Cell wall synthesis inhibitors Part 2

Pharmacology 3

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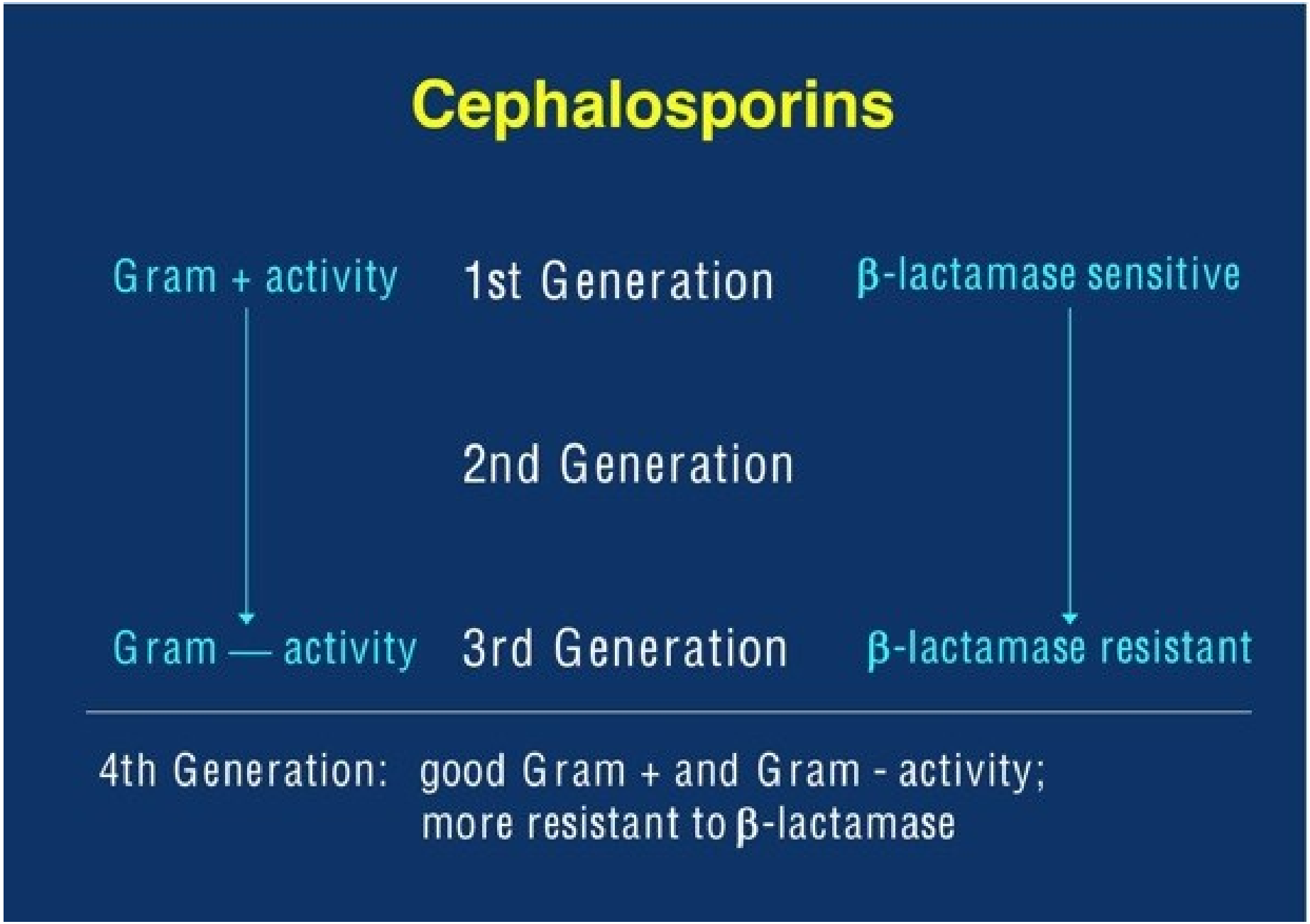
II. CEPHALOSPORINS

prefix : Cef or Ceph

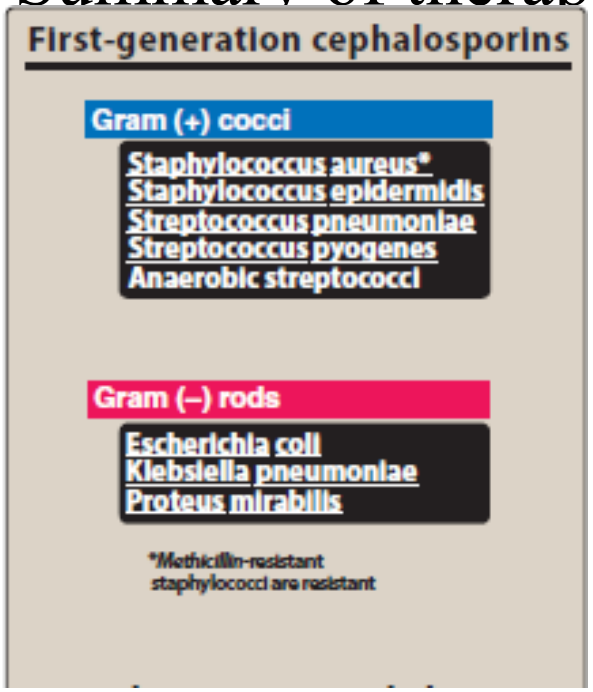
- A wider spectrum than penicillins.
- More resistance to B-lactmases enzyme.
- Eliminated by kidney.
- More expensive than penicillins.

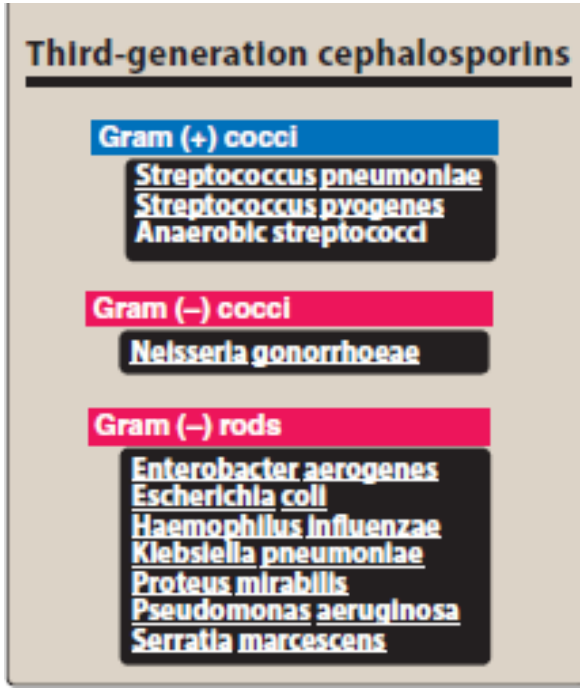
Cephalosporins



4th Generation: good Gram + and Gram - activity;
more resistant to β-lactamase

Summary of therapeutic applications of cephalosporins

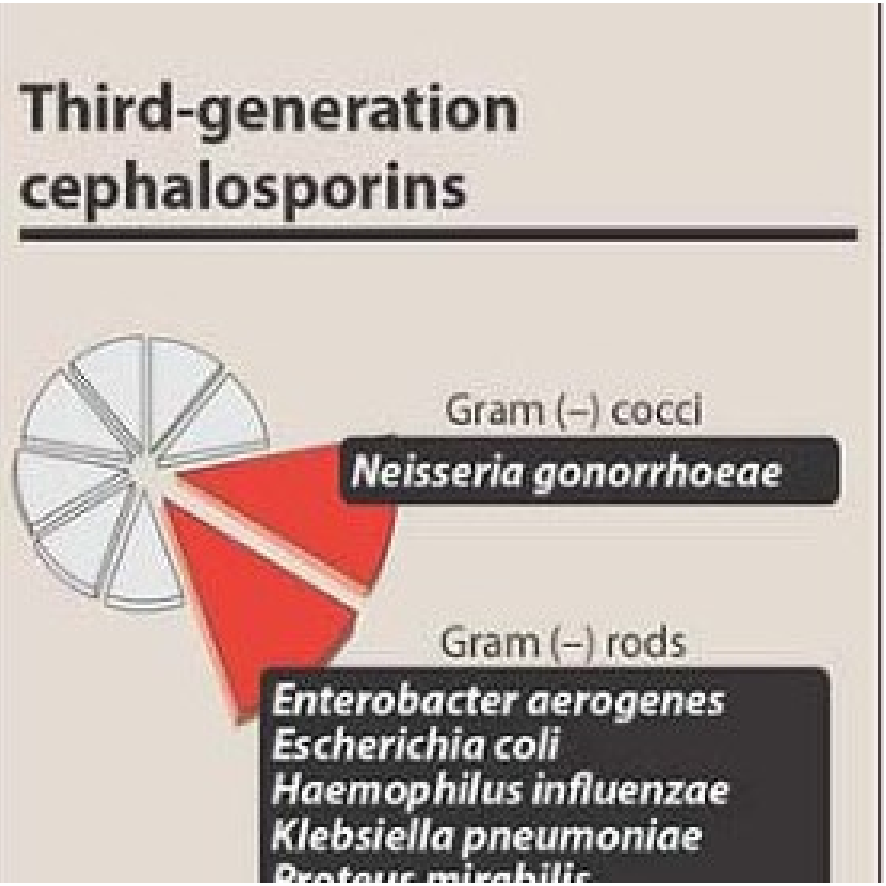




Cephalosporins

subgroups	indication
First generation (Cefazolin, cephalexin)	surgical prophylaxis
Second generation (Cefaclor, cefuroxime, and cefprozil)	active against H influenzae, sinusitis, otitis, and lower respiratory tract infections
Third generation (ceftriaxone, cefotaxime, cefpodoxime, cefdinir, cefixime)	Meningitis, endocarditis, empirical therapy of sepsis in both the immunocompetent and the immunocompromised patient
Fourth generation (Cefepime)	Pneumonia, Empiric therapy in febrile neutropenic patients, UTI
Advanced generation-5th (Ceftaroline)	complicated skin and soft tissue infections and community-acquired pneumonia

Third generation Cephalosporins



Adequate therapeutic levels in the CSF, regardless of inflammation, are achieved only with the **third-generation cephalosporins.**

Are effective in the treatment of neonatal and childhood **meningitis** caused by H.influenzae**.** meningococcal meningitis.

Third-generation cephalosporins must be used with caution, as they are associated with significant "**collateral damage**," including the induction of antimicrobial resistance and development of Clostridium difficile infection.

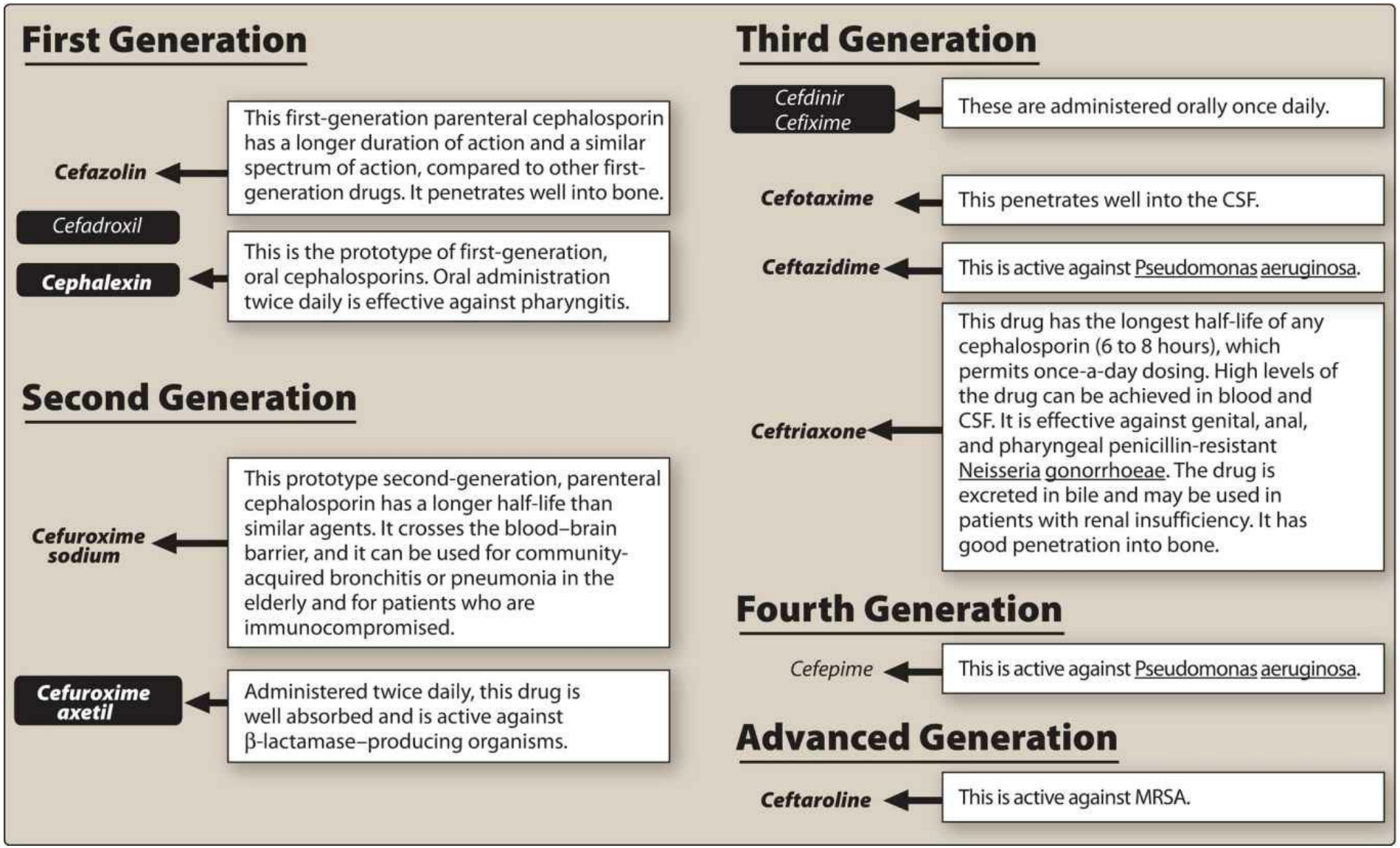
Cephalosporins Active against Methicillin-Resistant Staphylococci (advanced generation; 5th generation)

- **Ceftaroline.**

- The unique structure allows ceftaroline to bind to PBPs found in MRSA and penicillin-resistant Streptococcus pneumoniae.

- Ceftaroline is currently approved for the treatment of complicated skin and soft tissue infections and community-acquired pneumonia.

Therapeutic advantages of some clinically useful cephalosporins




Claforan® Sterile
cefotaxime for injection, USP
1g
FOR IM/IV ADMINISTRATION
sanofi aventis


Ceftriaxone Sandoz®
1 g
Ceftriaxone 1 g
(as Ceftriaxone Sodium)
Inj. B.P.
1 vial / flacon-ampoule / frasco ampolla
i.m./i.v.
SANDOZ


Fortum™
2 grams
Ceftazidime 2 grams
(as pentahydrate)
for injection
2 grams
gsk GlaxoSmithKline
Fortum™
1 gram
Ceftazidime 1 gram
(as pentahydrate)
for injection
1 gram
gsk GlaxoSmithKline

Pharmacokinetics

1. Administration:

•Many of them must be administered IV or IM because of their poor oral absorption (however some can be given orally)

2. Distribution:

•CPNs distribute very well into body fluids but not to CSF.

•**Cefazolin** penetrates well into most tissues. It is a drug of choice for surgical prophylaxis including orthopedic surgery because of its ability to penetrate bone.

•Only **ceftriaxone** or **cefotaxime** achieve therapeutic levels in the CSF and have become agents of choice for meningitis.

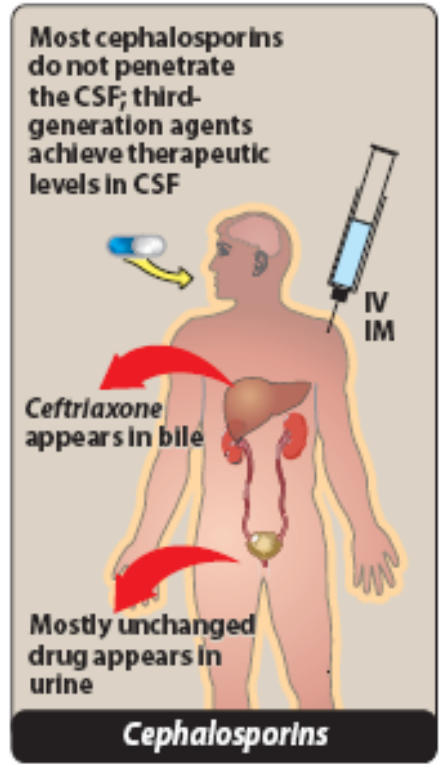
•All CPNs cross the placenta.

3. Elimination:

•Tubular secretion and/or glomerular filtration

•Doses must be adjusted in cases of renal failure

•Exception: **Ceftriaxone**, excreted through the bile…..Employed in patients with renal insufficiency



Adverse effects

✓Hypersensitivity reaction

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.**

Cephalosporins should be avoided or used with caution in individuals with penicillin allergy.

Patients who have had an **anaphylactic response**, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins **should not receive cephalosporins**.

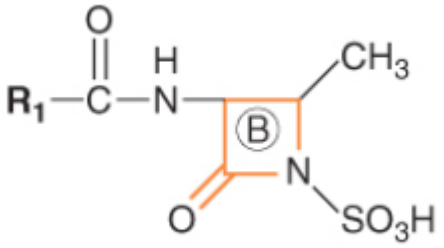
Adverse effects

- ✓pain after injection.
- ✓Diarrhea.

Some have anti-Vitamin K effect (bleeding).

Other B-Lactam Antibiotics- **Monobactams**

- They are drugs with a monocyclic β-lactam ring.
- Their spectrum of activity is limited to aerobic Gram-negative organisms (including *P aeruginosa*).
- **Aztreonam** is resistant to the action of B-lactamases.
- It is administered either IV or IM. Every 8 hrs
- this drug **may offer a safe** alternative for treating patients who are allergic to penic &/or cephalosporins.



Other B-Lactam Antibiotics- **Carbapenems**

- broad-spectrum B-lactam antibiotics.
- Examples: **Doripenem, Imipenem, Meropenem, Etrapenem**.
- They resist hydrolysis by most B-lactamases.
- Carbapenems are active against P aeruginosa and Acinetobacter species (except ertapenem).
- These agents have a very broad spectrum of action and are usually restricted to use in hospitals for treatment of serious infections.

Other B-Lactam Antibiotics- **Carbapenems**

- All are cleared renally, and the dose must be reduced in patients with renal insufficiency.
- Excessive levels of imipenem in patients with renal failure may lead to seizures.
- Imipenem undergoes cleavage by a **dehydropeptidase** found in the brush border of the proximal renal tubule. This enzyme **forms an inactive metabolite that is potentially nephrotoxic.**
  - Imipenem is formulated with cilastatin, which prevents hydrolysis of imipenem by renal dehydropeptidase.

Glycopeptide Antibiotics -

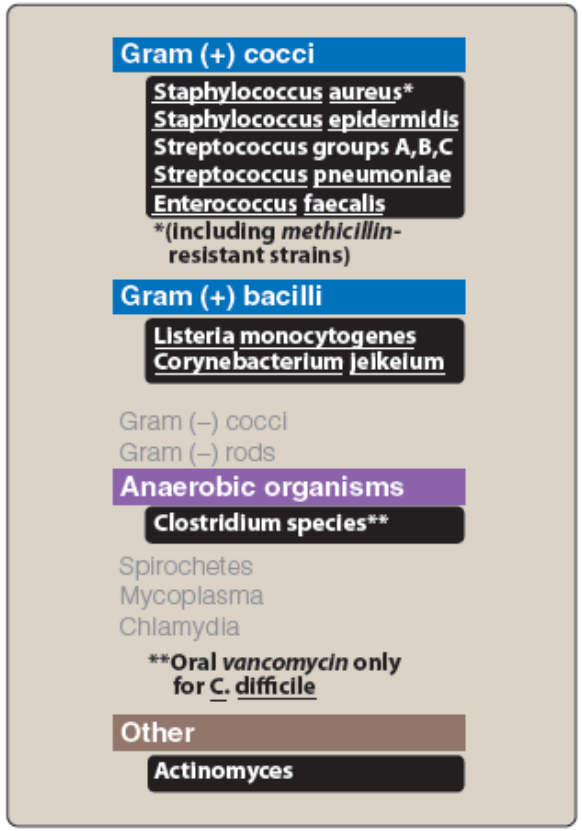
- **Vancomycin**

Vancomycin inhibits synthesis of bacterial cell wall by binding to the D-Ala-D-Ala terminus preventing further crosslinking.

- IV for systemic infections
- Not absorbed after oral administration (the use of the oral formulation is limited to the treatment of severe antibiotic-associated C. difficile colitis.)

Narrow spectrum(G+ ve)

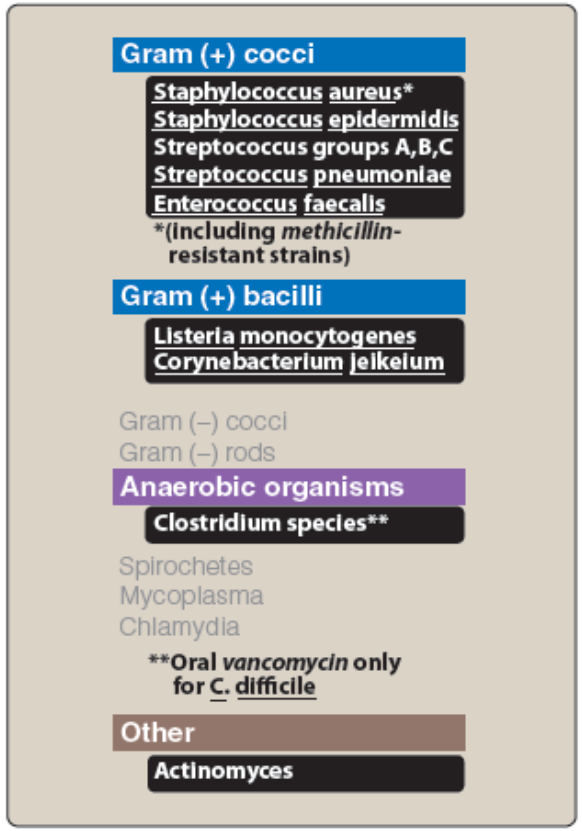
Bactericidal /not B-lactam.



Glycopeptide Antibiotics -

- **Vancomycin**
- **Orally:- every 6 hrs** for refractory pseudomembranous colitis due to C. difficile.
- **Slow IV infusion (1-2 hrs)** for treatment of systemic infections or prophylaxis.
  - is effective against MRSA.(DOC)
  - Vancomycin in combination with A.G alternative regimen to treatment of enterococcal endocarditis.

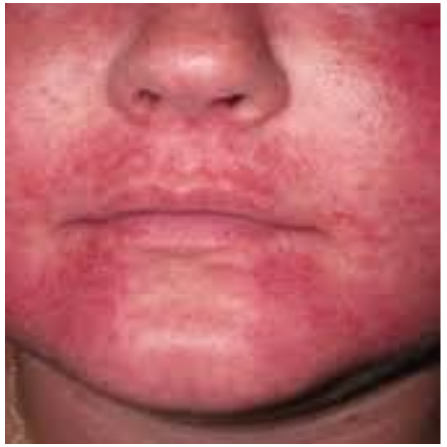
- **Teicoplanin** is a glycopeptide antibiotic that is very similar to vancomycin in mechanism of action and antibacterial spectrum.



Vancomycin

- S.E:-
- 1-Flushing (**red man syndrome**) with a **rapid** infusion.(**More common**)
- Prevented by prolonging the infusion period OR pretreatment with an antihistamine such as diphenhydramine.

- 2- phlebitis(inflammation of vein) at site of injection.
- 3- ototoxicity & nephrotoxicity (rare) but increased risk when administered with A.G.



Other Cell wall synthesis inhibitors

Fosfomycin:

Inhibits the formation N -acetylmuramic acid precursor.

- **Therapeutic use :** It is indicated for urinary tract infections caused by E. coli or E. faecalis.
- Rapidly absorbed after oral administration & distributes well to the kidneys, bladder, and prostate

Bacitracin:

Inhibits the carrier that transfers peptidoglycan subunits to the growing cell wall.

- It is highly nephrotoxic when administered systemically and is only used topically

Cell membrane active agents

- **Daptomycin** – is a new lipopeptide antibacterial drug.
- Binds to cell membrane causing depolarization and rapid cell death (doesn't work on cell wall).

- **Therapeutic use:**
- for treating infections caused by resistant gram-positive organisms, including MRSA and *vancomycin* resistant enterococci (VRE)
- is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus,
- **Adverse effect :**
  Myopathy and creatine phosphokinase levels elevation.

Questions??