Pharmacology I

Cell Wall Inhibitors

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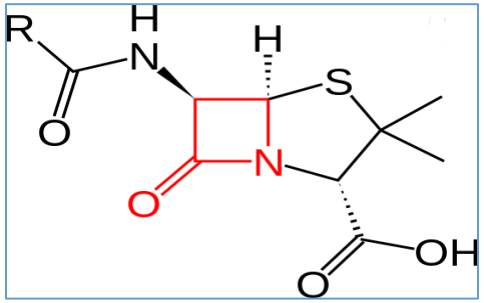
Lecture No. : 8

مستقبل له تاريخ

Cell Wall Inhibitors

- **Penicillins and cephalosporins** are the major antibiotics that inhibit bacterial cell wall synthesis.
- They are called beta-lactams because of the **4-member ring** that is common to all their members.
- The beta-lactams include some of the most effective, widely used, and well-tolerated agents available for the treatment of microbial infections.



Cell Wall Inhibitors

Penicillins

Cephalosporins

Carbapenems

Monobactam

β-lactamase inhibitors

Lipoglycopeptides

Others

- Synthetic Production of Penicillin Professor Alexander Fleming, holder of the Chair of Bacteriology at London University, **who first discovered the mould *Penicillium notatum***.
- Here in his laboratory at St Mary's, Paddington, London.

PENICILLINS

*Amoxicillin** AMOXIL
*Ampicillin*** GENERIC ONLY
*Dicloxacillin** GENERIC ONLY
Nafcillin GENERIC ONLY
Oxacillin GENERIC ONLY
Penicillin G PFIZERPEN
Penicillin G benzathine
Penicillin G benzathine G procaine BICILLIN C-R
*Penicillin V** GENERIC ONLY

CARBAPENEMS

Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin
Meropenem MERREM

MONOBACTAMS

Aztreonam AZACTAM

CEPHALOSPORINS

*Cefaclor** GENERIC ONLY
*Cefadroxil** GENERIC ONLY
Cefazolin ANCEF, KEFZOL
*Cefdinir** OMNICEF
Cefepime MAXIPIME
*Cefixime** SUPRAX
Cefotetan CEFOTAN
Cefoxitin MEFOXIN
*Cefprozil** CEFZIL
Ceftaroline TEFLARO
Ceftazidime FORTAZ
Ceftriaxone GENERIC ONLY
*Cefuroxime*** CEFTIN, ZIN
*Cephalexin** KEFLEX

β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS

Avibactam + ceftazidime AVYCAZ
Clavulanic acid + amoxicillin AUGMENTIN
Sulbactam + ampicillin UNASYN
Tazobactam + ceftolozane ZERBAXA
Tazobactam + piperacillin ZOSYN
Vaborbactam + meropenem VABOMERE

LIPOGLYCOPEPTIDES

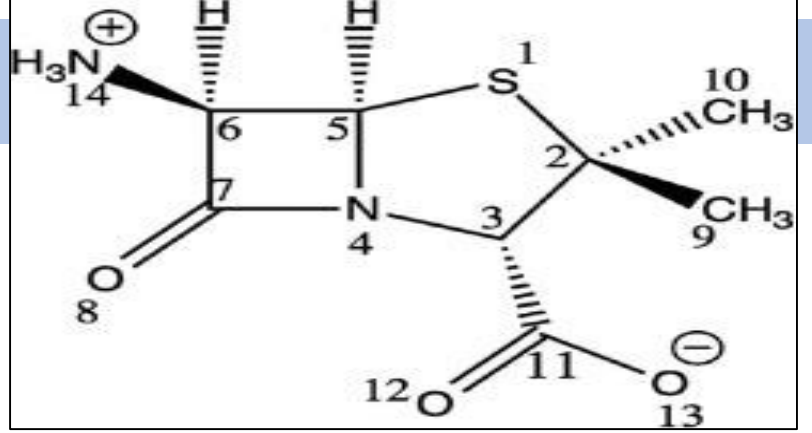
Dalbavancin DALVANCE
Oritavancin ORBACTIV
Telavancin VIBATIV

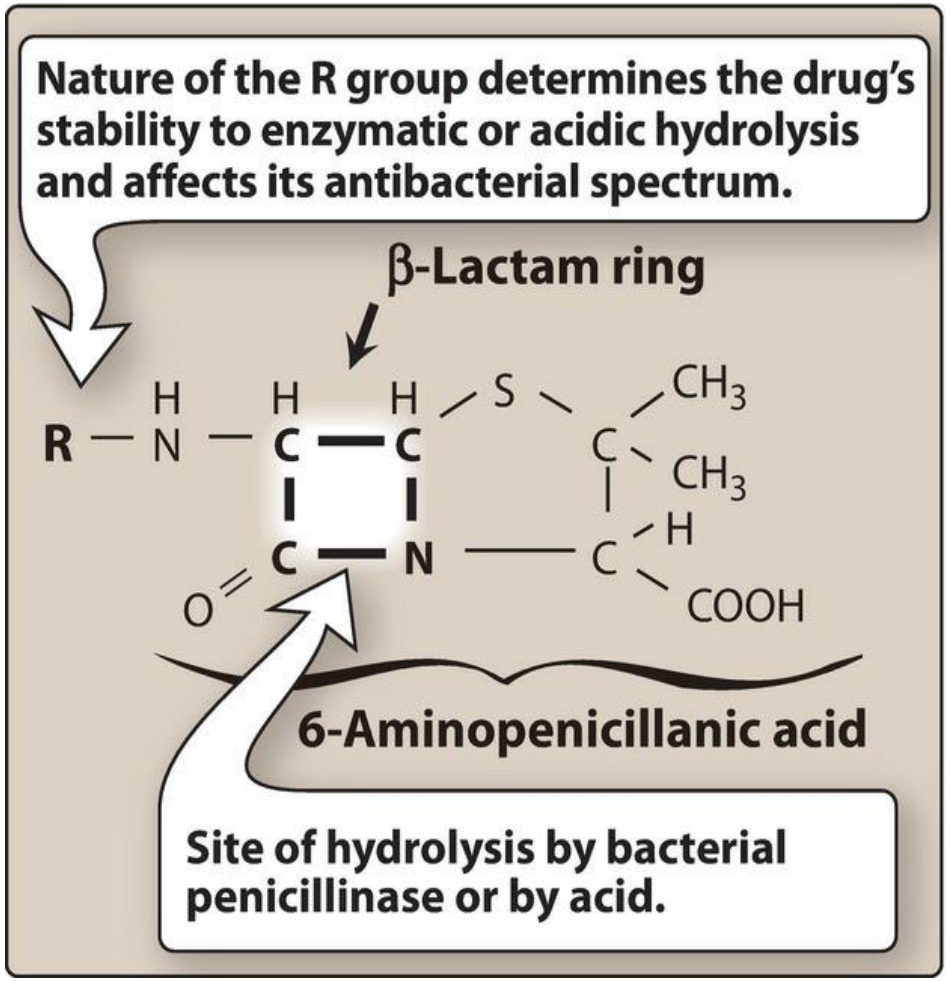
OTHER ANTIBIOTICS

Colistin COLY-MYCIN M
Daptomycin CUBICIN
Fosfomycin MONUROL
Polymyxin B GENERIC ONLY
Vancomycin VANCOCIN

PENICILLINS

- **Classification**
- All penicillins are derivatives ***of 6-aminopenicillanic acid*** and contain a **beta-lactam ring structure** that is essential for antibacterial activity.
- Penicillin subclasses have **additional chemical substituents (R group)** that confer differences in antimicrobial activity, susceptibility to acid and enzymatic hydrolysis, and biodisposition.





PENICILLINS

Pharmacokinetics

A. Routes of administration:

- The route of administration of a β-lactam antibiotic is determined **by the stability of the drug to gastric acid** and ***by the severity of the infection***.

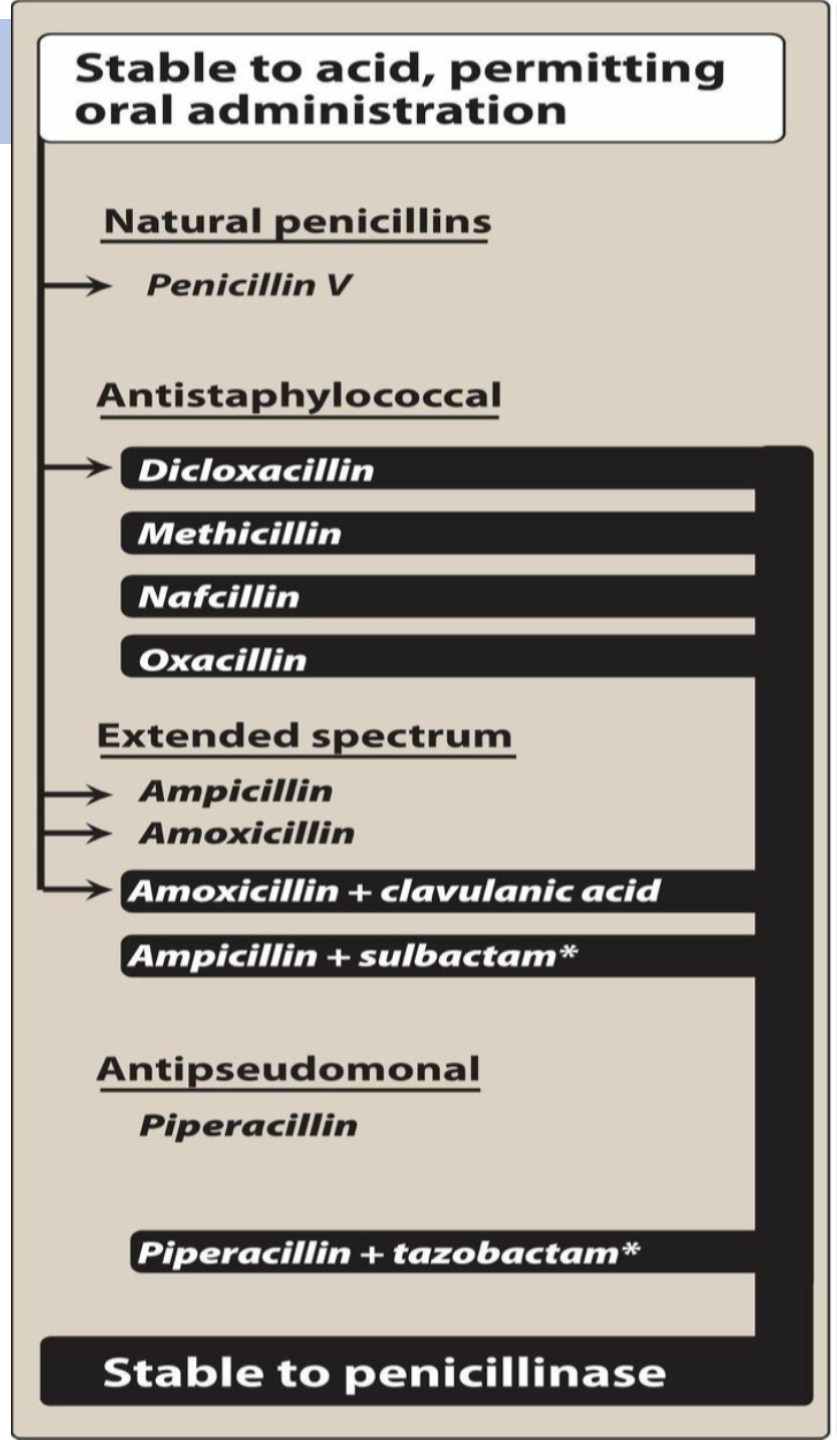
PENICILLINS

Pharmacokinetics

A. Routes of administration:

1. **The combination of *ampicillin with sulbactam*, ticarcillin with clavulanic acid**, and **piperacillin with tazobactam**, and antistaphylococcal penicillins **nafcillin and oxacillin** must be administered **intravenously (IV) or intramuscularly (IM).**

- ***Penicillin V, amoxicillin, and dicloxacillin*** *are available only as oral preparations.*
- Others are effective by the oral, IV, or IM routes.

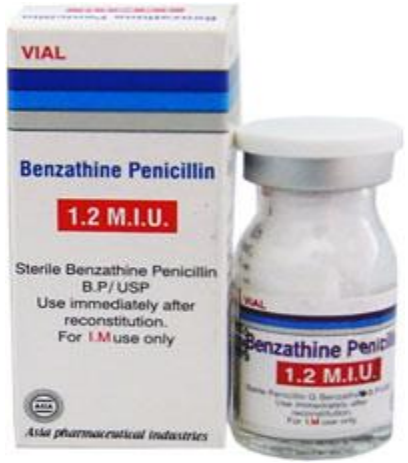


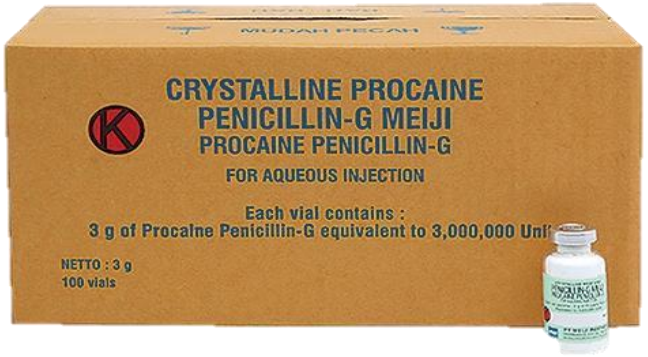
PENICILLINS

Pharmacokinetics

2- Depot forms:

- **Procaine penicillin G** and **benzathine penicillin G** are administered IM and serve as depot forms.
- They are slowly absorbed into the circulation and persist at low levels over a long time period.





PENICILLINS

Pharmacokinetics

B. Absorption:

- Most of the penicillins are **incompletely** absorbed after oral administration, and they **reach the intestine** in sufficient amounts to affect the composition of the intestinal flora.
- **Food decreases the absorption** of all the **penicillinase-resistant penicillins** because as **gastric emptying time increases**, the drugs are **destroyed by stomach acid**. Therefore, they should be taken **on an empty stomach**.

Absorption of most oral penicillins (amoxicillin being an exception) is impaired by food, and the drugs should be administered at least 1–2 hours before or after a meal.

PENICILLINS

Pharmacokinetics

C. Distribution:

- All the penicillins distribute **well & cross** the **placental barrier**, but none have been shown to have **teratogenic effects**.
- However, penetration into **bone** or **CSF** is **insufficient** for therapy **unless these sites are inflamed**.

PENICILLINS

Pharmacokinetics

D. Excretion:

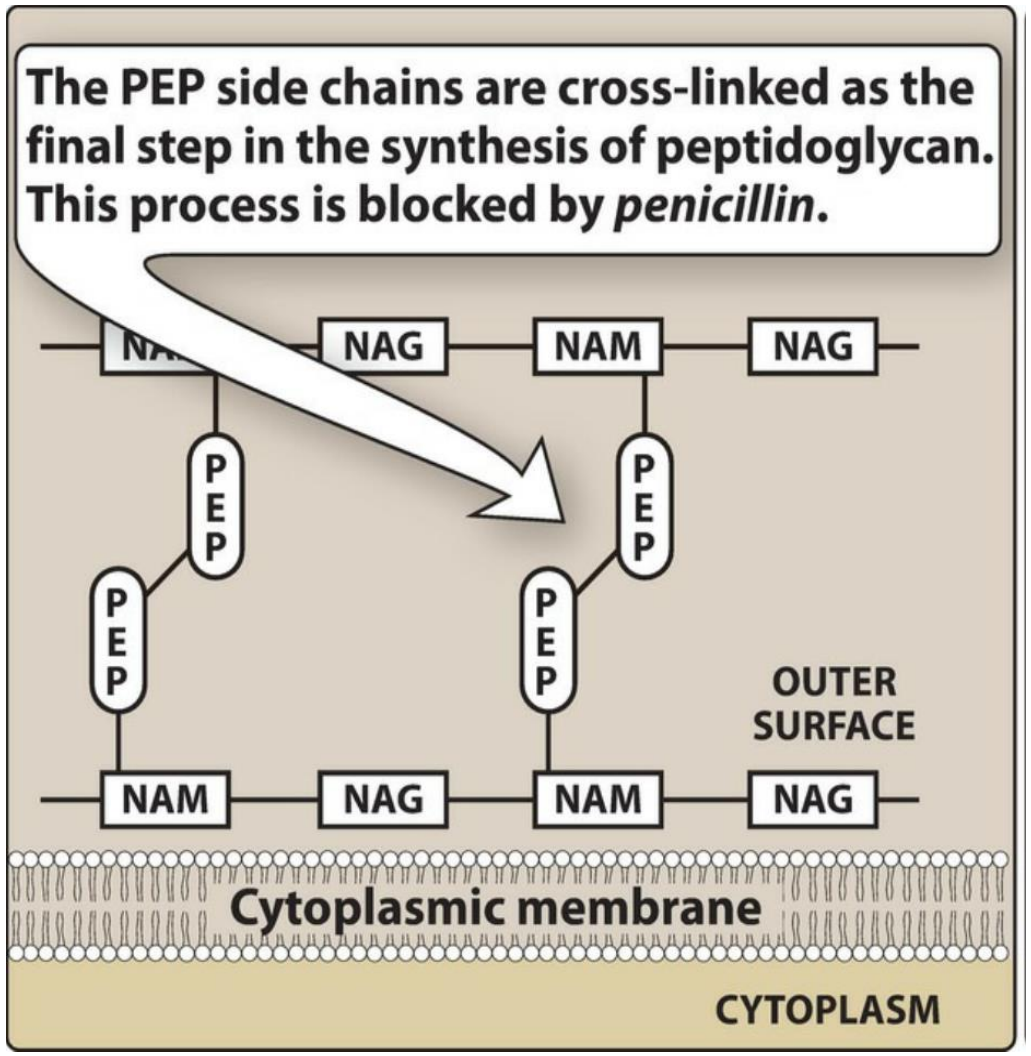
- The primary route of excretion is **by glomerular filtration**.
- Patients with **impaired renal function must have dosage regimens adjusted**.
- **Nafcillin and oxacillin** are **metabolized** in the **liver**.
- **Probenecid inhibits the secretion of penicillins** by **competing for active tubular secretion** via the **organic acid transporter** and, thus**, can increase blood levels**.

PENICILLINS

Mechanisms of Action and Resistance

❑ 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 and **cell death**.



Bacterial cell wall of gram-positive bacteria. NAM = *N*-acetylmuramic acid; NAG = *N*-acetylglucosamine; PEP = cross-linking peptide.

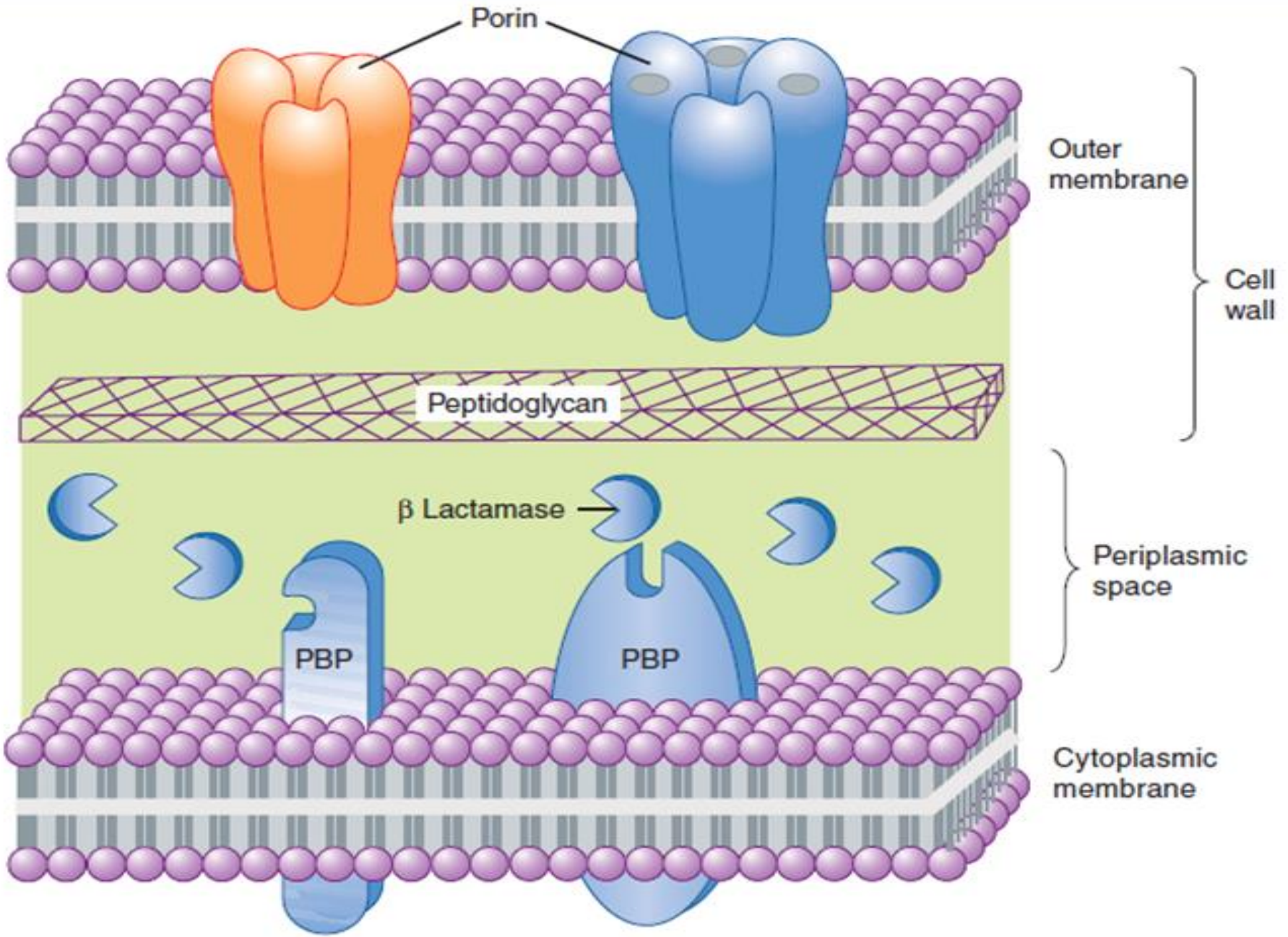


FIGURE 43–1 Beta-lactams and bacterial cell wall synthesis. The outer membrane shown in this simplified diagram is present only in gram-negative organisms. It is penetrated by proteins (porins) that are permeable to hydrophilic substances such as beta-lactam antibiotics.

PENICILLINS

- **Mechanism of bacterial resistance:**

1. β-Lactamase production

- The **formation of beta-lactamases** (penicillinases) by most **Staphylococci** and many **gram-negative** organisms.
- **Inhibitors** of these bacterial enzymes (eg, **clavulanic acid, sulbactam, tazobactam**) are often used in combination with penicillins to prevent their inactivation.

Gram-Negative Bacteria Producing β-Lactamase:

1.Enterobacterales:

1. *Escherichia coli*
2. *Klebsiella pneumoniae*
3. *Enterobacter spp.*
4. *Serratia marcescens*
5. *Proteus spp.*
6. *Morganella morganii*
7. *Providencia spp.*
8. *Citrobacter spp.*

2.Non-Fermenters:

1. *Pseudomonas aeruginosa*
2. *Acinetobacter baumannii*
3. *Stenotrophomonas maltophilia*

3.Other Gram-Negative Bacteria:

1. *Haemophilus influenzae*
2. *Neisseria gonorrhoeae*
3. *Moraxella catarrhalis*

PENICILLINS

- **Mechanism of bacterial resistance:**

2. Structural change in target PBPs

- **PBPs** is responsible for methicillin resistance in **staphylococci** (MRSA) and for resistance to **penicillin G in pneumococci** (eg, PRSP, penicillin resistant *Streptococcus pneumoniae*) and ***enterococci***.

3. Decreased permeability to the drug

- 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.

PENICILLINS

- **Clinical Uses**

1. Narrow-spectrum (penicillinase-susceptible agents)

❑ **Penicillin G is the prototype of a subclass of penicillins.**

- **Clinical uses include** therapy of infections caused by common

1. **Streptococci,**
2. **Meningococci,**
3. **Gram-positive bacilli,**
4. **Spirochetes**.

PENICILLINS

1. Narrow-spectrum (penicillinase-susceptible agents)

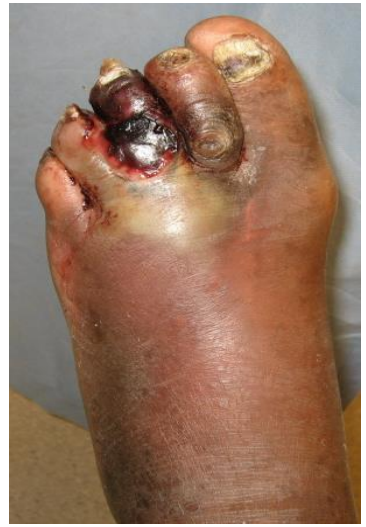
❑ **Penicillin G is the prototype of a subclass of penicillins.**

- **Resistant strains**

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

PENICILLINS

1. Narrow-spectrum (penicillinase-susceptible agents)



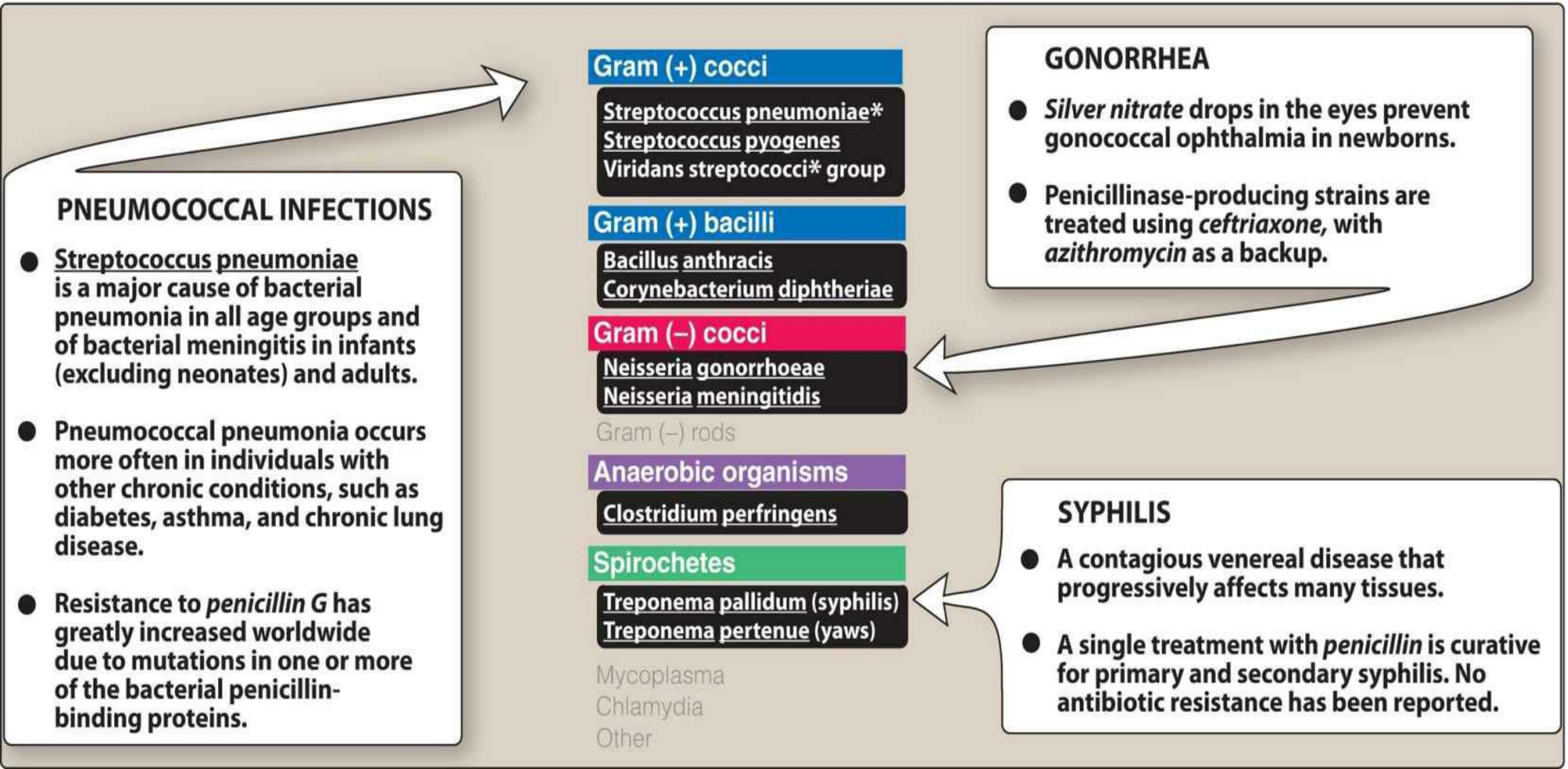
❑**Penicillin G is the prototype of a subclass of penicillins.**

- **Penicillin G remains** the **drug of choice** for

1. **Gas gangrene** (Clostridium perfringens) and
2. **Syphilis** (Treponema pallidum).
3. Activity against **enterococci** is enhanced by coadministration of **aminoglycosides**.

❑**Penicillin V** is an oral drug used mainly in **oropharyngeal infections**.

Typical therapeutic applications of penicillin G



PENICILLINS

2. Very-narrow-spectrum

❑Penicillinase-resistant drugs (antistaphylococcal)

- This subclass of penicillins includes

1. **Methicillin** (The prototype, but rarely used owing to its **nephrotoxic** potential),
2. **Nafcillin**, And
3. **Oxacillin**.

- Their primary use is in the treatment of known or suspected **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.

PENICILLINS

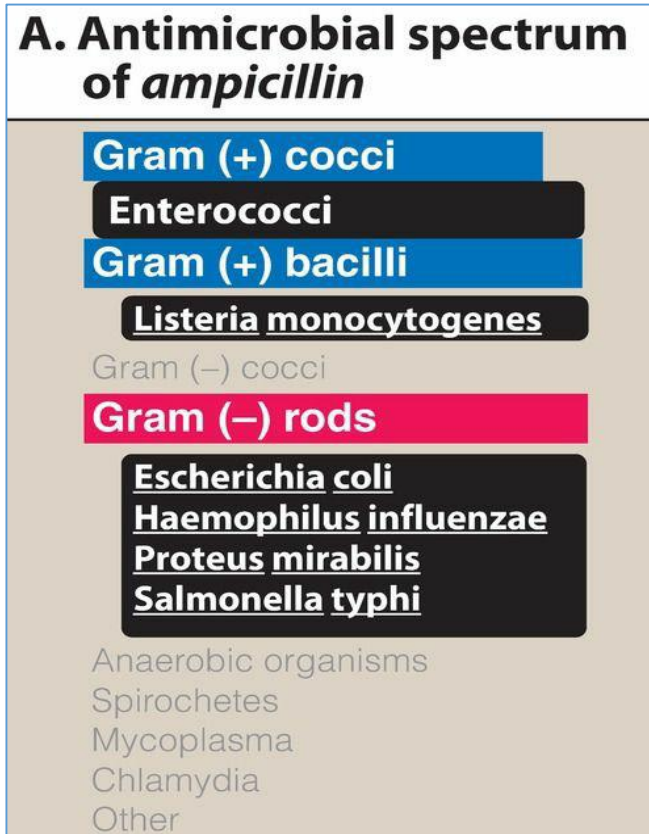
3. Wider-spectrum

❑Penicillinase-susceptible drugs (Semisynthetic penicillins)

A. 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

1. ***Enterococci,***
2. ***Listeria monocytogenes,***
3. ***Escherichia coli,***
4. ***Proteus mirabilis,***
5. ***Haemophilus influenzae, and***
6. ***Moraxella catarrhalis,*** although resistant strains occur.

1. *streptococci,*
2. *meningococci,*
3. *gram-positive bacilli,*
4. *spirochetes*.



PENICILLINS

3. Wider-spectrum

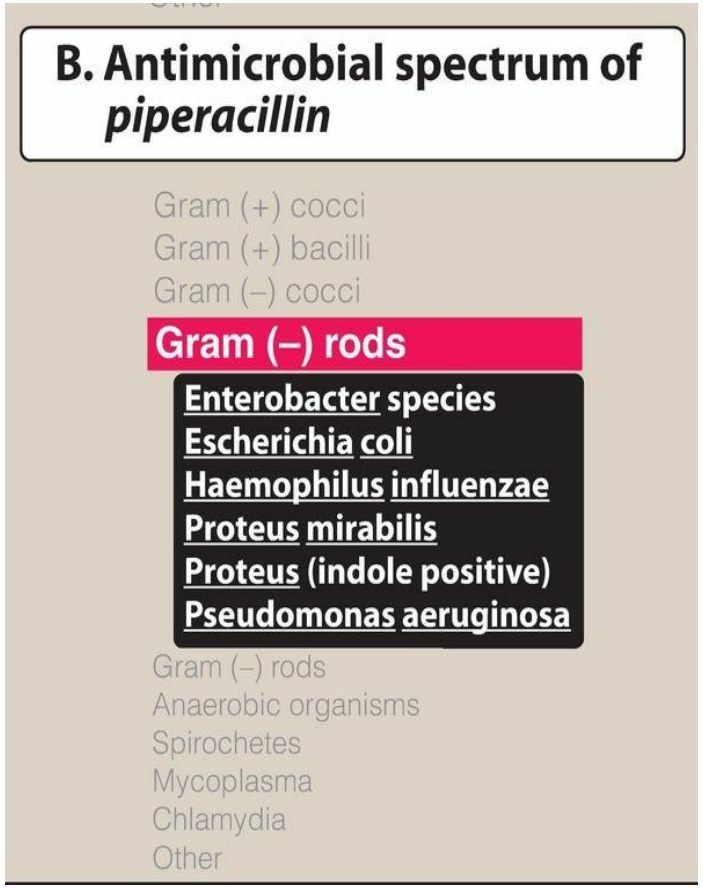
❑Penicillinase-susceptible drugs (Semisynthetic penicillins)

- When used in combination with inhibitors of **penicillinases** (eg, clavulanic acid), their antibacterial activity is often enhanced.
- In **enterococcal** and **listerial** infections, **Ampicillin** is synergistic with **aminoglycosides**.

PENICILLINS

b. Piperacillin and ticarcillin (Antipseudomonal penicillin)

- These drugs have activity against several **gram-negative rods**, including ***Pseudomonas, Enterobacter*, and in some cases *Klebsiella species***.
- Most drugs in this subgroup have synergistic actions with **aminoglycosides** against such organisms.



PENICILLINS

b. Piperacillin and ticarcillin (Antipseudomonal penicillin)

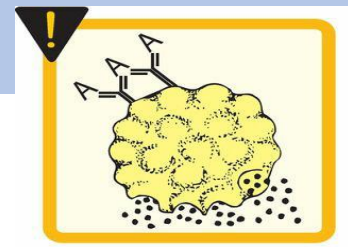
- ***Piperacillin and ticarcillin*** are susceptible to penicillinases and are often used in combination with penicillinase inhibitors (eg, tazobactam and clavulanic acid) to enhance their activity.

PENICILLINS

E. Adverse effects

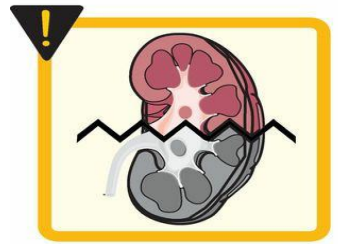
1. Allergy

- Allergic reactions include urticaria, severe pruritus, fever, joint swelling, **hemolytic anemia**, nephritis, and anaphylaxis.
- **Methicillin** causes **interstitial nephritis**, and **nafcillin** is associated with **neutropenia**.
- Complete **cross-allergenicity** between different penicillins should be assumed.

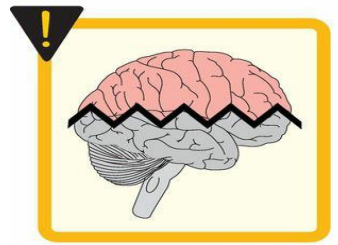


Hypersensitivity

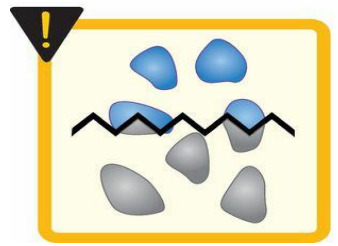
Diarrhea



Nephritis



Neurotoxicity



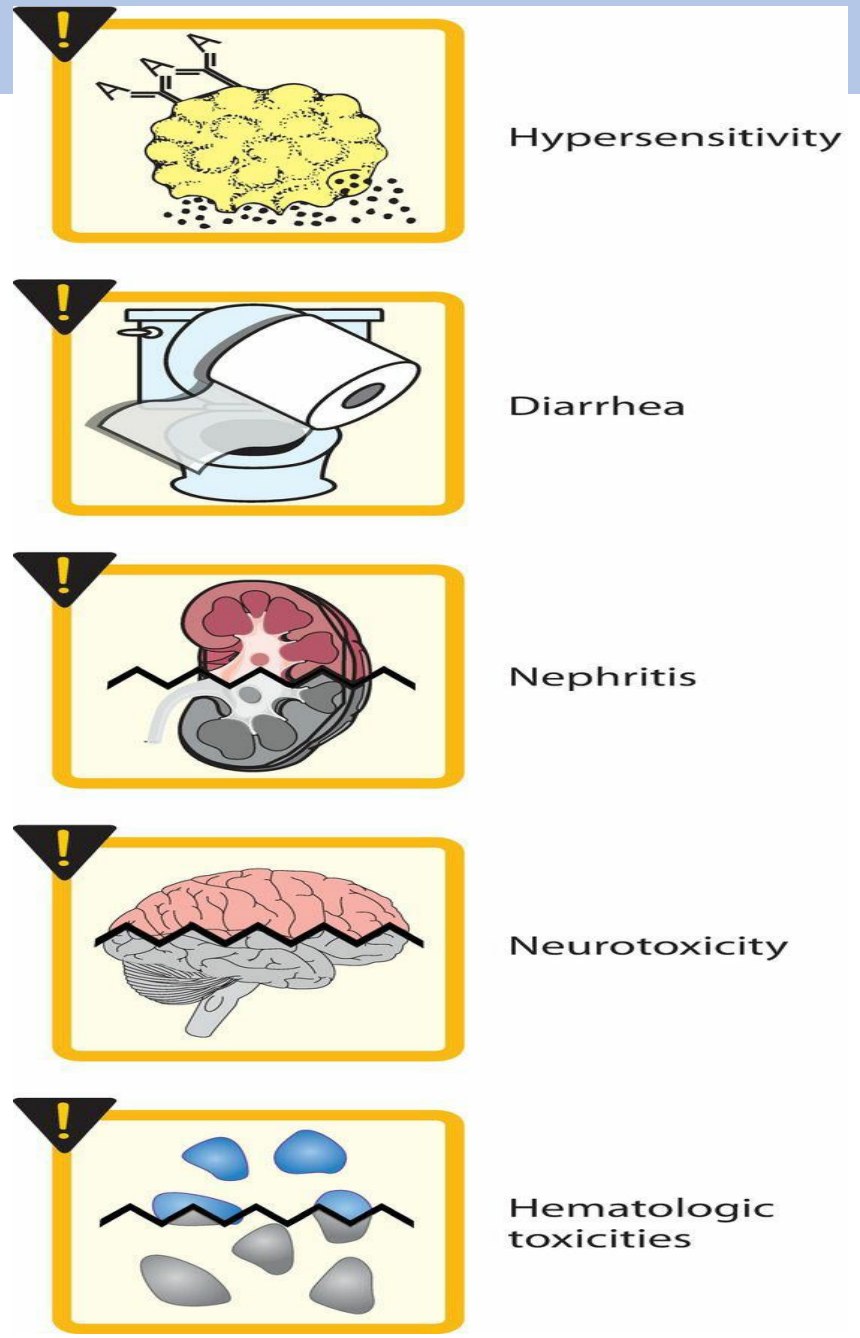
Hematologic toxicities

PENICILLINS

E. Adverse effects

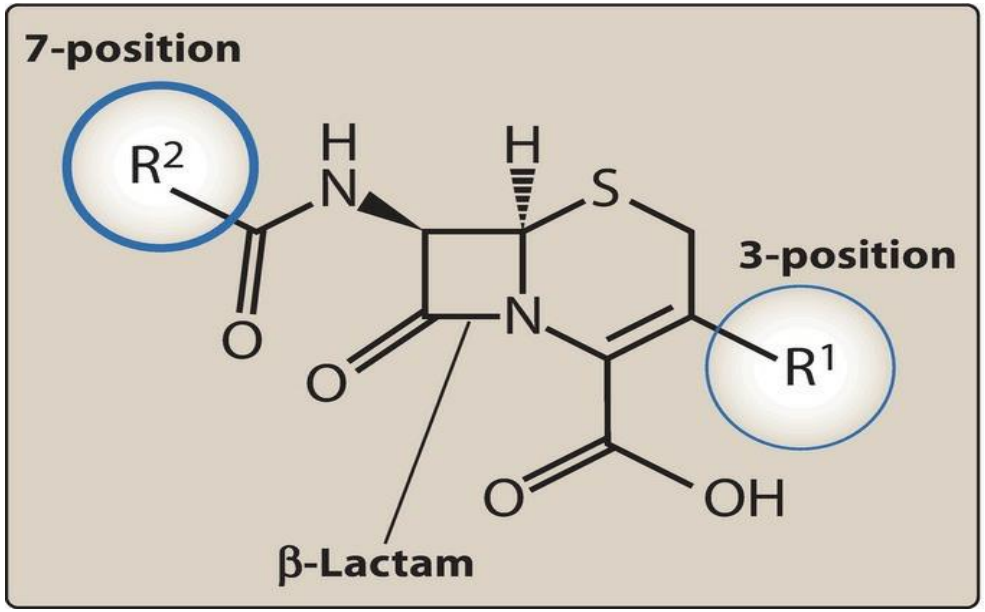
2. Gastrointestinal disturbances

- 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.



III. 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 than the penicillins to certain β-lactamases.***



III. Cephalosporins

- **Pharmacokinetics:**
- Several cephalosporins are **available for oral use**, but most are administered **parenterally**.
- Cephalosporins with **side chains** may undergo **hepatic metabolism**, but the major **elimination** mechanism for drugs in this class is **renal excretion** via active tubular secretion.
- **Cefoperazone and ceftriaxone** are excreted **mainly in the bile**.
- ***Most first- and second-generation cephalosporins do not enter the cerebrospinal fluid even when the meninges are inflamed***.

III. Cephalosporins

- **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.

III. Cephalosporins

- **Mechanisms of Action and Resistance**
- 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 are also resistant to cephalosporins**.

III. Cephalosporins

- **Clinical Uses**

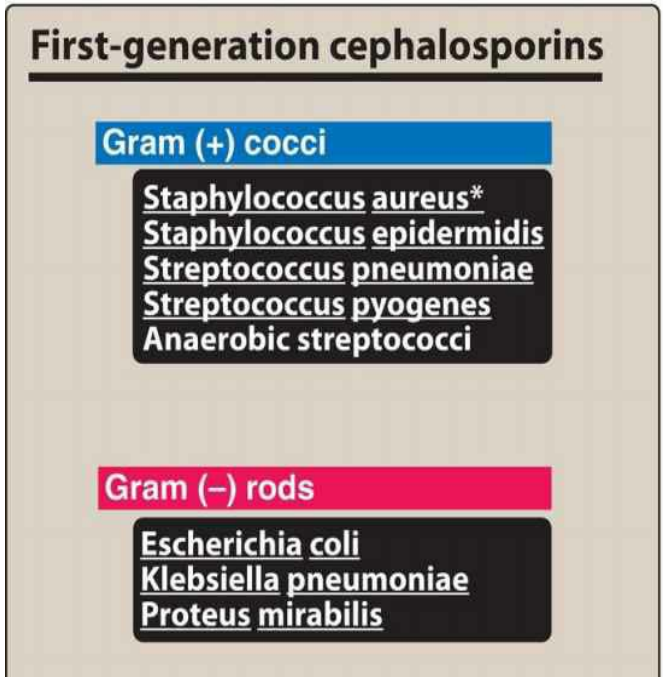
1. **First-generation drugs**

- **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* (**Gram-negative rods**) are also sensitive.

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

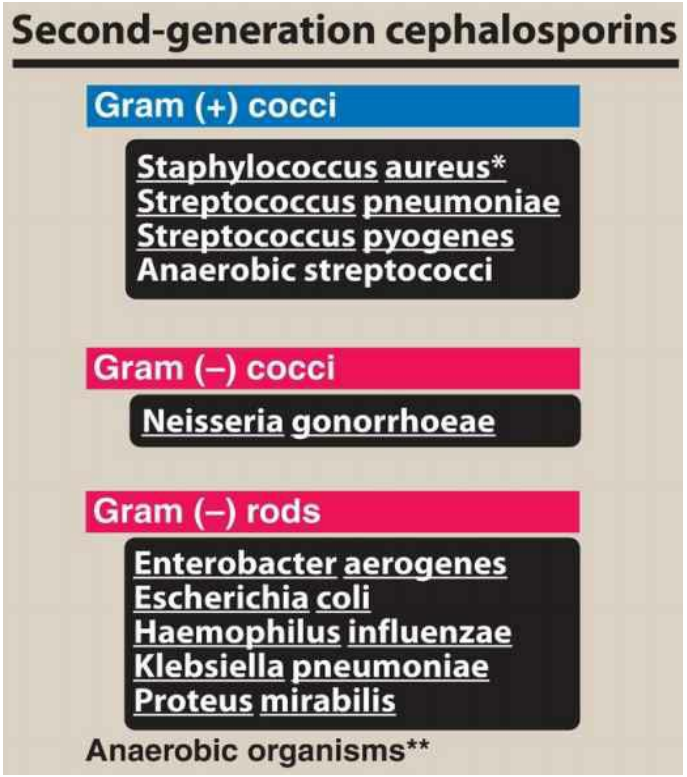


Cefazolin
Cephalexin
Cephradine
Cefadroxil

III. Cephalosporins

2. Second-generation

- It have slightly **less activity** **against gram-positive organisms** than the first-generation drugs
- But **have an extended gram-negative coverage** such as **H. influenzae, Klebsiella species, Proteus species, Escherichia coli, and Moraxella catarrhalis,**
- Marked differences in activity occur among the drugs in this subgroup.



Cefotetan,
Cefoxitin,
Cefamandole,
Cefuroxime,
Cefaclor

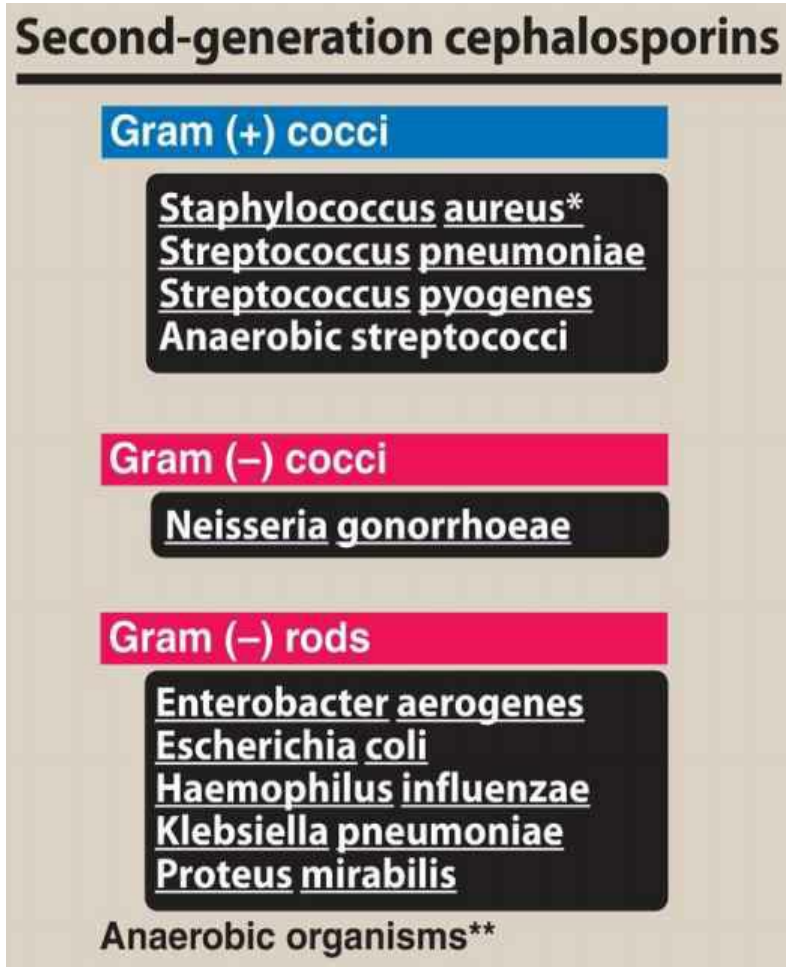
III. Cephalosporins

2. Second-generation

- **Examples of clinical uses** *include infections caused by the:*

1. ***Gram –ve* Anaerobe *Bacteroides fragilis*** (cefotetan, cefoxitin). They are the only cephalosporins with considerable activity against **gram-negative anaerobic bacteria**

2. Sinus, ear, and respiratory infections caused by ***H influenzae*** *or* ***M. catarrhalis*** (cefamandole, cefuroxime, cefaclor).



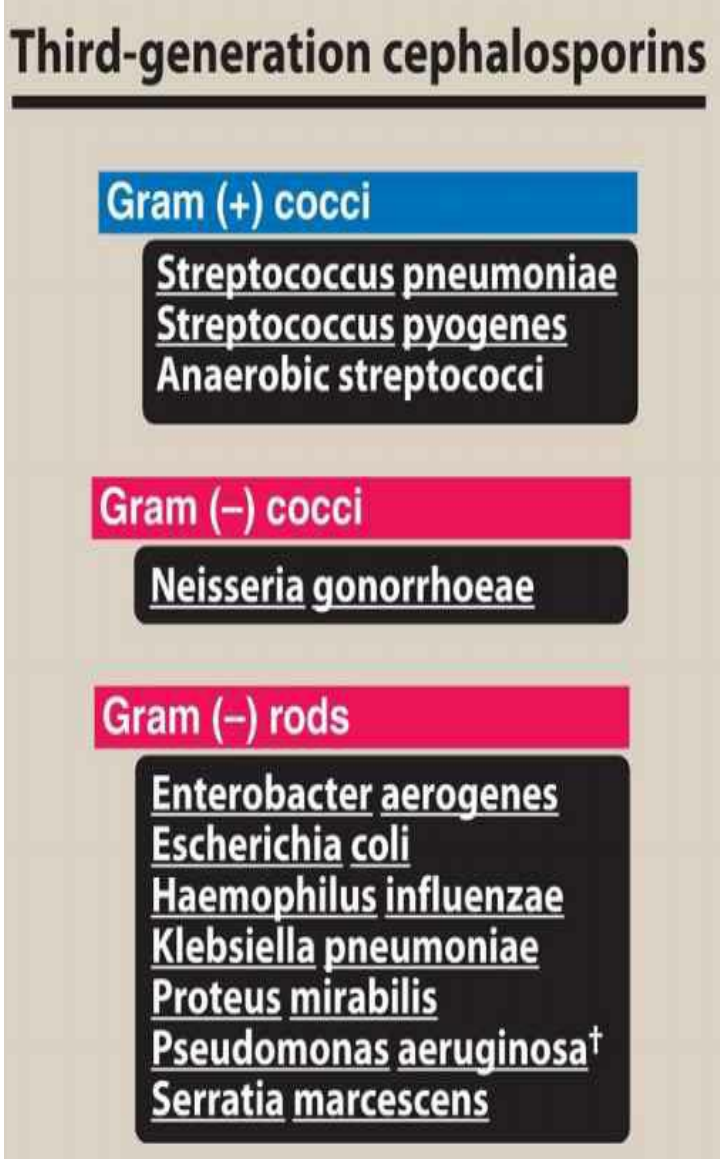
III. Cephalosporins

3. Third-generation drugs:

- (eg, **ceftazidime, cefoperazone, cefotaxime, ceftriaxone cefixime**)

1. It include **increased activity against gram-negative organisms,** resistant to other β-lactam drugs and ability to penetrate the blood-brain barrier (**EXCEPT cefoperazone and cefixime**).
2. Most are active against ***Providencia, Serratia marcescens***, and

❑β-lactamase producing strains of ***H influenzae*** **and** ***Neisseria***.



III. Cephalosporins

3. Third-generation drugs:

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

❑ Also have activity against ***Pseudomonas*** (**cefoperazone**, **ceftazidime**) and ***B fragilis*** (**ceftizoxime**).

❑ **Ceftriaxone** (parenteral) and **cefixime** (oral), currently **drugs of choice** in ***gonorrhea***.

III. Cephalosporins

4. Fourth-generation drugs

- **Cefepime** combines the **gram-positive** activity of first-generation agents with the wider **gram-negative spectrum** of third-generation cephalosporins.
- **Cefepime** is more *resistant to beta-lactamases* produced by **gram-negative organisms**, including *Enterobacter, Haemophilus, Neisseria*, and some *penicillin resistant pneumococci*.

- **Ceftaroline** has activity in infections caused by **methicillin-resistant staphylococci**.

Fourth-generation cephalosporins

Antibacterial coverage comparable to that of the third-generation class; however, demonstrate greater stability against β-lactamases

III. Cephalosporins

Adverse effects

1. **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%).

III. Cephalosporins

Adverse effects

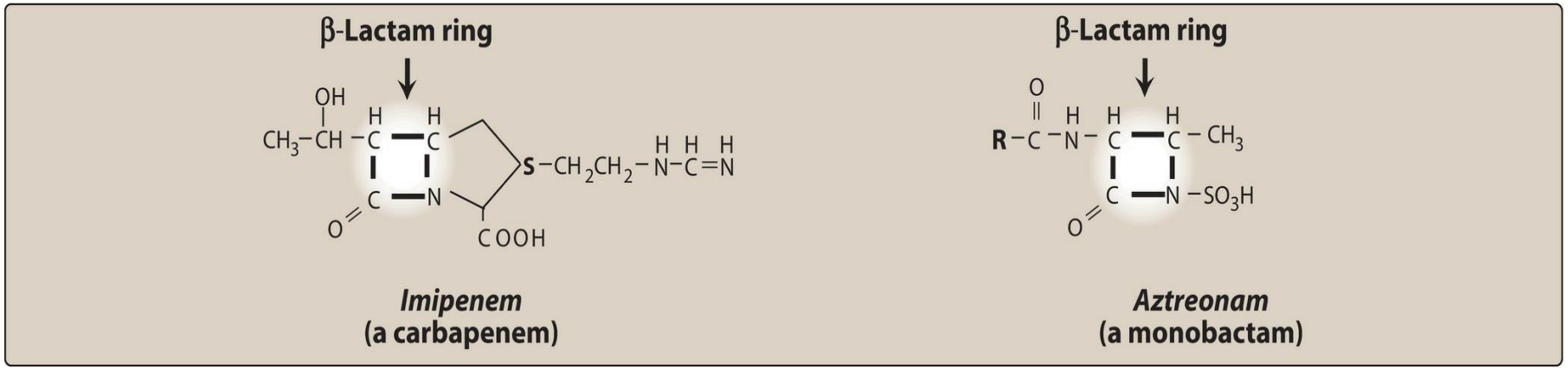
2. Cephalosporins may cause **pain** **at intramuscular** injection sites and **phlebitis** **after I.V** administration.

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

IV. OTHER BETA-LACTAM DRUGS:

A. Aztreonam

- Aztreonam is a **monobactam** that is **resistant** to β-lactamases produced by certain **gram-negative rods**, including *Klebsiella, Pseudomonas, and Serratia*.
- The drug has **no activity** against **gram positive bacteria** or **anaerobes**.



IV. OTHER BETA-LACTAM DRUGS:

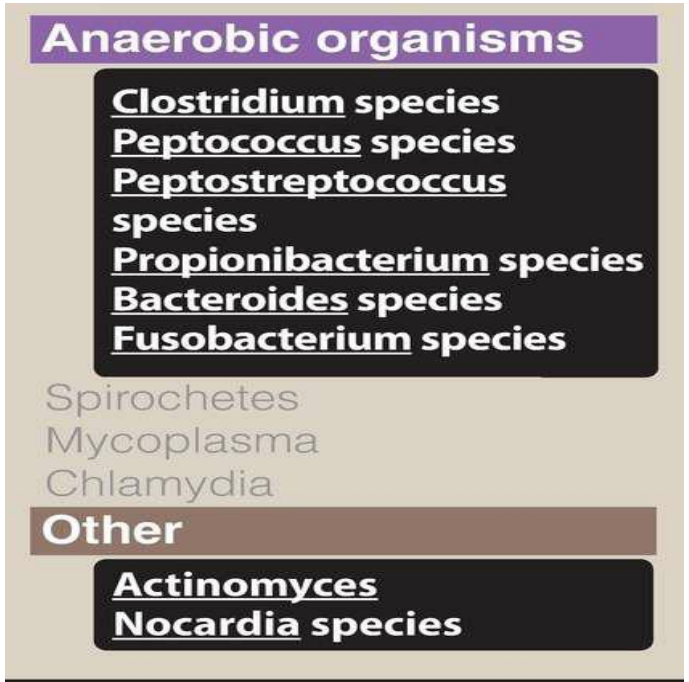
A. Aztreonam

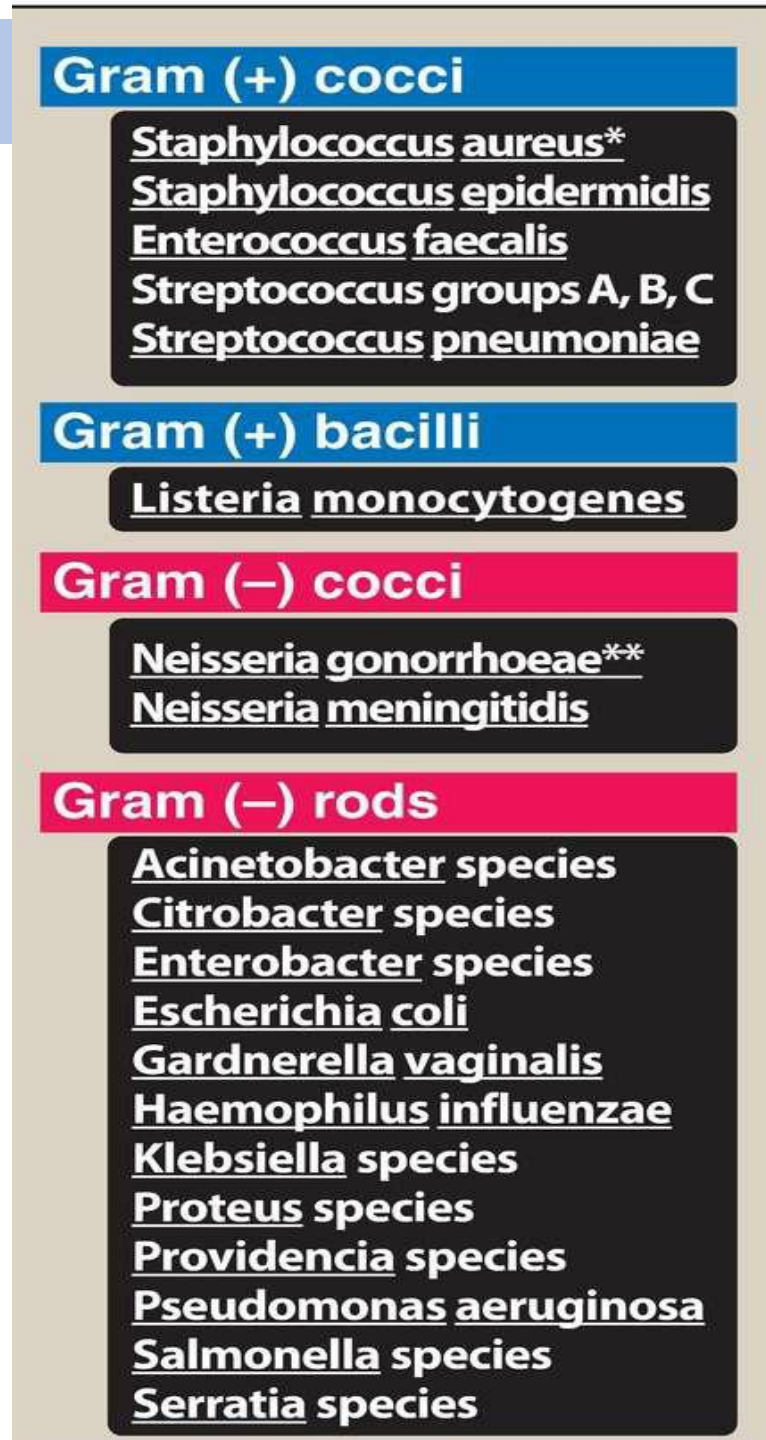
- Aztreonam is administered **intravenously** and is eliminated via **renal tubular secretion**.
- Its half-life is **prolonged** in renal failure.
- **Adverse effects** include **gastrointestinal upset** with possible **superinfection**, **vertigo** and **headache**, and rarely **hepatotoxicity**, **skin rash**
- **NO cross allergenicity** with penicillins.

IV. OTHER BETA-LACTAM DRUGS:

B. Imipenem, Doripenem, Meropenem, and Ertapenem: parenterally

- These drugs are **carbapenems** (chemically different from penicillins but retaining the **beta-lactam ring structure**)





IV. OTHER BETA-LACTAM DRUGS:

B. Imipenem, Doripenem, Meropenem, and Ertapenem: parenterally

- They have wide activity against

1. **Gram-positive cocci** (including some penicillin resistant pneumococci),
2. **Gram-negative rods**,
3. **Anaerobes**.

- For **pseudomonal infections**, they are often used in combination with an **aminoglycoside**.
- MRSA strains of staphylococci are **resistant.**

IV. OTHER BETA-LACTAM DRUGS:

B. Imipenem, Doripenem, Meropenem, and Ertapenem: parenterally

- **Imipenem** is rapidly **inactivated** by renal **dehydropeptidase-**I and therefore it is administered in fixed combination with **cilastatin**, an inhibitor of this enzyme.

- **Cilastatin**

1) **increases the plasma half life of imipenem** and

2) **inhibits** the formation of potentially **nephrotoxic metabolite**.

IV. OTHER BETA-LACTAM DRUGS:

B. Imipenem, Doripenem, Meropenem, and Ertapenem: parenterally

- **Adverse effects of imipenem-cilastatin** include

1. Gastrointestinal distress,
2. Skin rash, and,
3. At very high plasma levels, CNS toxicity (confusion, encephalopathy, seizures).

❑ There is **partial cross allergenicity** with the penicillins.

IV. OTHER BETA-LACTAM DRUGS:

C. Beta-Lactamase Inhibitors

- **Clavulanic acid, sulbactam**, and **tazobactam** are used in fixed combinations with certain **hydrolyzable penicillins**.
- They are most **active** against **plasmid-encoded beta-lactamases** such as those produced by

1. ***Streptococci,***
2. ***Gonococci,***
3. ***E coli,***
4. ***H influenzae.***

IV. OTHER BETA-LACTAM DRUGS:

C. Beta-Lactamase Inhibitors

- **Clavulanic acid, sulbactam**, and **tazobactam**
- They are **NOT good inhibitors** of **inducible chromosomal beta-lactamases** formed by

1. ***Enterobacter,***
2. ***Pseudomonas,* and**
3. ***Serratia*.**

IV. Other Cell Wall Or Membrane-active Agents:

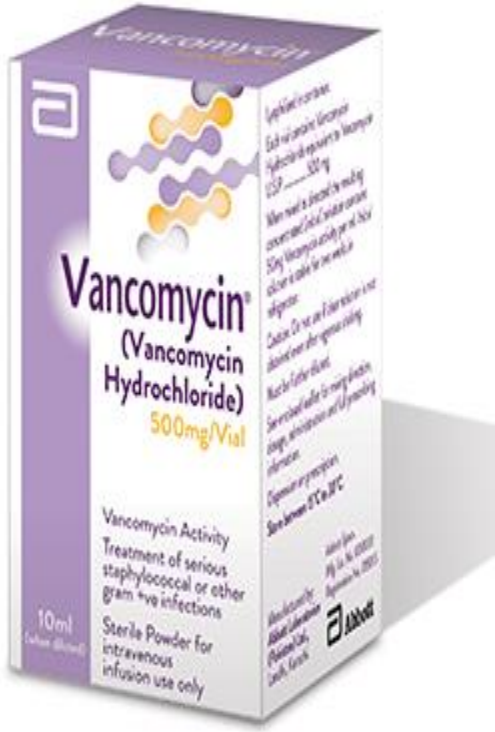
A. Vancomycin

- Vancomycin is a **bactericidal** glycoprotein that **binds** to the ***d-Ala-d-Ala*** **terminal** of the ascent peptidoglycan pentapeptide side chain and **inhibits transglycosylation**.
- This action **prevents elongation** of the peptidoglycan chain and interferes with crosslinking.

IV. Other Cell Wall Or Membrane-active Agents:

A. Vancomycin

- **Resistance** in strains of **enterocci** (vancomycin-resistant enterococci [VRE]) and **staphylococci** (vancomycin-resistant S aureus [VRSA]) **involves a decreased affinity of vancomycin for the binding site**.

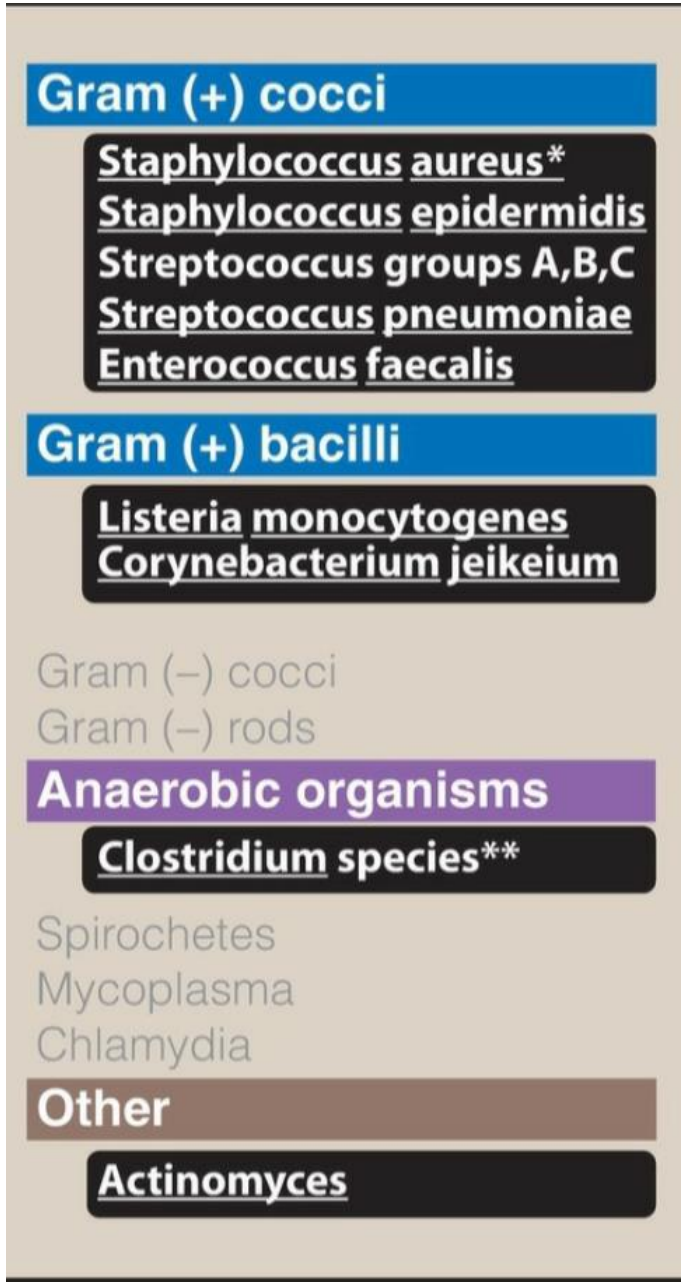


IV. OTHER CELL WALL OR MEMBRANE-ACTIVE AGENTS:

A. Vancomycin

- Vancomycin has a narrow spectrum of activity and is *used for*

1. *Serious infections caused by **drug-resistant gram-positive** **organisms***, including methicillin resistant staphylococci (MRSA)
2. In combination with **ceftriaxone** for treatment of **penicillin-resistant** **streptococcus** **pneumoniae** (PRSP).
3. Vancomycin is a backup drug for treatment of infections caused by **clostridium difficile**.

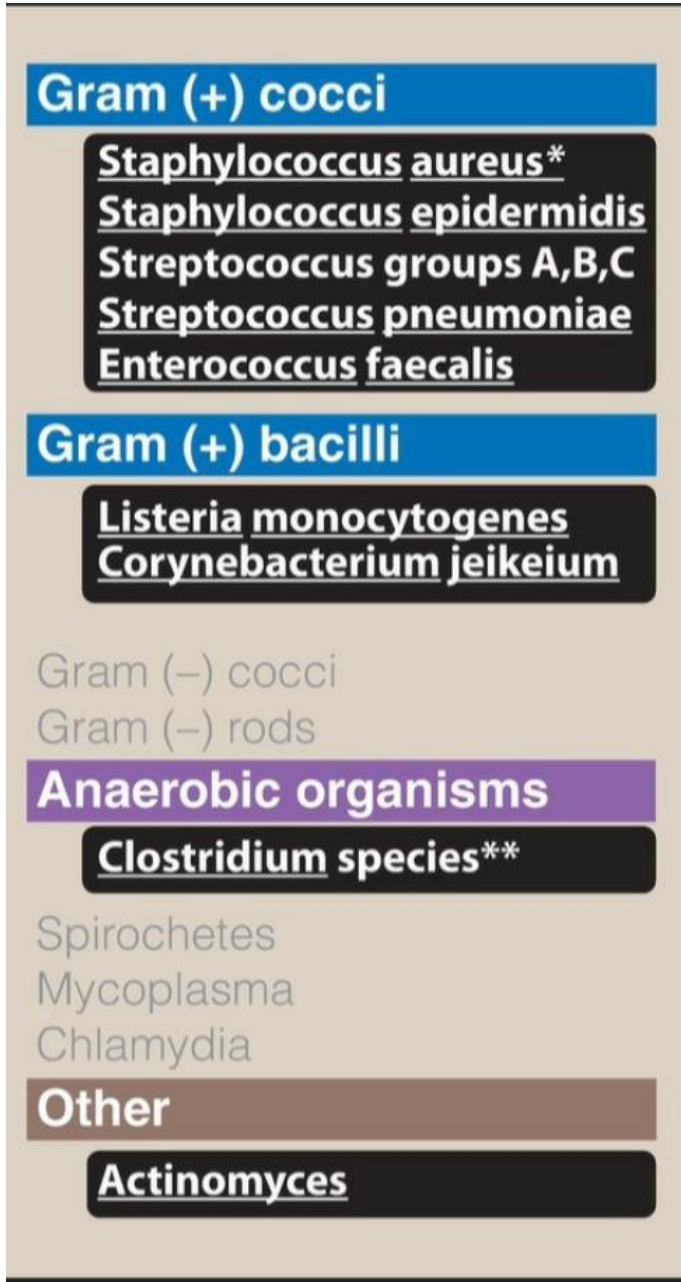


IV. OTHER CELL WALL OR MEMBRANE-ACTIVE AGENTS:

A. Vancomycin

- **Toxic effects of vancomycin** include #

1. Chills, fever,
2. Phlebitis,
3. Ototoxicity, and
4. Nephrotoxicity
5. Rapid intravenous infusion may cause diffuse flushing ("red man syndrome") from histamine release.



IV. Other Cell Wall Or Membrane-active Agents:

B. Fosfomycin

- Fosfomycin is an **antimetabolite inhibitor of cytosolic enolpyruvate transferase**.
- This action **prevents** the formation of **N-acetylmuramic acid, an essential precursor molecule for peptidoglycan chain formation**.

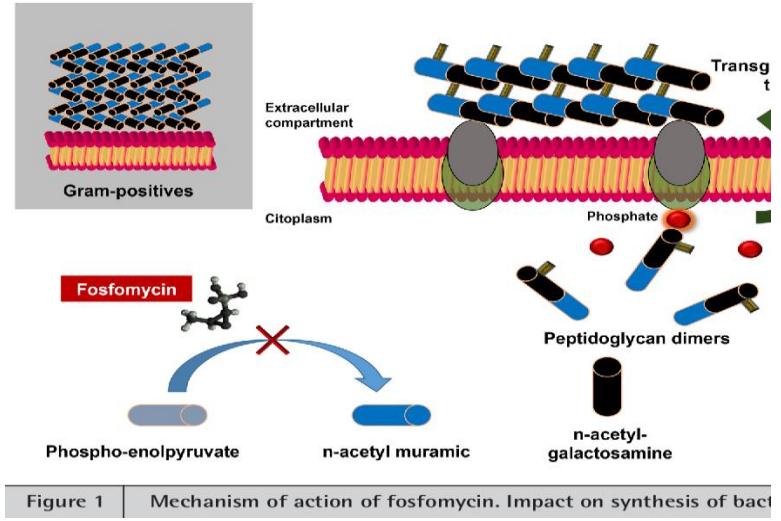


Figure 1 | Mechanism of action of fosfomycin. Impact on synthesis of bact

IV. OTHER CELL WALL OR MEMBRANE-ACTIVE AGENTS:

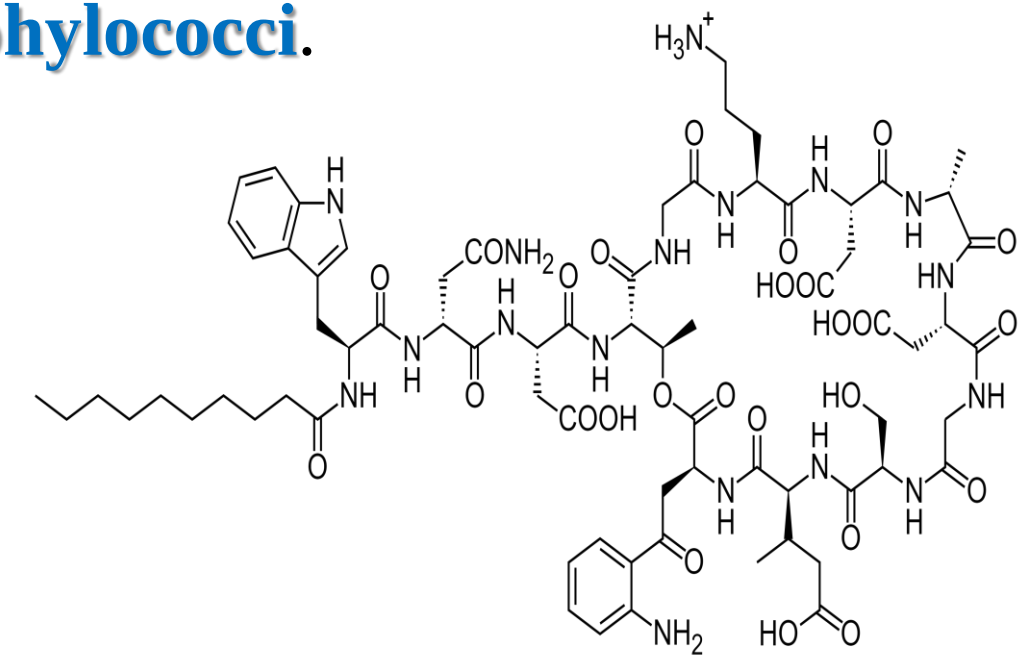
B. Fosfomycin

- Fosfomycin is ***excreted*** *by the kidney*, with urinary *levels exceeding the minimal inhibitory concentrations* (MICs) ,So It is **indicated for urinary tract infections** caused by ***E. coli*** or ***Enterococcus faecalis***.
- It maintains high concentrations in the urine over several days, allowing for a **one-time dose**
- **Adverse effects** include diarrhea, vaginitis, nausea, and headache.

IV. Other Cell Wall Or Membrane-active Agents:

C. Daptomycin

- Daptomycin is a **bactericidal**, a novel cyclic lipopeptide with spectrum similar to vancomycin **but active against vancomycin-resistant strains of enterococci and staphylococci**.



Gram (+) cocci

- Enterococcus faecalis
- Enterococcus faecium
- Staphylococcus aureus (MRSA and MSSA)
- Streptococcus pneumoniae (*penicillin* resistant)
- Streptococcus pyogenes

Gram (+) bacilli

- Corynebacterium jeikeium

Gram (–) cocci
Gram (–) rods
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other

IV. Other Cell Wall Or Membrane-active Agents:

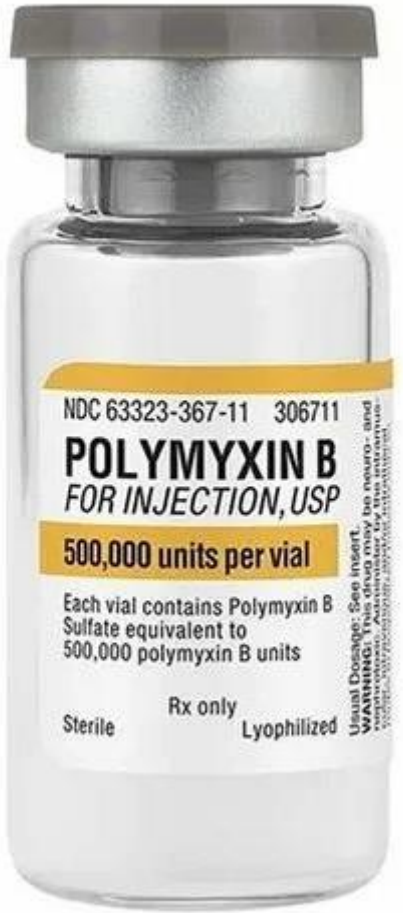
C. Daptomycin

- Daptomycin **is indicated for the treatment** of **complicated skin and skin structure infections** and **bacteremia** caused by **S. aureus**.
- Daptomycin is **inactivated by pulmonary surfactants**; thus, it should ***never*** be used in the treatment of **pneumonia**.
- **Creatine phosphokinase** should be monitored since daptomycin may cause **myopathy**.

Iv. Other Cell Wall Or Membrane-active Agents:

D. 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 ultimately cell death.

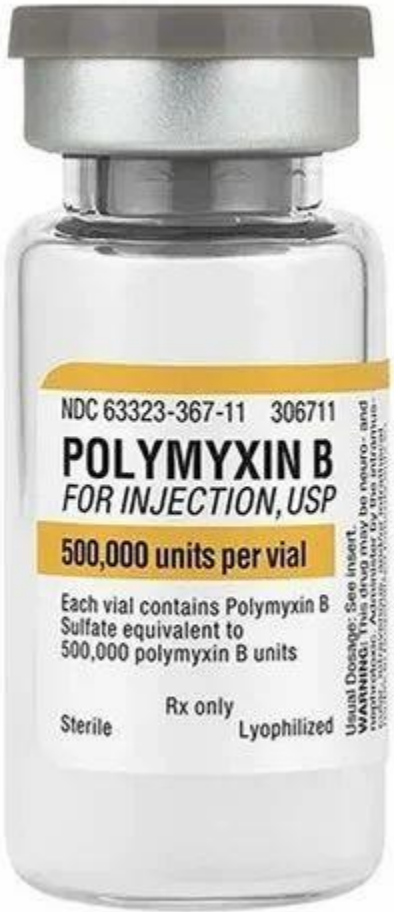


Iv. Other Cell Wall Or Membrane-active Agents:

D. POLYMYXINS

- Polymyxins are **concentration-dependent bactericidal** agents with activity against

1. **P. aeruginosa,**
2. **E. coli,**
3. **K. pneumoniae,**
4. **Acinetobacter species, and**
5. **Enterobacter species.**



IV. Other Cell Wall Or Membrane-active Agents:

D. POLYMYXINS

- Only two forms of polymyxin are in clinical use today,

1. **Polymyxin B**
2. **Colistin** (polymyxin E).

- **Polymyxin B** is available in **parenteral**, **ophthalmic**, **otic**, and **topical** preparations.

IV. Other Cell Wall Or Membrane-active Agents:

D. POLYMYXINS

- **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 for a long time, due to the increased **risk** of **nephrotoxicity and neurotoxicity** (slurred speech, muscle weakness) when used systemically.