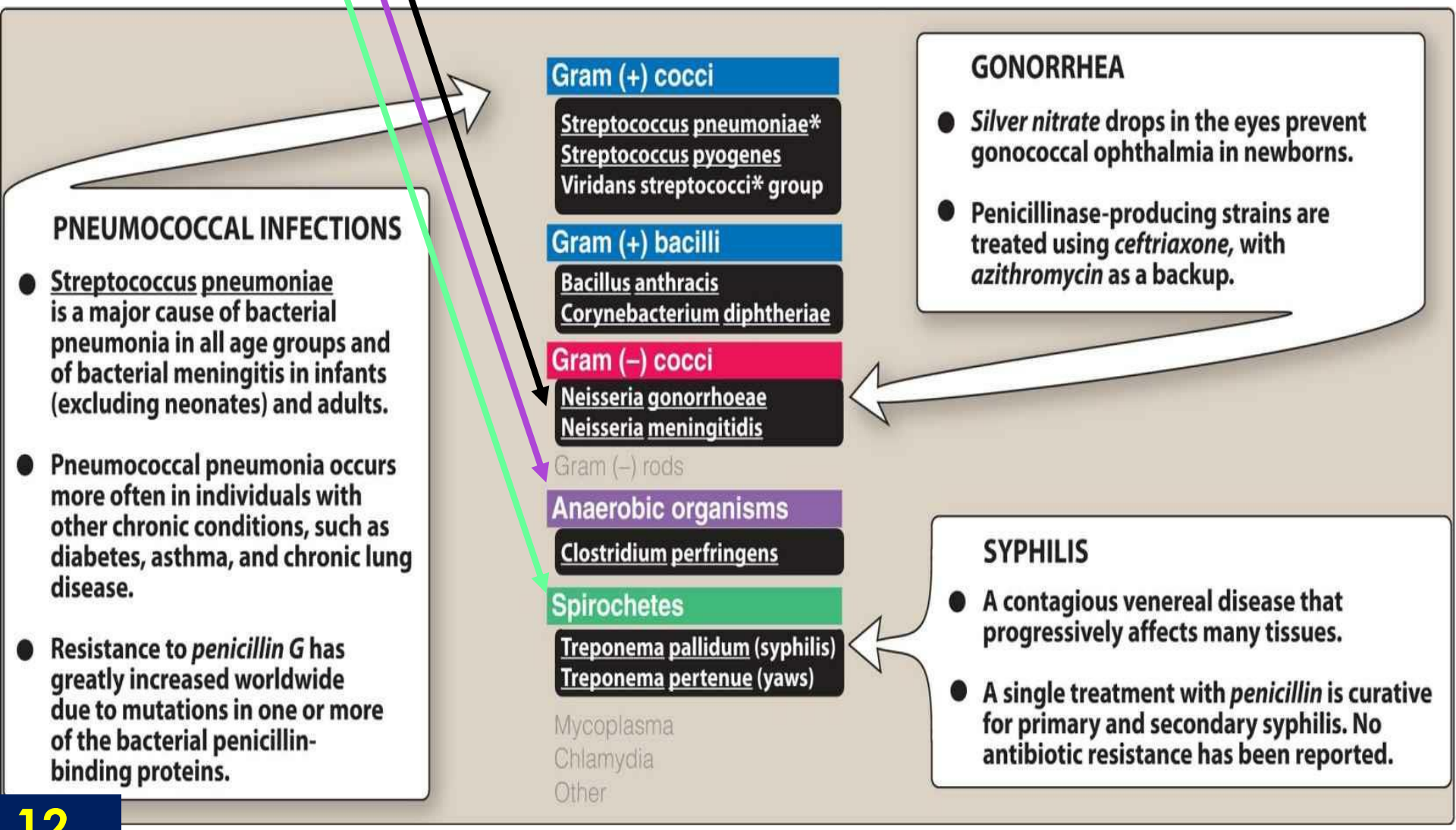
- Penicillin V is only available in **oral** formulation.
- It has a spectrum similar to that of penicillin G, but it is not used for treatment of severe infections because of its limited oral absorption.
- Penicillin V is **more acid stable** than is penicillin G.
- It is the oral agent employed in the treatment of less severe infections.

Bacterial strains typically treated by Penicillin G are:

- *Streptococcus pneumoniae* – a major cause of bacterial pneumonia in all age groups, and bacterial *meningitis* in infants, resistance is emerging by some strains.
- *Bacillus anthracis* – *Corynebacterium diphtheria* – both G (+) rods.

Beta-lactam and other cell-wall inhibitors

- And (see the figure below).



2. SEMISYNTHETIC PENICILLINS:

- **Ampicillin** and **amoxicillin** (also known as **aminopenicillins** or **extended-spectrum** penicillins) are created by chemically attaching different R groups to the 6-aminopenicillanic acid nucleus.
- Addition of R groups extends the **gram-negative antimicrobial activity** of aminopenicillins to include *Haemophilus influenzae*, *Escherichia coli*, and *Proteus mirabilis.*
- These extended-spectrum agents are also widely used in the treatment of **respiratory infections**.
- **Amoxicillin** is employed prophylactically by dentists in high-risk patients for the prevention of bacterial **endocarditis**.
- These drugs are coformulated with β-lactamase inhibitors, such as **clavulanic acid** or **sulbactam**, to combat infections caused by β-lactamase–producing organisms.

- For example, without the β-lactamase inhibitor, **methicillin**-sensitive *Staphylococcus aureus* (MSSA) is resistant to ampicillin and amoxicillin.
- Resistance in the form of plasmid-mediated penicillinases is a major clinical problem, which limits use of aminopenicillins with some gram-negative organisms.
- **Plasmid**: a genetic structure in a cell that can replicate independently of the chromosomes.

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3. ANTISTAPHYLOCOCCAL PENICILLINS:

- **Methicillin**, **nafcillin**, **oxacillin**, and **dicloxacillin** are β-lactamase (penicillinase)-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including MSSA.
- **Methicillin** is not used clinically; used in lab test to identify resistant strains [**NEPHRITIS**].

- Methicillin-resistant *Staphylococcus aureus* (**MRSA**) is currently a source of serious community and nosocomial (hospital-acquired) infections and **IS RESISTANT TO MOST COMMERCIALLY AVAILABLE β-LACTAM ANTIBIOTICS**.
- The penicillinase-resistant penicillins have minimal to no activity against gram-negative infections.

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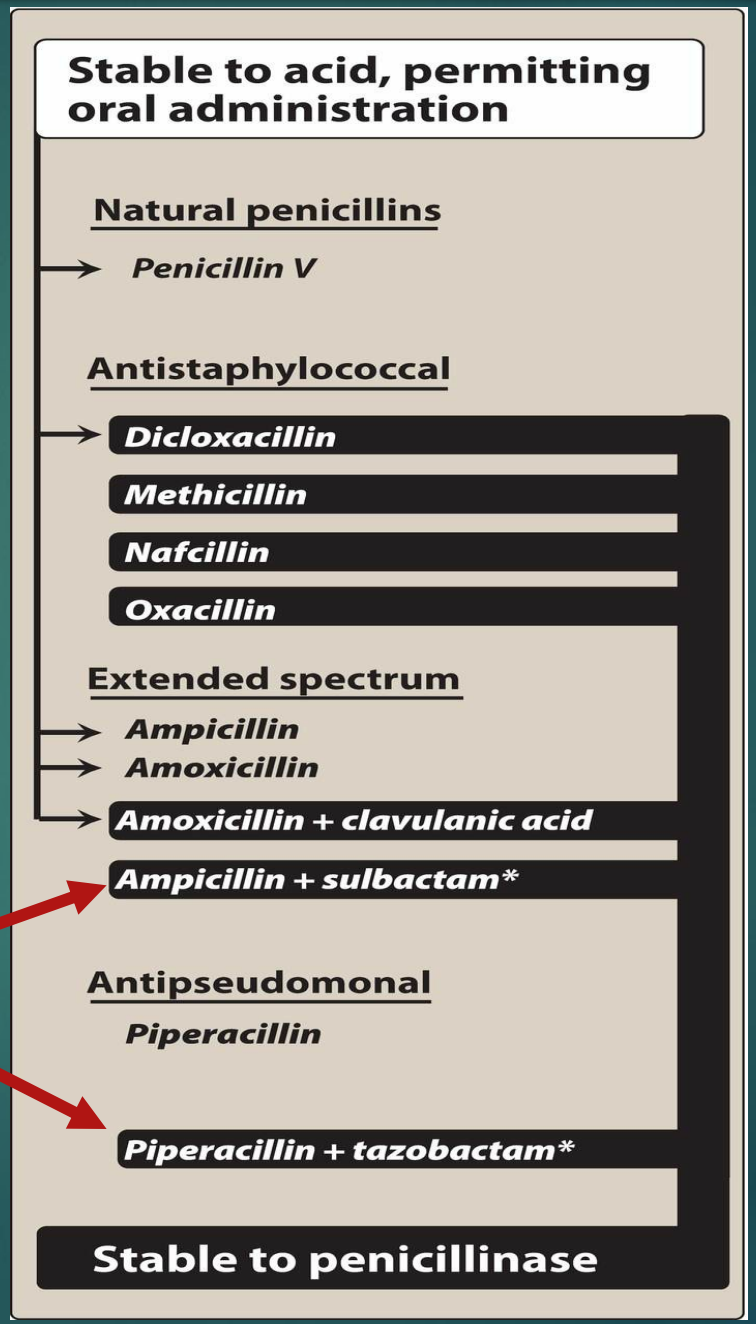
4. ANTIPSEUDOMONAL PENICILLIN:

- **Piperacillin** is also referred to as an antipseudomonal penicillin because of its activity against *Pseudomonas aeruginosa*.
- Formulation of piperacillin with tazobactam extends the antimicrobial spectrum to include penicillinase-producing organisms (for example, most Enterobacteriaceae and Bacteroids spp).

SUMMARY:

- Stability of the penicillins to acid or the action of penicillinase.
- *: Available only as parenteral preparation.



RESISTANCE:

- Resistance to penicillins and other β-lactams is due to one of four general mechanisms:

1. Inactivation of antibiotic by **β-lactamase**.
2. Modification of target **PBPs**.
3. Impaired penetration of drug to target **PBPs**.
4. Antibiotic efflux.

- Beta-lactamase production is the most common mechanism of resistance.
- Hundreds of different β-lactamases have been identified.
- Some, such as those produced by *Staphylococcus aureus*, *Haemophilus influenzae*, and *Escherichia coli*, are relatively **NARROW** in substrate specificity, preferring penicillins to cephalosporins.

- Other β-lactamases, eg, those produced by *Pseudomonas aeruginosa*, *Enterobacter* sp and *Enterobacteriaceae*, hydrolyze both cephalosporins and penicillins.
- Carbapenems are highly **resistant** to hydrolysis by penicillinases and cephalosporinases, but they are **hydrolyzed** by metallo-β-lactamases and carbapenemases.
- Bacteria resistant to **methicillin**, such as *Staphylococci* and *Enterococci* produce PBPs that have low affinity for binding β-lactam antibiotics, and they are not inhibited except at relatively high, often clinically unachievable, drug concentrations.
- Resistance due to impaired penetration of antibiotic occurs only in **GRAM-NEGATIVE** species because of the impermeable outer membrane of their cell wall, which is absent in Gram-positive bacteria

Beta-lactam and other cell-wall inhibitors

- Beta-lactam antibiotics cross the outer membrane and enter Gram-negative organisms via outer membrane protein channels called **porins**.
- Absence of the proper channel or down-regulation of its production can greatly impair drug entry into the cell.
- Poor penetration alone is usually not sufficient to confer resistance because enough antibiotic eventually enters the cell to inhibit growth.
- However, this **barrier** can become important in the presence of a **β-lactamase**, even a relatively inefficient one, as long as it can hydrolyze drug faster than it enters the cell.
- Gram-negative organisms also may produce an efflux pump, which consists of cytoplasmic and periplasmic protein components that efficiently transport some β-lactam antibiotics from the periplasm back across the cell wall outer membrane.

Metabolism:

- Host metabolism [in the liver] of the β-lactam antibiotics is usually **insignificant**.
- Some metabolism of **penicillin G** may occur in patients with impaired renal function.
- **Nafcillin** and **oxacillin** are exceptions to the rule and are primarily metabolized in the **liver**.

Excretion:

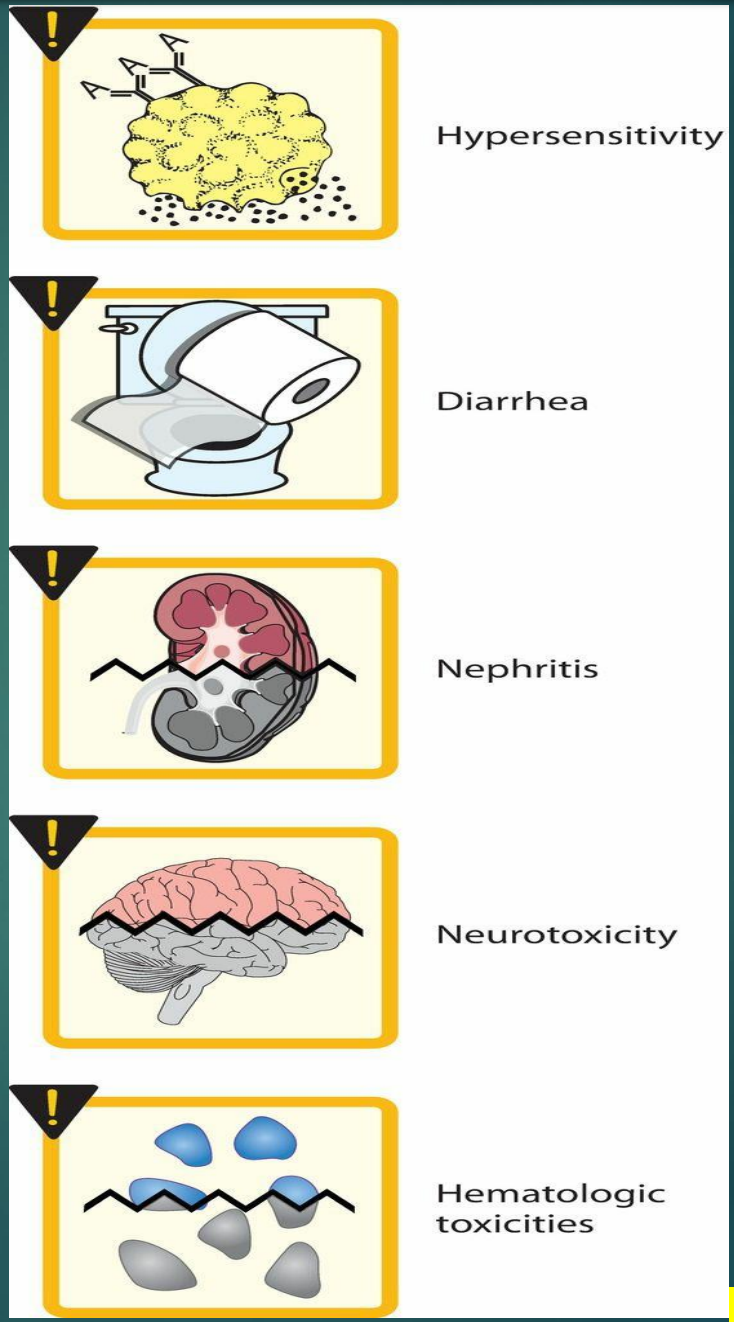
- The primary route of excretion is through {1} **tubular secretion** in the kidney as well as by {2} **glomerular filtration**.
- Patients with impaired renal function **must** have dosage regimens adjusted.

- Because **nafcillin** {beta-lactamase-resistant} and **oxacillin** are primarily metabolized in the liver, they do not require dose adjustment for renal insufficiency.
- **Probenecid INHIBITS** the secretion of penicillins by competing for active tubular secretion, thus, can increase blood levels.
- The penicillins are also excreted in breast milk.

Adverse reactions:

- Penicillins are among the **safest** drugs.
- However, adverse reactions may occur.

Summary of the adverse effects of penicillins:



1. Hypersensitivity:

- Approximately **10%** of patients self-report allergy to penicillin.
- Reactions range from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis.
- **Cross-allergic** reactions occur among the **β-lactam antibiotics**.
- It is essential to determine whether the patient has a history of allergy or not.

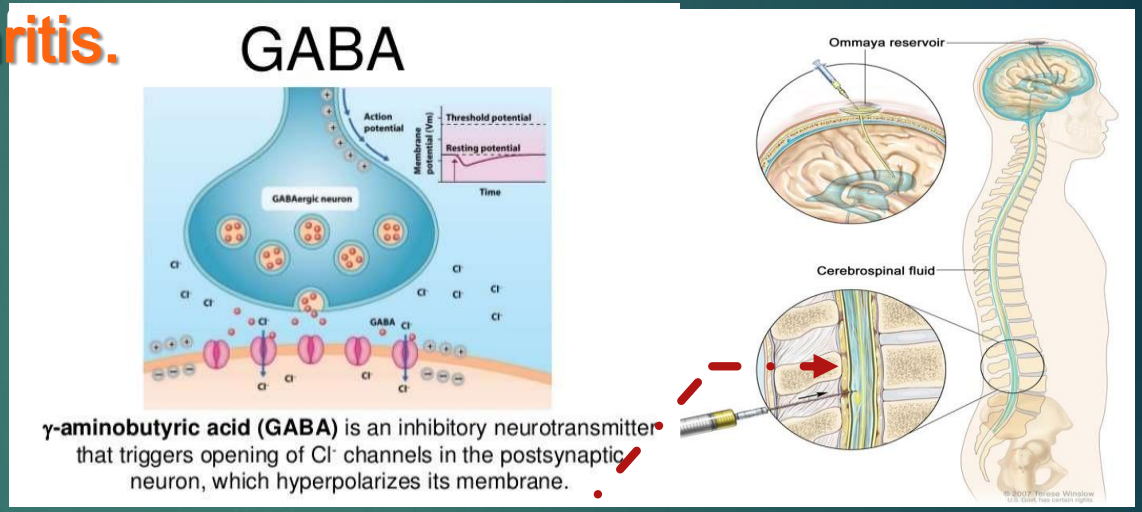
2. Diarrhea:

- Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms.
- It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum.

- **Pseudomembranous colitis** from *Clostridium difficile* and other organisms may occur with penicillin use.

3. Nephritis: {inflammation-related}

- Penicillins, particularly **methicillin**, have the potential to cause acute interstitial **nephritis.**
- **Methicillin** is therefore no longer used clinically.



γ-aminobutyric acid (GABA) is an inhibitory neurotransmitter that triggers opening of Cl^- channels in the postsynaptic neuron, which hyperpolarizes its membrane.

4. Neurotoxicity:

- The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached.
- **Epileptic** patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

5. Hematologic toxicities:

- Decreased coagulation may be observed with high doses of **piperacillin** and **nafcillin** (and, to some extent, with **penicillin G**).

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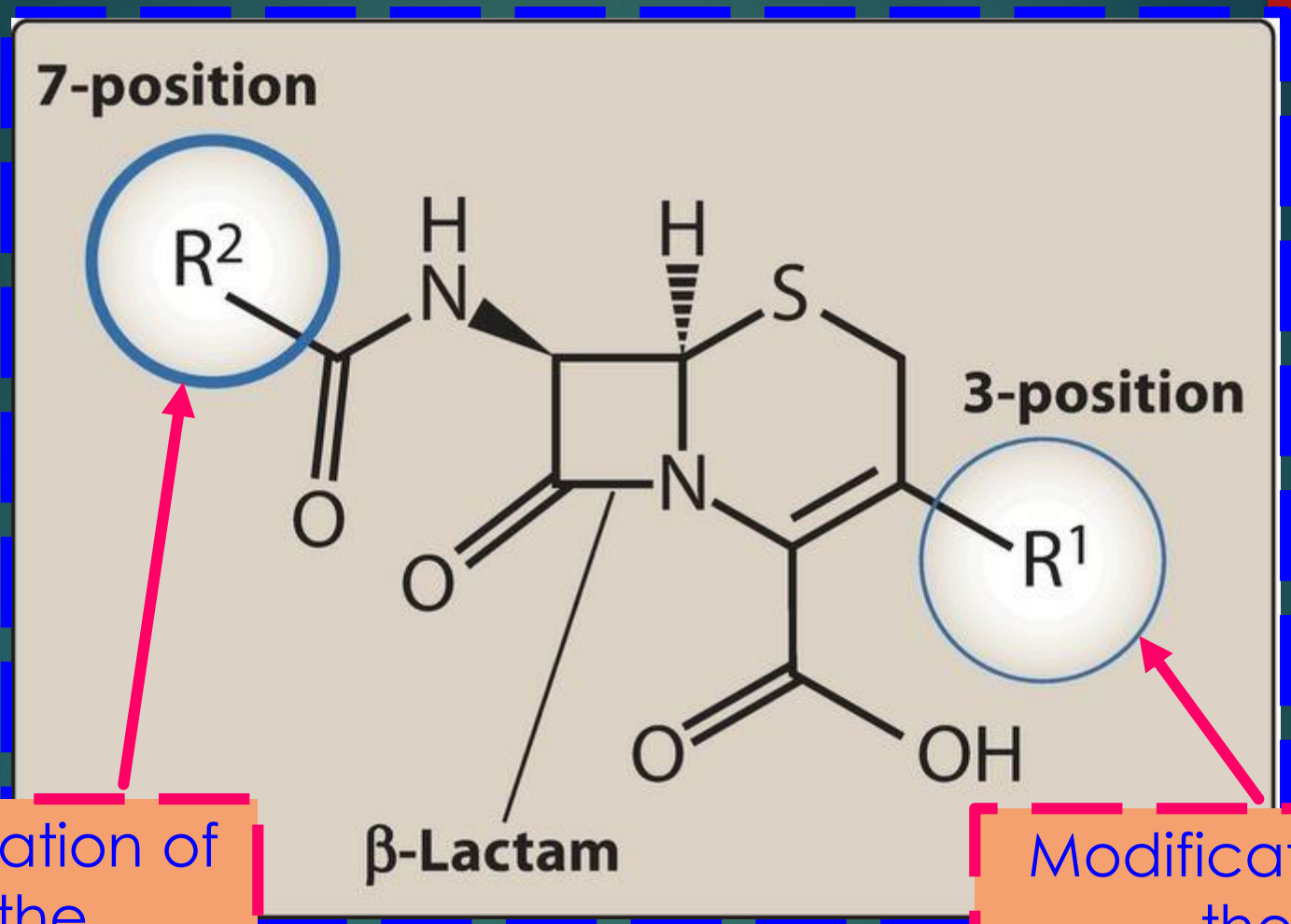
CEPHALOSPORINS:

- The cephalosporins are β-lactam antibiotics closely related both structurally and functionally to penicillins.
- Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid.
- Structural changes on the acyl side chain at the 7-position alter antibacterial activity and variations at the 3-position modify the pharmacokinetic profile.

Beta-lactam and other cell-wall inhibitors



Alteration of the **antibacterial** activity

Modification of the **pharmacokinetic** profile

- Cephalosporins have the **same mode of action** as penicillins.
- They are affected by the **same resistance mechanisms**.
- However, they tend to **BE MORE RESISTANT** than the penicillins to certain β-lactamases.

L. monocytogenes

ANTIBACTERIAL SPECTRUM:

- Cephalosporins have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial **susceptibility** patterns and **resistance** to β-lactamases.
- Commercially available cephalosporins are **ineffective** against *L. monocytogenes, C. difficile*, and the *enterococci*.
- **Note:** *L. monocytogenes* grow at T below 0 C°; invasion of foodstuffs – **AMPICILLIN IS THE DRUG OF CHOICE**.

Beta-lactam and other cell-wall inhibitors

Generally, increasing activity from G+ cocci towards G- cocci and rods, and increasing this activity in the G – zone.

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2

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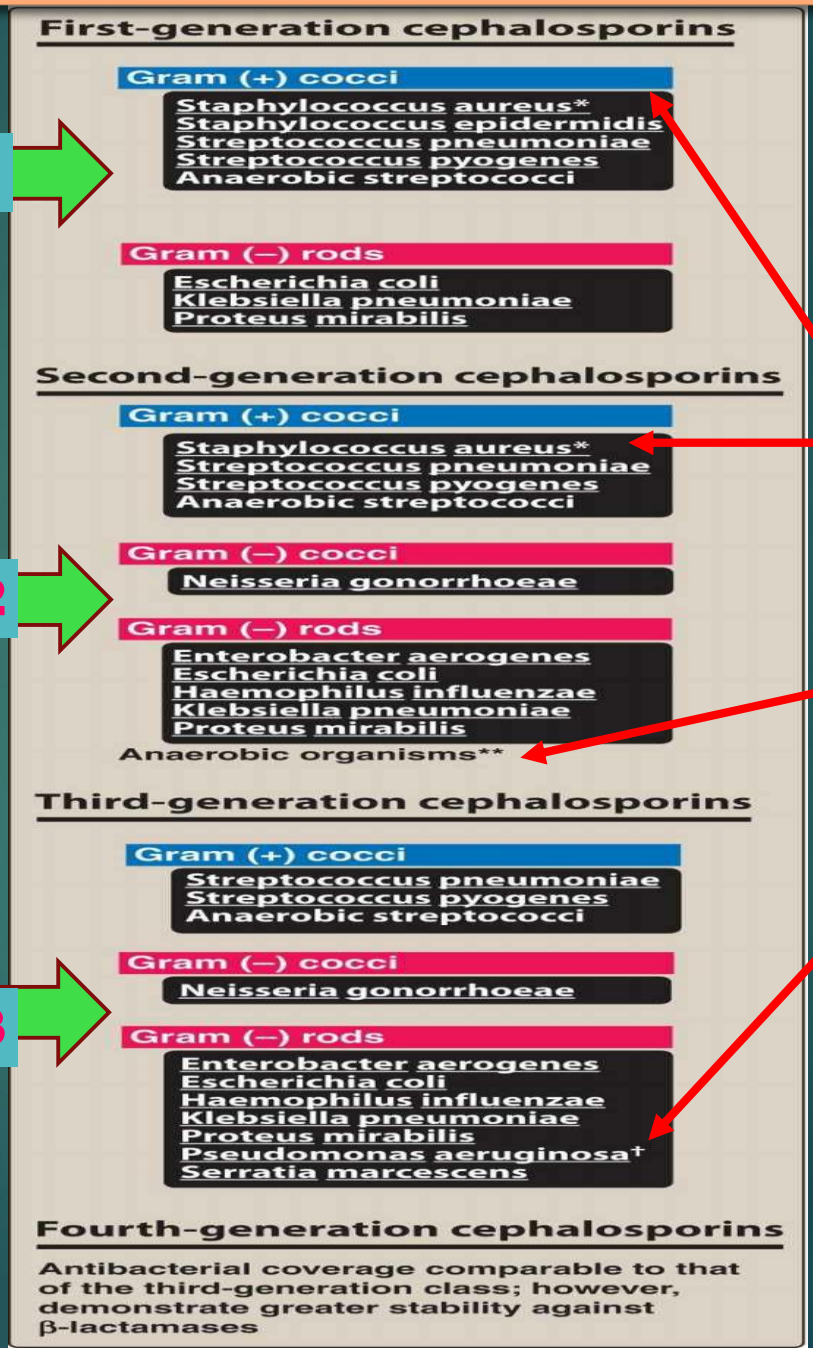


Summary of therapeutic applications of cephalosporins

- **Methicillin*-resistant staphylococci are resistant.
- ***Cefoxitin* and *cefotetan* have anaerobic coverage.
- †*Ceftazidime* only

Cephalosporin antibiotics

1st Generation	2nd Generation	3rd Generation	4th Generation
• Cefadroxil • Cefazedone • Cefazolin • Cephalexin • Cephalothin • Cephradine • Cephaloridine • Cephapirin etc.	• Cefaclor • Cefamandole • Cefoxitin • Cefuroxime • Ceforanid • Cefonicid etc.	• cefixime • Cefoperazone • cefotaxime • cefpiramide • cefpodoxime • Ceftibuten • ceftizoxime • ceftriaxone etc.	• Cefepime • cefluprenam • Cefozopran • cefpirome • cefquinome etc. **5th generation:** • Ceftopibrole • Ceftaroline • Ceftolozane
Good against **Gram +**, Moderate against **Gram -**	**Good** against **Gram -**, Moderate against **Gram +**	**Good** against **Gram -**, Weak against **Gram +**	**Good** against **Gram -**, Extended activity against **Gram +**

1. FIRST GENERATION:

- Act as **penicillin G** substitutes.
- They are resistant to the staphylococcal penicillinase (that is, they cover MSSA).
- Isolates of *S. pneumoniae* resistant to penicillin are also resistant to first-generation cephalosporins.
- Agents in this generation also have modest activity against *Proteus mirabilis*, *E. coli*, and *K. pneumoniae* [**all are G- rods**].

2. SECOND GENERATION:

- Display **greater** activity against **gram-negative** organisms, such as *H. influenzae*, *Klebsiella* species, *Proteus* species, *Escherichia coli*, and *Moraxella catarrhalis*.
- Where, activity against **gram-positive** organisms is **weaker**.

3. THIRD GENERATION:

- **These cephalosporins have assumed an important role in the treatment of infectious diseases.**
- Although they are **less potent** than **first**-generation cephalosporins against MSSA, the third-generation cephalosporins have **enhanced activity** against **gram-negative bacilli**, including β-lactamase producing strains of *H. influenzae* and *Neisseria gonorrhoeae*.
- **Ceftriaxone** and **cefotaxime** have become agents of **CHOICE IN THE TREATMENT OF MENINGITIS.**
- **Ceftriaxone** and **cefotaxime** are the **most active** cephalosporins against **PENICILLIN NON-SUSCEPTIBLE STRAINS OF PNEUMOCOCCI.**
- **Ceftriaxone** and **cefotaxime** are recommended for **empirical therapy** of serious infections that may be caused by these strains.

- **Ceftazidime** has activity against *P. aeruginosa*; however, resistance is increasing and use should be evaluated on a case-by-case basis.

4. FOURTH GENERATION:

- **Cefepime** is classified as a fourth-generation cephalosporin and must be administered parenterally.
- **Cefepime** has a **WIDE** antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are methicillin susceptible).
- **Cefepime** is also effective against aerobic gram-negative organisms, such as *Enterobacter* species, *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa.*

5. ADVANCED GENERATION: {including 5th generation}

- **Ceftaroline** is a broad-spectrum, advanced-generation cephalosporin.
- It is the only β-lactam in the United States with **activity against MRSA.**
- Generally, the members of this generation have equivalent activity to 3ED-generation agents, but they are:
  - Active against MRSA.
  - Inactive against *P. aurogenosa.*
- It is indicated for the treatment of
  - ✓ Complicated skin and skin structure infections [e.g. diabetic foot].
  - ✓ Community-acquired pneumonia.

- The unique structure allows **ceftaroline** to bind to PBPs found in MRSA and penicillin-resistant *Streptococcus pneumoniae*.
- In addition to its **{1}** broad gram-positive activity, it also has similar **{2}** gram-negative activity to the third-generation cephalosporin **ceftriaxone**.
- **{3}** Important gaps in coverage include *P. aeruginosa*, and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. (**NOT active**).

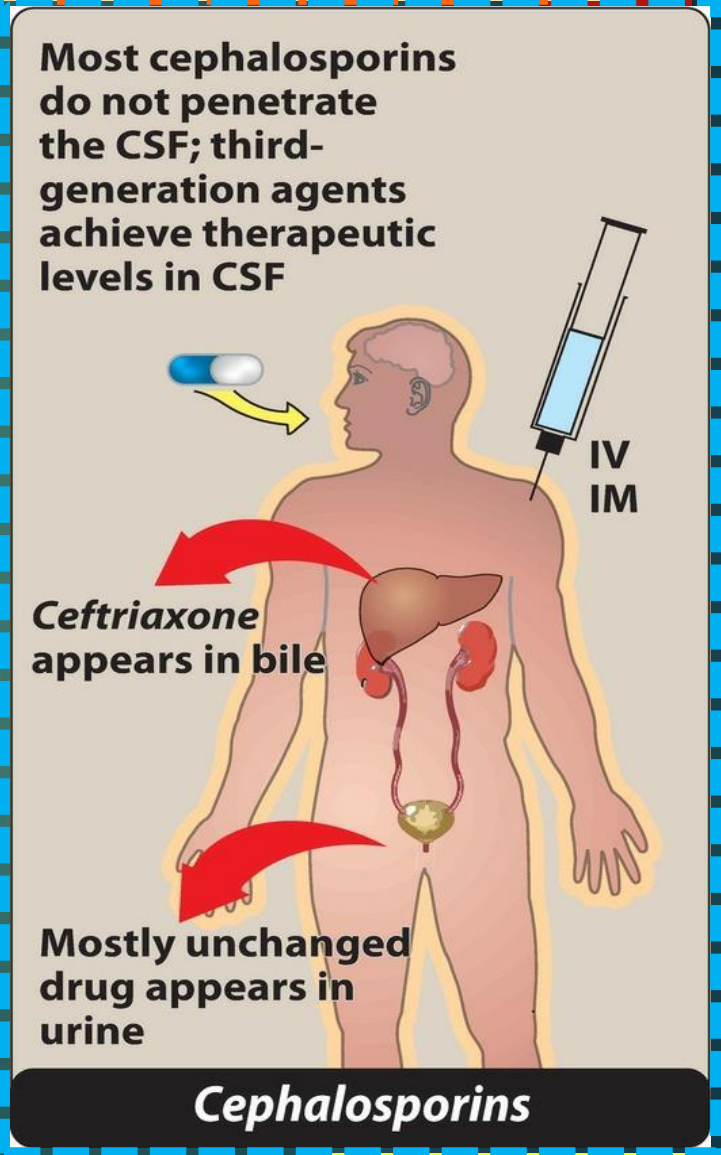
RESISTANCE:

- Resistance to the cephalosporins is either due to:

1. The hydrolysis of the beta-lactam ring by ***β-lactamases***.
2. Reduced affinity for ***PBPs***.

Pharmacokinetics

- **Cefuroxime** axetil (2nd): twice/day – Beta lactamase-producing bacteria.
- **Ceftriaxone** (3ed): has the longest $t_{1/2}$; parenterally only - once-daily-appears in the CSF – excreted in the bile; so used in patients with renal insufficiency.
- **Cefipime** (4th): against *P. aeruginosa.*
- **Ceftaroline** (5th): against MRSA.



DISTRIBUTION:

- All cephalosporins distribute very well into body fluids.
- However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few cephalosporins.
- For example, **ceftriaxone** and **cefotaxime** (both 3ed G) are effective in the treatment of neonatal and childhood meningitis caused by *H. influenzae*.
- **Cefazolin,** (1st G), is commonly used for surgical prophylaxis due to its activity against penicillinase-producing *S. aureus*, along with its good tissue and fluid penetration.

ELIMINATION:

- Cephalosporins are eliminated through tubular secretion and/or glomerular filtration, accordingly, this necessitates **dose adjustment in renal impairment.**

- One exception is **ceftriaxone**, which is excreted through the **bile** into the feces and, therefore, is frequently employed in patients with renal insufficiency.

ADVERSE EFFECTS:

- Like the penicillins, the cephalosporins are generally well tolerated.
- However, allergic reactions are a concern.
- Patients who have had an anaphylactic response, Stevens-Johnson syndrome {a rare, serious disorder. Often, it begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters}, or toxic epidermal necrolysis {potentially life-threatening dermatologic disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis and/or death} to penicillins should not receive cephalosporins.

- Cephalosporins should be avoided or used with caution in individuals with penicillin allergy.
- Current data suggest that the cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the *similarity in the side chain*, *not the β-lactam structure*.
- The highest rate of allergic cross-sensitivity is between penicillin and first-generation cephalosporins.

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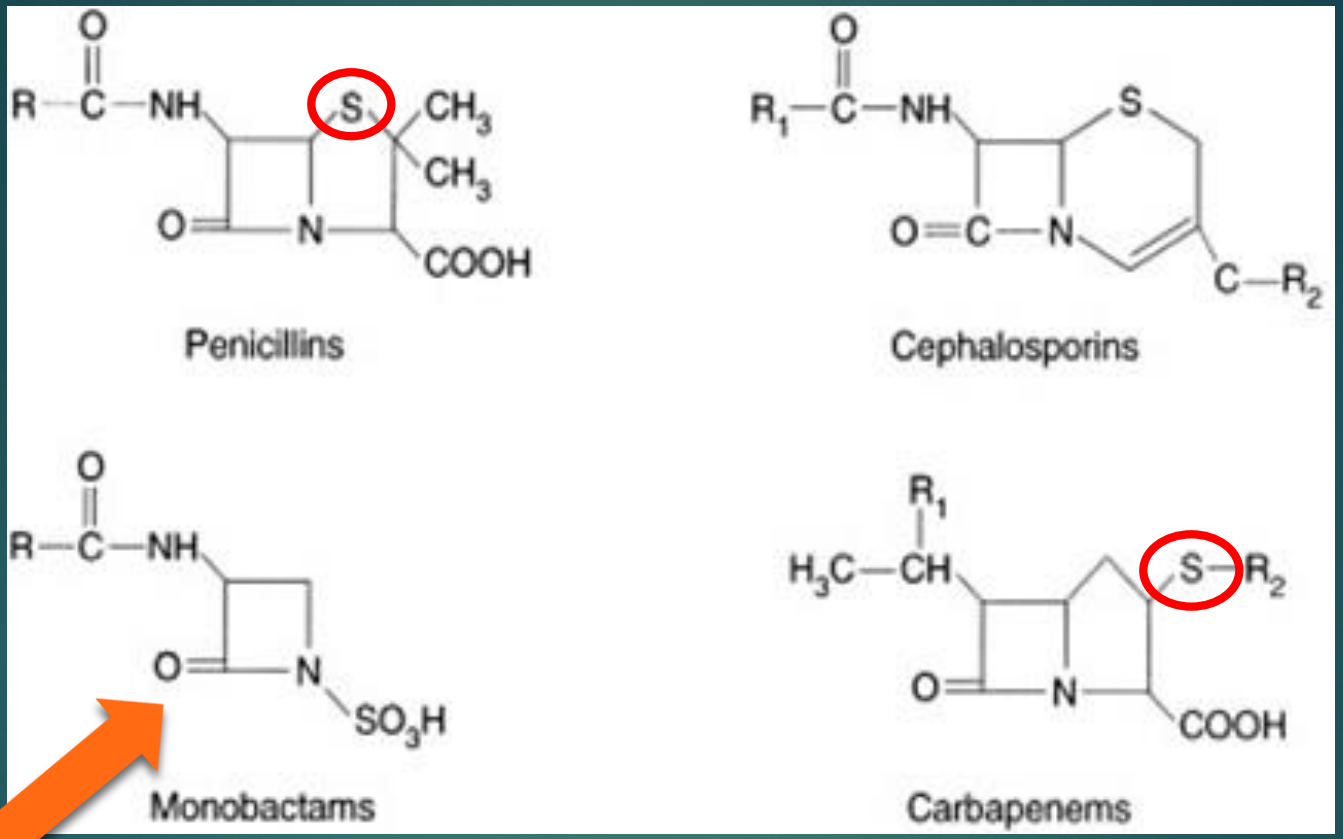
OTHER BETA-LACTAM ANTIBIOTICS:

CARBAPENEMS:

- Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring has been externalized and replaced by a carbon atom.

Beta-lactam and other cell-wall inhibitors



with a monocyclic β-lactam ring

General structures of β-lactam antibiotics

- **Imipenem**, **meropenem**, **doripenem**, and **ertapenem** are drugs in this group.

Antibacterial spectrum:

- Imipenem resists hydrolysis by most β-lactamases, but not the **metallo-**β-lactamases.
- This drug plays a role in **empiric therapy** because it is active against **β-lactamase–producing** gram-positive and gram-negative organisms, anaerobes, and *P. aeruginosa*.

Empiric (empirical) therapy:

- Medical treatment or therapy based on experience and "educated guess" in the absence of complete or perfect information.
- **Meropenem** and **doripenem** have antibacterial activity similar to that of **imipenem**.

- Doripenem may retain activity against resistant isolates of *Pseudomonas*.
- Unlike other carbapenems, ertapenem lacks coverage against *P. aeruginosa*, *Enterococcus* species, and *Acinetobacter* species.
- **MRSA** strains are **resistant** to carbapenems.

Pharmacokinetics:

- Imipenem, meropenem, and doripenem are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed.
- Meropenem is known to reach therapeutic levels in bacterial meningitis even **without** inflammation.
- These agents are excreted by glomerular filtration.

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

ADVERSE EFFECTS:

- Imipenem/cilastatin can cause nausea, vomiting, and diarrhea.
- Eosinophilia and neutropenia are less common than with other β-lactams.

- Seizures with imipenem; less probable with other agents.
- Structural similarity may confer cross-reactivity with penicillins.
- the cross-reactivity rate seen in studies is very low (less than 1%).
- Those with true penicillin allergy should use carbapenems cautiously.

MONOBACTAMS:

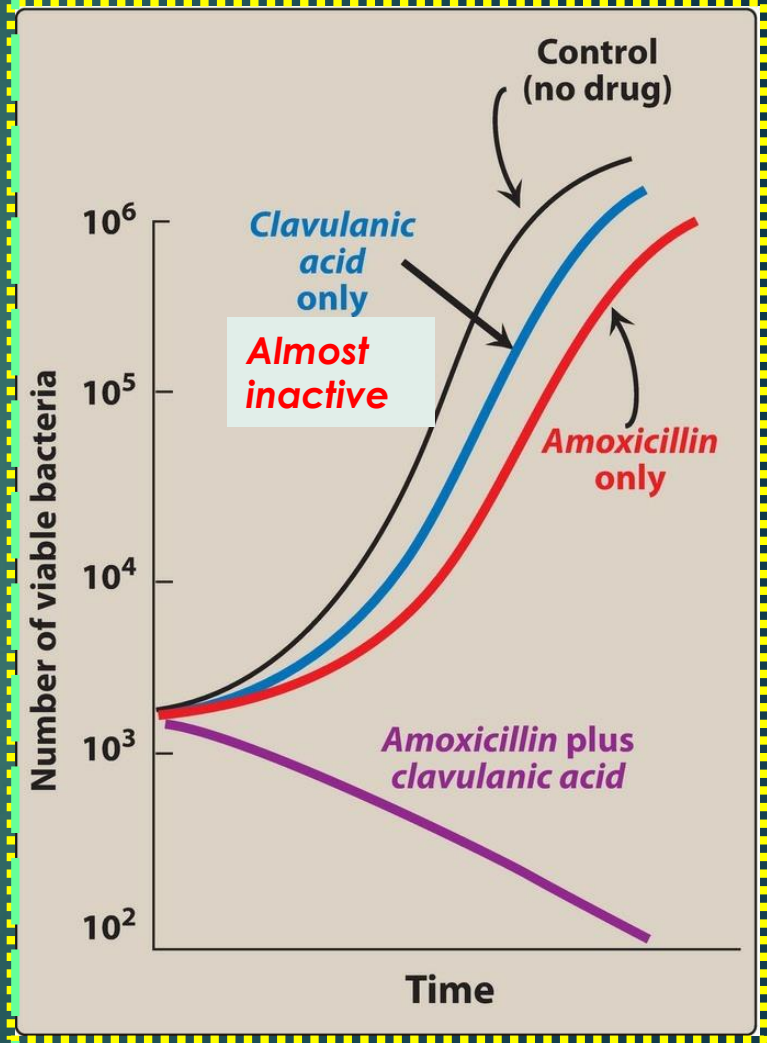
- They are unique because the β-lactam ring is not fused to another ring.
- **Aztreonam** is the only commercially available monobactam.
- Its antimicrobial activity: primarily against gram-negative pathogens, including the **Enterobacteriaceae** and *P. aeruginosa.*

- It has structural similarities to **ceftazidime**, and its Gram-negative spectrum is similar to that of the third-generation cephalosporins.
- It lacks activity against gram-positive organisms and anaerobes.
- IV or IM administration.
- Penicillin-allergic patients tolerate aztreonam without reaction.
- Because of its structural similarity to ceftazidime, there is potential for cross-reactivity; aztreonam should be used with caution in the case of documented severe allergies to ceftazidime.
- In patients with a history of penicillin anaphylaxis, **aztreonam** may be used to treat serious infections such as pneumonia, meningitis, and sepsis caused by susceptible Gram-negative pathogens.

B-LACTAMASE INHIBITORS:

- Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic.
- β-Lactamase inhibitors, such as **clavulanic acid**, **sulbactam**, and **tazobactam** contain a β-lactam ring but, by themselves, do not have significant antibacterial activity or cause any significant adverse effects.
- **Avibactam** and **vaborbactam** are also β-lactamase inhibitors; however, their structures lack the core β-lactam ring.
- β-Lactamase inhibitors function by inactivating β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes.

- The β-lactamase inhibitors are, therefore, formulated in combination with β-lactamase–sensitive antibiotics, such as amoxicillin, ampicillin, and piperacillin.
- **Ceftazidime/avibactam** and **meropenem/vaborbactam** are novel combinations to treat multifactorial resistant bacteria such as carbapenem-resistant Enterobacteriaceae {CRE}.
- However, when treating infections caused by such strains, testing the sensitivity CRE to these antibiotic combinations should preferably be done.



- **Ceftazidime/avibactam** has broad gram-negative activity including Enterobacteriaceae and *P. aeruginosa .*
- Addition of avibactam allows the drug to resist hydrolysis against broad spectrum β-lactamases (e.g. carbapenemases) with the exception of metallo-β-lactamases.
- **Ceftolozane** (5th G) / **tazobactam**.
- IV administration.
- Indicted in the treatment of resistant Enterobacteriaceae and multidrug-resistant *Pseudomonas aeruginosa*.
- This combination has narrow gram-positive and very limited anaerobic activity.
- The above two combinations are indicated for the treatment of intra-abdominal infections (in combination with metronidazole) and for the management of complicated urinary tract infections.

VANCOMYCIN:

- A tricyclic glycopeptide active against aerobic and anaerobic **gram-positive** bacteria, including MRSA, methicillin-resistant *Staphylococcus epidermidis* (MRSE), *Enterococcus* spp., and *Clostridium difficile.*
- Disrupts cell wall integrity.
- It is commonly used in patients with skin and soft tissue infections, infective endocarditis, and nosocomial pneumonia (caused by MRSA),
- Frequency of administration is dependent on **renal** function.
- Common adverse events include nephrotoxicity, infusion-related reactions (red man syndrome and phlebitis), and ototoxicity.

LIPOGLYCOPEPTIDES:

- **Telavancin**, **oritavancin**, and **dalbavancin** are bactericidal semisynthetic lipoglycopeptide antibiotics with activity against gram-positive bacteria.
- Spectrum of activity is similar to vancomycin including staphylococci, streptococci, and enterococci.
- Owing to structural differences, they are more potent than vancomycin.
- Like vancomycin, these agents inhibit bacterial cell wall synthesis; the lipid tail is essential in anchoring the drug to the cell walls to improve target site binding.
- **Telavancin** is considered an alternative to **vancomycin** in treating acute bacterial skin and skin structure infections and hospital-acquired pneumonia caused by resistant gram-positive organisms, including **MRSA**.

- The use of telavancin in clinical practice may be limited by its adverse effect profile, which includes:
  - [1] Nephrotoxicity, [2] risk of fetal harm, and [3] interactions with medications known to prolong the QT-interval (for example, fluoroquinolones, macrolides).
- In contrast to telavancin, oritavancin and dalbavancin have prolonged half-lives (245 and 187 hours, respectively); single-dose administration.

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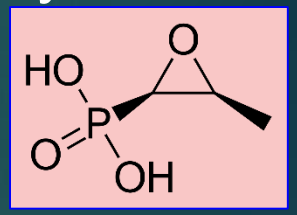
DAPTOMYCIN:

- A novel cyclic lipopeptide antibiotic that is an alternative to other agents, such as vancomycin or linezolid, for treating infections caused by resistant gram-positive organisms, including MRSA and vancomycin-resistant enterococci (VRE).

- Daptomycin is inactivated by pulmonary surfactants; thus, IT SHOULD NEVER BE USED IN THE TREATMENT OF PNEUMONIA.

FOSFOMYCIN:

- It is a bactericidal synthetic derivative of phosphonic acid.
- It blocks cell wall synthesis by inhibiting the enzyme enolpyruvyl transferase, a key step in peptidoglycan synthesis.
- It is indicated for **urinary tract infections** caused by *E. coli* or *Enterococcus faecalis*.
- It is considered first-line therapy for acute **cystitis**.



- Due to its unique structure and mechanism of action, cross-resistance with other antimicrobial agents is unliskely.
- Fosfomycin is rapidly absorbed after oral administration and distributes well to the kidneys, bladder, and prostate.

- The drug is excreted in its **active** form in the urine and maintains high concentrations over **several days**, allowing for a one-time dose.
- A parenteral formulation is available in select countries and has been used for the treatment of systemic infections.
- The most commonly reported adverse effects include diarrhea, vaginitis, nausea, and headache.

POLYMYXINS:

- The polymyxins are **cation** polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria.
- They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and cell death.

- They are bactericidal agents with activity against most clinically important GRAM-NEGATIVE bacteria, including *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *Acinetobacter* spp. [Infective especially to debilitated patients in hospitals], and *Enterobacter* spp. [can cause numerous infections, including cerebral abscess, pneumonia, meningitis, septicemia, and wound, urinary tract (particularly catheter-related UTI), and abdominal cavity/ intestinal].
- Only two forms of polymyxin are in clinical use today, **polymyxin B** and **colistin** (**polymyxin E**).
- **Polymyxin B** is available in parenteral, ophthalmic, otic, and topical preparations.
- Colistin is only available as a prodrug, colistimethate sodium, which is administered **IV** or **inhaled** via a nebulizer.

- The use of these drugs has been limited due to the increased risk of **nephrotoxicity** and **neurotoxicity** (for example, slurred speech, muscle weakness) when used systemically.
- However, with increasing gram-negative resistance, they are now commonly used in patients with **multidrug-resistant infections.**
- Careful dosing and monitoring of adverse effects are important to maximize the safety and efficacy of these agents.

THE END

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