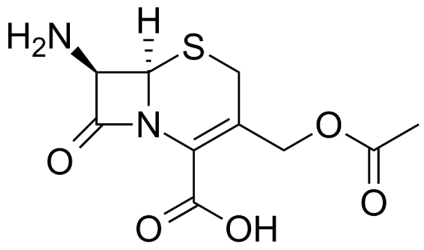
Cephems;
Cephalosporins & Cephamycins

Introduction

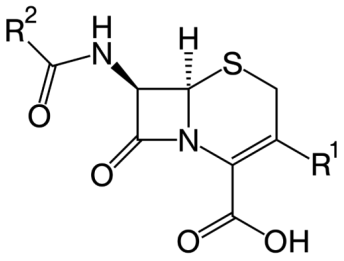
- **Cephems** are a sub-group of β-lactam antibiotics- it includes **cephalosporins & cephamycins**.
- Cephalosporins are β-lactam antibiotics closely related structurally and functionally to penicillins.
  - Have the same mechanism of action & affected by the same resistance mechanisms.
- Cephalosporins produced semisynthetically by the chemical attachment of **side chains** to **7-aminocephalosporanic acid**.
- **More stable to many bacterial β-lactamases than penicillins →**
  - Have a broader spectrum of activity.
- Cephalosporins can be classified into **five major groups** or generations, depending on the **spectrum of antimicrobial activity & resistance to β-lactamases.**
- **Cephamycins are a group of β-lactam antibiotics very similar to cephalosporins- sometimes classified as cephalosporins.**
- **Both cephalosporins & cephamycins sometimes called cephems.**

Cephems; Cephalosporins & Cephamycins

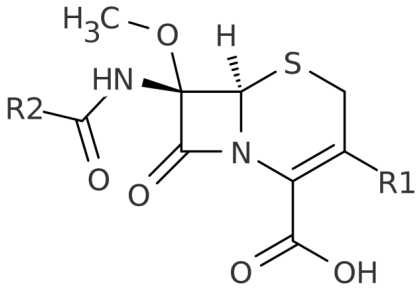
- The core of the basic structure consists of a two ring system which includes a **β-lactam ring condensed with dihydrothiazine ring**.



7-aminocephalosporanic acid



Core structure of the cephalosporins



Core structure of the cephamycins

Possess a methoxy group at the 7-alpha position

Very efficient antibiotic against anaerobic microbes.

Ex. Cefoxitin, Cefotetan, Cefmetazole

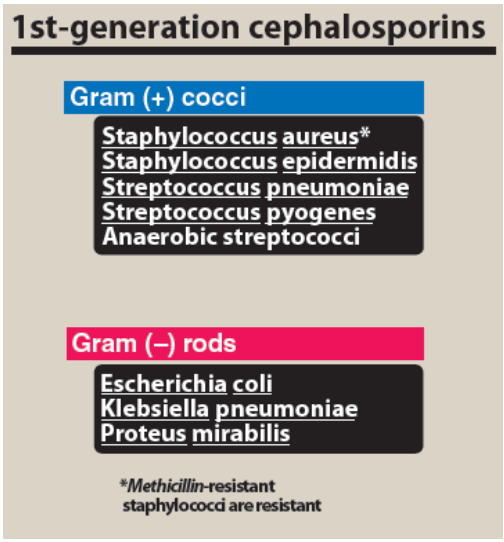
Classification of Cephalosporins

1st Generation "FA/PHA"	2nd Generation "Everything Else"	3rd Generation "ONE/TEN/IME"	4th Generation "PI"	5th Generation "ROL"
* CEFAZOLIN CEFADROXIL * CEPHALEXIN CEPHALOTHIN CEPHAPIRIN CEPHRADINE	CEFOXITIN CEFOTETAN CEFMETAZOLE CEFPROZIL CEFACLOR CEFUROXIME	* CEFTRIAXONE CEFTIBUTEN * CEFOTAXIME * CEFTAZIDIME CEFPODOXIME CEFIXIME CEFDINIR MOXALACTAM	* CEFEPIME CEFPIROME	* CEFTAROLINE CEFTOBIPROLE

			Pseudomonas	MRSA
+++	++	+	++	++
-	- -	- - -	- - -	- - -
1st Gen	2nd Gen	3rd Gen	4th Gen	5th Gen
Gram +		Gram -	Pseudomonas	MRSA

I. First generation

- Agents: **Cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, & cephradine**
- **Penicillin G substitutes.**
- Have good activity against gram-positive cocci.
- They are resistant to the **staphylococcal penicillinase (they cover MSSA).**
- **Modest activity** against gram-negative microorganisms → Active against ***Proteus mirabilis*, *E. coli*, and *Klebsiella pneumonia*** (acronym PEcK has been suggested).

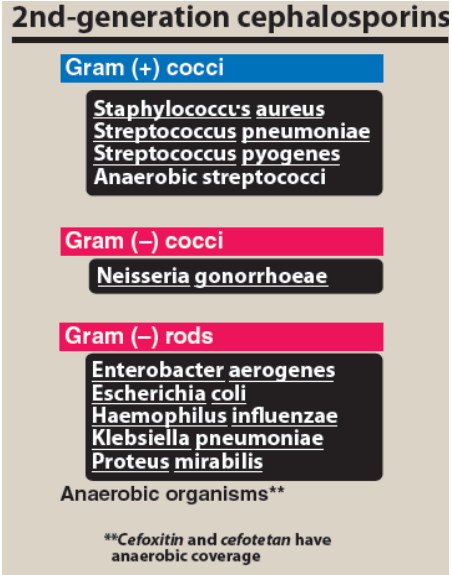


I. First generation…. *Continued*

- Cefazolin penetrates well into most tissues→ the drug of choice for **surgical prophylaxis**.
  - Cefazolin does not penetrate the central nervous system and can't be used to treat meningitis
- Orally effective drugs (Cephalexin) are used in treating susceptible bacteria that cause:
  - Skin and soft tissue.
  - Uncomplicated UTI.

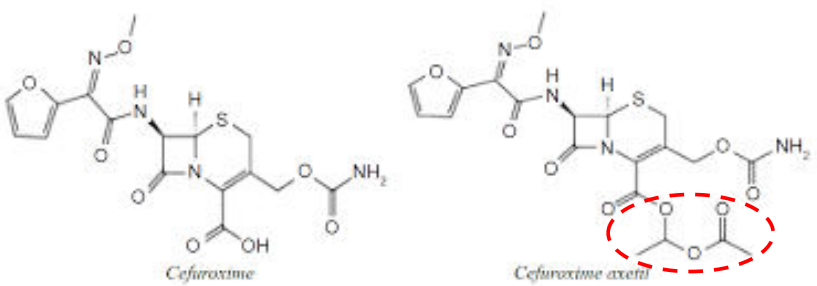
II. Second Generation

- **Agents:**
  - **Cephalosporins**: cefaclor, cefamandole, cefonicid, cefuroxime, cefprozil, loracarbef & ceforanide
  - **Cephamycins:** cefoxitin, cefmetazole and cefotetan.
- Display greater activity against gram-negative microorganisms:
  - ***H. influenzea***
  - **Enterobacter areogenes**
  - **Some *Niesseria* species**
- **Activity against gram-positive organisms is weaker** (acronym **HENPEcK** has been suggested with the second generation's increased coverage).
- Antimicrobial coverage of **cefotetan and cefoxitin** also includes the anaerobe, *Bacteroides fragilis*.
  - **However, neither is the preferred treatment because of the increasing prevalence of resistance amongst to both agents.**
- Like 1st generation: none is active against **enterococci or *P. aeuroginosa***.



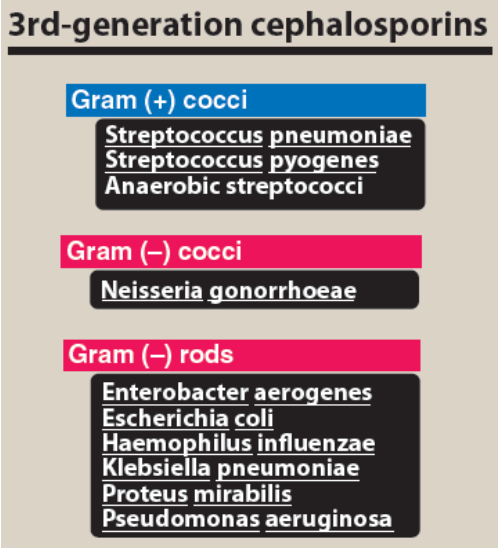
II. Second Generation …. *Continued*

1. Used to treat otitis media, sinusitis & lower RTI (*H. influenza & B. catarrhallis*)
2. **Cefoxitin, cefotetan or cefmetazole**: used to treat mixed anaerobic infections such as **peritonitis or diverticulitis**.
3. **Cefuroxime**: used in treating community acquired pneumonia, particularly in cases where β-lactamase- producing *H. influenzae* or *K. pneumoniae* is a consideration.
   - Cefuroxime axetil is an **acetoxyethyl ester prodrug** of cefuroxime which is effective when **taken by mouth.**



III. Third Generation

- **Agents:**
  - Ceftriaxone, cefotaxime, ceftazidime, cefoperazone, cefdinir, cefixime, ceftibutin, etc.
- More effective against gram-negative bacteria than the first and second generations.
- They are usually effective against bacteria that may be resistant to previous generations of cephalosporins.
  - Inferior to first-generation cephalosporins against MSSA.
- Important for **treating infectious diseases** (Intra-abdominal infection, CNS infections, skin and soft tissue infections, UTIs, lower RT infections, Gynecological infections, Bone & joint infections, Sepsis)



- **Enhanced activity against gm -ve bacilli, most *enteric organisms* and *Serratia marcescens*.**
- Active against ***B-lactamase producing strains of haemophilus and Neisseria spp.***

III. Third Generation …. *Continued*

- Able to cross the BBB -**Ceftriaxone and cefotaxime** are agents of choice in treating meningitis.
  - Most widely used parenteral 3rd-generation cephalosporins is **ceftriaxone**.
  - Vancomycin and a 3rd-generation cephalosporin recommended as initial therapy for meningitis until culture susceptibility results are available.
  - Ceftriaxone offers convenient **once daily dosing** to treat most infections.
- **Ceftazidime** active against *P. aeureginosa*→ resistance is increasing and appropriate use should be evaluated on a case-by-case basis.
- Third generation cephalosporins can produce "collateral damage,"→ induction and spread of **antimicrobial resistance** [fluoroquinolones also cause collateral damage.]

IV. Fourth Generation

- **Agents:**
  - Cefepime, cefpirome.
- Cefepime must be administered parenterally.
- Has a wide antibacterial spectrum→
  - Active against **streptococci and staphylococci (only MSSA).**
  - Effective against **aerobic gram-negative organisms**
    - ***Enterobacter species***
    - ***E. coli***
    - ***K. pneumonia***
    - ***P. mirabilis***
    - ***P. aeruginosa***

- When treating ***P. aeruginosa***, clinicians should refer to their local antibiograms (laboratory testing for sensitivity of the isolated bacterial strain to different antibiotics).

V. Fifth Generation

- **Agents:**

  5th generation cephalosporins→ **ceftaroline, ceftobiprole**.

- Known as **advanced- generation cephalosporins**.
- Activity is similar to 3rd-generation cephalosporins, except it is **not effective** against ***Pseudomonas aeruginosa***.
- Used to treat bacteria, including:
  - **Resistant Staphylococcus aureus (MRSA).**
  - **Streptococcus species resistant to penicillin antibiotics.**

Resistance to Cephalosporins

- Resistance to cephalosporins is similar to penicillins.

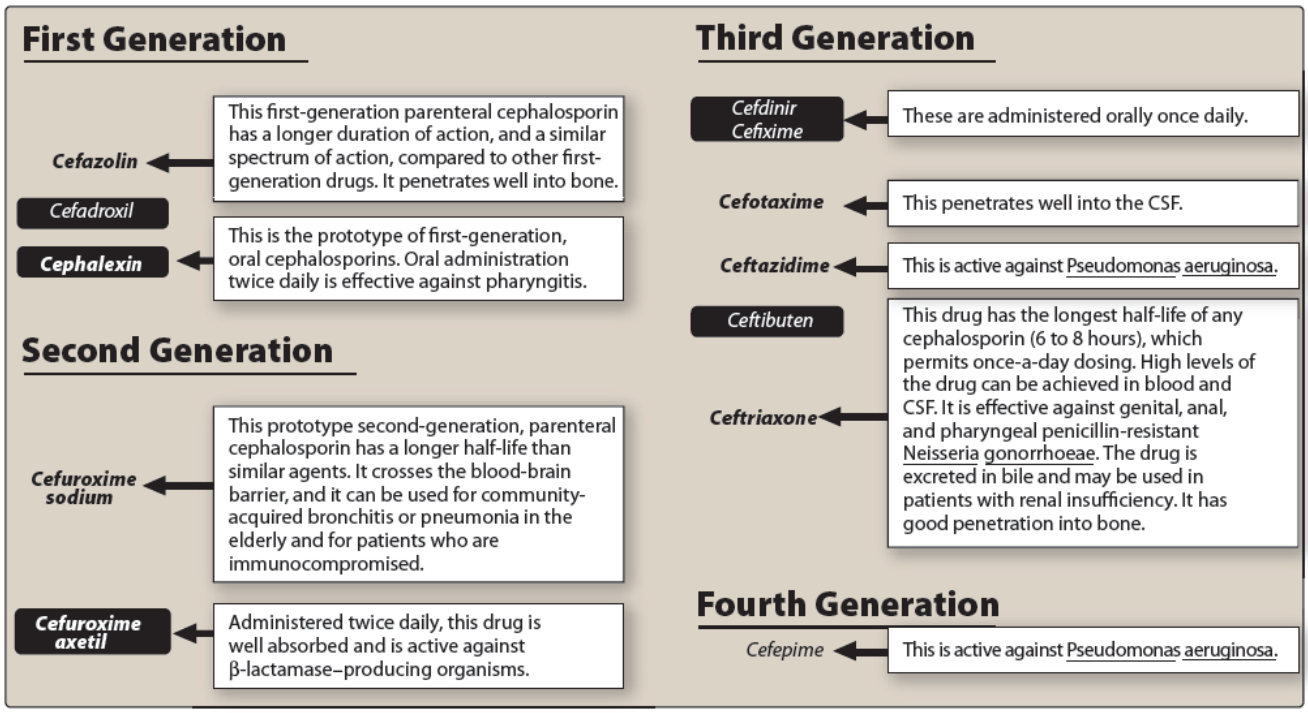
Pharmacokinetics of Cephalosporins

1. Administration: Many of the cephalosporins must be administered IV or IM because of their poor oral absorption.
  - Exceptions noted in next slides.

2. Distribution: **All cephalosporins distribute very well into body fluids.**
  - Adequate therapeutic levels in the CSF - only with select a few cephalosporins.
    - **Ceftriaxone or cefotaxime → treatment of neonatal and childhood meningitis caused by *H. influenza*.**
  - **Cefazolin** finds application as a **single prophylaxis dose** prior to surgery because of its **1.8-hour half-life and its activity against penicillinase-producing S. aureus**.
    - Additional intra-operative doses may be required if the surgical procedure lasts longer than 3 hours.
  - **Cefazolin** is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone.
  - **All cephalosporins cross the placenta.**

3. Elimination:
  - Biotransformation by the host is not clinically important.
  - Elimination occurs through tubular secretion and/or glomerular filtration.
    → Dose adjusted in severe renal failure (Exception **ceftriaxone** excreted in bile to feces- use in cases of renal insufficiency).

Summary of therapeutic advantages of some clinically useful cephalosporins



- **Drugs administered orally are shown in reverse type.**
- **More useful drugs shown in bold.**

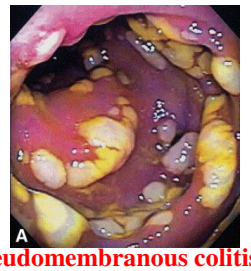
Adverse effects of cephalosporins

- **Allergy:** Patients who have had an **anaphylactic response, stevens-Johnson syndrome, toxic epidermal necrolysis to penicillins should not receive cephalosporins.**
  - ❖ Avoid cephalosporins or use with caution in individuals who are allergic to penicillins (**8 to 10% cross-sensitive**).
  - ❖ **Cross-reactivity between penicillin and cephalosporins** determined by similarity in the side chain, not the β-lactam structure.
  - ❖ Highest allergic cross sensitivity is between penicillin and 1st generation cephalosporins.
  - ❖ **Symptoms of anaphylaxis:** hives, flushed skin, swollen tongue and throat, breathing difficulties, low blood pressure, rapid or weak pulse, nausea or vomiting, diarrhea, dizziness, fainting.

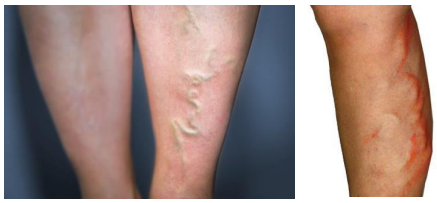
Adverse effects of cephalosporins … *continued*

- Pain if **given IM, thrombophelebitis if given IV**
- Renal toxicity.
- Hypo-prothrombinemia.
- Disulfiram like reaction.
- **Superinfection-**
  - **Yeast infection or oral thrush.**
  - One serious side effect is ***C. difficile*** infection.
    - Occurs after a long course of antibiotics
    - Can be life-threatening
    - Symptoms: watery diarrhea, abdominal pain, fever, nausea, ↓ appetite…
      - **Prevent stomach upset and diarrhea by:**
        - **Probiotics**, add good bacteria to your digestive tract.
        - **Follow instructions for medication**→ antibiotics should be taken with food vs. should be taken on an empty stomach.
        - **Avoid foods that produce stomach upset** (spicy or greasy foods).

Oral thrush



Pseudomembranous colitis (Clostridium difficile)

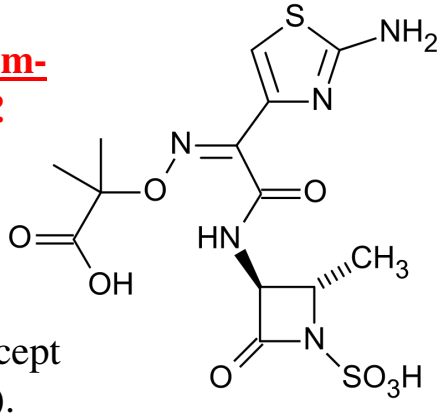


Thrombophelebitis

OTHER β-LACTAM ANTIBIOTICS

Monobactams: Aztreonam (Only commercially available monobactam)

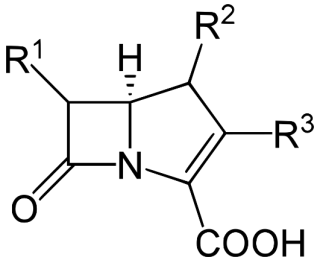
- Disrupt bacterial cell wall synthesis- the β-lactam ring is not fused to another ring.
- Spectrum of activity is limited to **aerobic gram-negative rods**, **(Enterobacteriaceae)** including ***P. aeruginosa.***
- Has no activity against gram-positive bacteria or anaerobes.
    - Cannot be used alone in empiric therapy
    - Resist the action of most β-lactamases except extended-spectrum β-lactamases (ESBLs).



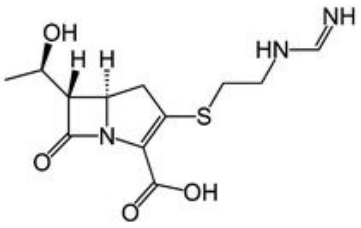
- Given IV or IM and excreted in urine (accumulate in renal failure).
- Shows little cross-reactivity with other β-lactam antibiotics.
- ADRs: phlebitis, skin rash, and abnormal liver function tests.
- **Low immunogenic potential-** little cross-reactivity with antibodies induced by other β-lactams- a safe alternative in patients allergic and cannot tolerate penicillins and/or cephalosporins.

Carbapenems

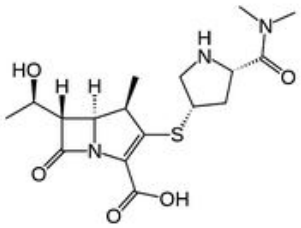
- **Synthetic β-lactam antibiotics….**
- Sulfur atom of the thiazolidine ring in penicillins has been externalized and replaced by a carbon atom.
- **Agents:** Imipenem, meropenem, doripenem and ertapenem.



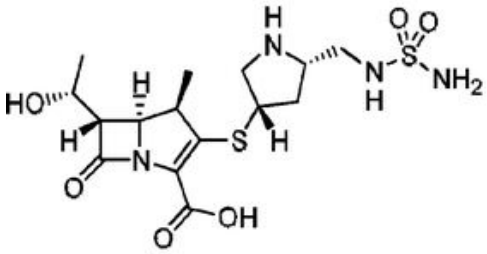
Backbone of carbapenems



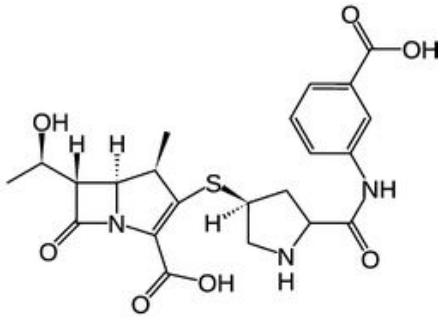
imipenem



meropenem



doripenem

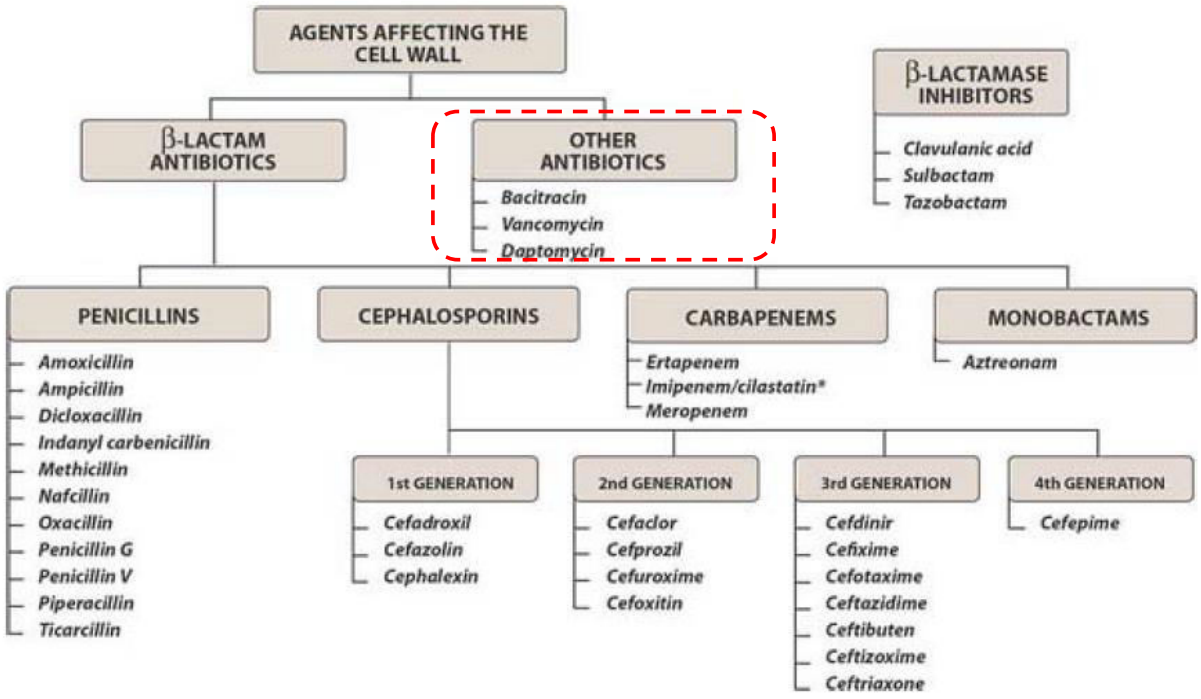


ertapenem

Imipenem

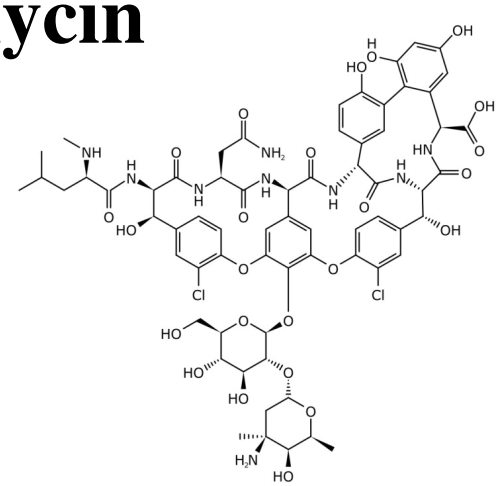
- **Resists hydrolysis by most to β-lactamses -Wide spectrum**
  - Resists most β-lactamases producing bacteria, gram **-ve** rods, including ***P. aeruginosa*****,** gram **+ve** organisms, and anaerobes)→ Used in empiric treatment….
    - Imipenem drug of choice for enterobacter infections
    - **Meropenem and doripenem** have similar spectrum.
    - **Ertapenem** does not cover ***P. aeruginosa, Enterococcus species and Acinetobacter species***
- **Given parenteral via IV or IM**
- Imipenem rapidly metabolized by **dehydropeptidase in brush border of the proximal renal tubule**- nephrotoxic metabolite.
  - **Cilastatin a peptidase inhibitor→ blocks renal dehydropeptidase → increases plasma half-life & inhibits nephrotoxic metabolite formation.**
  - **Other carbopenemes do not require co-administration of cilistatin.**
- ADE: GI distress, skin rash, CNS toxicity (confusion, encephalopathy and seizures)- Partial cross allergenicity with penicillins

Summary of Antimicrobial Agents Affecting Cell Wall Synthesis



***Cilastatin* is not an antibiotic but a peptidase inhibitor that protects *imipenem* from degradation.**

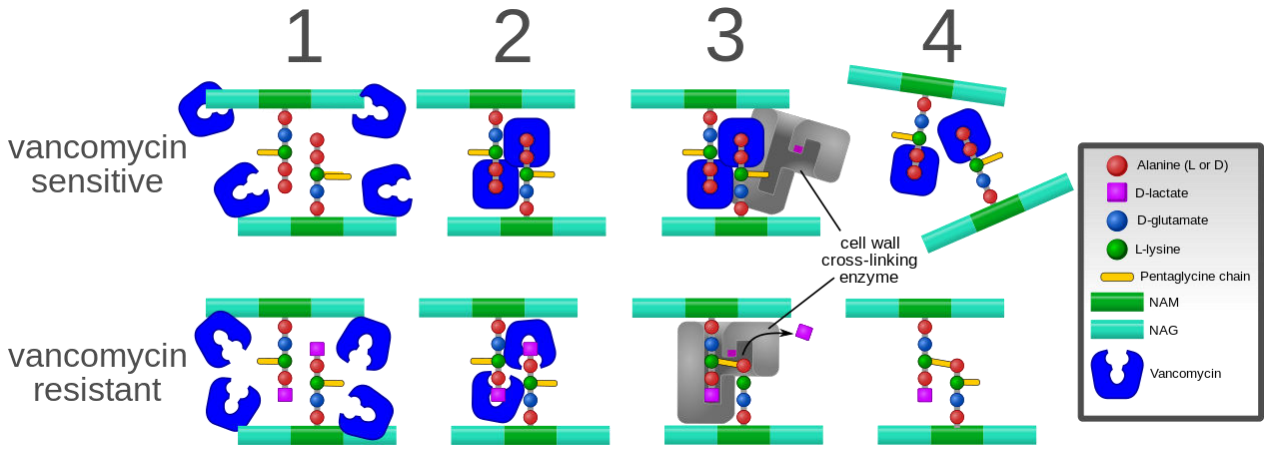
Vancomycin



- **Tricyclic glycopeptide –**
- Active only against gram-positive bacteria, particularly staphylococci.
- No activity against gram-negative organisms
- Effective against multiple drug resistant organisms, such as MRSA and enterococci.

- Inhibits synthesis of **bacterial cell wall phospholipids** and **peptidoglycan polymerization** in a time-dependant fashion by binding to the D-Ala-D-Ala side chain of the precursor pentapeptide (see next slide)
- Poorly absorbed from the intestines.
- Slow IV infusion (60–90 minutes) of vancomycin is employed for treatment of systemic infections or for prophylaxis.
- Metabolism of the drug is minimal, and 90 to 100 percent is excreted by glomerular filtration (adjust in renal failure).

Mechanism of Vancomycin Action & Resistance



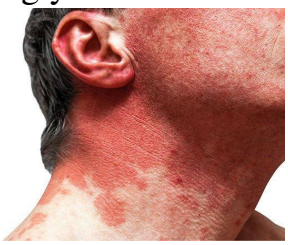
- The diagram shows one of two ways vancomycin acts against bacteria (inhibition of cell wall cross-linking) and one of many ways how bacteria becomes resistant.
- Vancomycin is added to bacterial environment while it is synthesizing new cell wall.
- Vancomycin recognizes and binds to the two D-ala residues on the end of the peptide chains.
- Resistant bacteria→ last D-ala replaced by D-lactate→ vancomycin cannot bind.
- In the sensitive bacteria, cross-links cannot be formed and the cell wall falls apart.
- In the resistant bacteria, stable cross-links are formed.
- This weakens the cell wall and damages the underlying cell membrane.
- Resistance also occurs via plasmid-mediated changes in permeability to the drug.

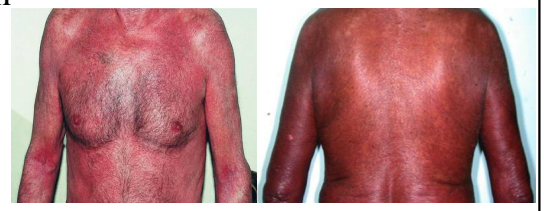
Clinical Uses of Vancomycin

1. The drug is lifesaving in treatment of MRSA, methicillin-resistant staphylococcus epidermidis (MRSE) & enterococcal infections.
2. **Main indication: Sepsis or Endocarditis caused by MRSA.**
3. Methicillin-susceptible staphylococci (MSSA) in patients allergic to penicillins or cephalosporins.
4. **Oral vancomycin is limited to treatment for potentially life-threatening, antibiotic-associated colitis due to C. difficile.**
5. **IV vancomycin used in patients with prosthetic heart valves** and in patients undergoing implantation of prosthetic devices (decrease risk of MRSA or MRSE infection).
6. **Vancomycin acts synergistic with aminoglycosides**→ combined with gentamicin as an alternative regimen for treating enterococcal endocarditis in patients with serious penicillin allergy.
7. **Vancomycin combined with cefotaxime, ceftriaxone or rifampin** to **treat meningitis** suspected or caused by a **penicillin-resistant strain of pneumococcus (Inflammation allows meningeal penetration).**

Adverse Reactions of Vancomycin

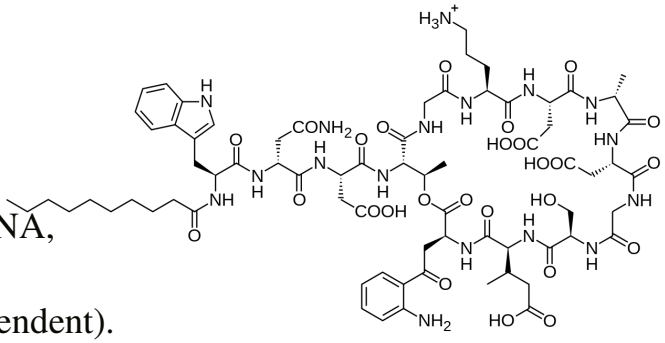
- **Fever, chills…**
- **Phlebitis at site of injection.**
- **Ototoxicity and Nephrotoxicity** - rare with current preparations –
  - Dose-related hearing loss occurs in patients with renal failure due to drug accumulation.
  - More common when co-administered with aminoglycosides.
- **Red man or red neck syndrome:** associated with rapid infusions → Flushing and shock as a result of excessive release of histamine
  - Slow infusion rate so the dose is given over 2 hours.
  - Increase the dilution volume
  - Pretreat with antihistamine
  - The red man syndrome is treated with antihistamines & steroids.



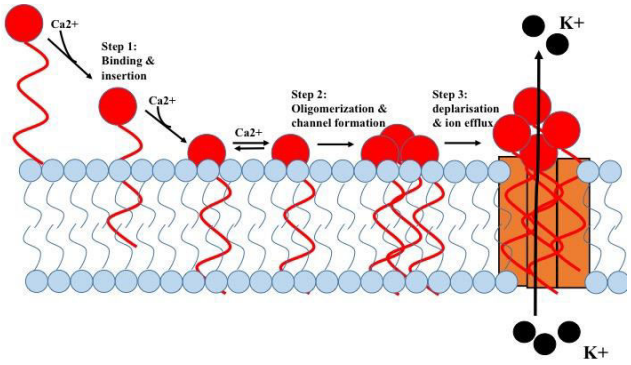


Daptomycin

- A cyclic lipopeptide antibiotic.
  - Binds the bacterial cytoplasmic membrane & induces rapid depolarization of the membrane → Disrupts membrane function
  - Inhibits intracellular synthesis of DNA, RNA, and protein.



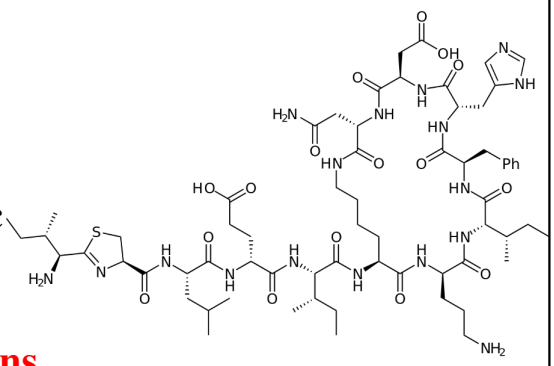
- Bactericidal (effect is concentration dependent).
- Activity limited to **gram-positive organisms → for treating infections caused by resistant gram-positive organisms, including MRSA and vancomycin-resistant enterococci (VRE).**
- Indicated for treatment of bacteremia and endocarditis…



- Daptomycin binds and inserts into the cell membrane.
- It aggregates in the membrane.
- It alters the shape of the membrane to form a hole, allowing ions in and out of the cell easily.

Bacitracin

- *Bacitracin* is a mixture of cyclic polypeptides that inhibits bacterial cell wall synthesis.
- Active against a wide variety of gram +ve organisms.
- Restricted to topical application because of potential for **nephrotoxicity with systemic use.**
- **Safe when used topically…**
- Bacitracin used to **prevent wound infections, treat pneumonia and empyema in infants, and to treat skin and eye infections.**



Bacitracin-containing topical preparations remain a possible alternative to silver sulfadiazine for burn patients with a sulfa allergy.

Bacitracin zinc salt, in combination with other topical antibiotics (usually polymyxin B and neomycin) as an ointment ("triple antibiotic ointment," with the brand name Neosporin)