



CEPHALOSPORINS

B-lactam antibiotics

MECHANISM OF ACTION

- Inhibit bacterial cell wall synthesis by binding to PBPs which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes while cell wall assembly is arrested.



○ **Antimicrobial properties:**

- Bactericidal
- Time dependent killing

○ **Mechanism of resistance:**

- B-lactamase activity
- decreased permeability to the drug
- altered PBP



○ **Members of each group and administration route:**

- **First generation:** Cephalexin(PO), Cefadroxil (PO), Cefazolin(IV/IM)
- **Second generation:** Cefaclor(PO), Cefprozil (PO), Cefuroxime(IV/IM/PO) and cephamycins: Cefoxitin (IV, IM), Cefotetan(IV/IM) and cefmetazole (IV).



- **Third generation:** Cefixime (PO), Cefpodoxime (PO), Ceftributen (PO), Cefdinir (PO), Cefditoren (PO), Cefotaxime(IV/IM), Ceftazidime(IV/IM/Neb/intravitreal), Ceftriaxone(IV/IM)
- **Fourth generation:** Cefepime (IV/IM)
- **Fifth generation:** Ceftaroline fosamil (IV), Ceftobiprole (IV), Ceftolozane/tazobactam (IV)



COVERAGE:

lose Gram positive activity; gain Gram negative activity



- **1st Generation**
 - cefazolin
 - cephalexin
 - cefadroxil
- **2nd Generation**
 - cefuroxime
 - cefaclor
 - cefprozil
 - cefaclor
- **3rd Generation**
 - ceftriaxone
 - cefotaxime
 - ceftazidime,
 - cefixime
- **4th Generation**
 - cefipime



lose Gram negative activity; gain Gram positive activity

First Generation

- Narrow spectrum:
 - aerobic gram positives (MSSA, β -hemolytic *Streptococcus*)
 - Some aerobic gram negatives (PEcK: *Proteus*, *E.coli*, *Klebsiella*)
- Useful for: MSSA, β -hemolytic *Streptococcus*
- Not useful for: *Enterococci*, *gut anaerobes*



Second Generation

- “Middle of the road” coverage*
- Covers everything that 1st generations cover*:
 - Gram positives: MSSA, *Streptococcus*
 - Gram negatives: PEcK + *H. influenzae* & *Moraxella*
 - Oral anaerobes, NOT gut anaerobes*
- *exception: *cefoxitin* – poor Gram positive coverage; covers *B.fragilis* (but resistance ~20%)
- Place in Therapy: oral stepdown for CAP



Third Generation: (ceftriaxone, cefotaxime)

- Broad-spectrum
 - Gram positive coverage: *MSSA* (reasonable coverage), *Streptococcus* (excellent coverage)
 - Gram negatives: *N.menigitidis*, *N.gonorrhoea* (ceftriaxone)
 - oral anaerobes
- NOT useful for *Enterococcus*, *Pseudomonas*, gut anaerobes.



(ceftazidime)

- Less broad-spectrum vs. ceftriaxone/cefotaxime
 - Gram positive coverage: *poor*
 - Gram negatives: *including Pseudomonas*
- NOT useful for: *enterococcus, gut anaerobes*
- Useful for: treatment of documented Pseudomonal infections, empiric Gram negative coverage where Pseudomonal coverage is desired.



(Cefixime)

- Less broad-spectrum vs. ceftriaxone/cefotaxime
 - Gram positive coverage: poor
 - Gram negatives: *N. gonorrhoea*
- NOT useful for: enterococcus, gut anaerobes, Pseudomonas
- Useful for: treatment of *N. gonorrhoea* (*niche*)
(*increasing resistance rate & treatment failures*)



(Cefdinir)

- Less broad-spectrum vs. ceftriaxone/cefotaxime
 - *Gram positive coverage: Good, >20% of Pneumococcus resistant*
 - *Gram negatives: Moraxella, H.influenza*
- NOT useful for: enterococcus, gut anaerobes, Pseudomonas



Fourth Generation (Cefepime)

- broad-spectrum
 - Like ceftriaxone, but:
 - Gram positives: better activity vs. MSSA
 - Gram negatives: *Pseudomonas*
- NOT useful for: enterococcus, gut anaerobes
- Useful for: treatment of documented *Pseudomonal* infections, empiric Gram negative coverage where *Pseudomonal* coverage is desired

Fifth Generation:

-Ceftaroline:

- Similar activity to ceftriaxone but with improved GM+ve activity
- Active against MRSA/MRSE
- No anaerobic activity
- Considered to be ineffective against *P.aeruginosa*, *Enterococcus* species (including vancomycin-susceptible and -resistant isolates), ESBL producing or AmpC overexpressing *Enterobacteriaceae*.

-Ceftolozone/tazobactam:

- Active against most ESBL/AmpC producers
pseudomonase
 - No MRSA/MRSE activity
 - Still weak anaerobic activity
- ceftobiprole: cover pseudomonas, No MRSA.



- All of the cephalosporins achieve therapeutic levels in pleural, pericardial, peritoneal and synovial fluids and urine.
- 1st and 2nd generation cephalosporins enter into CSF poorly. Other generations achieve more reliable CSF concentration in patients with meningeal irritation.



○ Side effects:

1. Allergic reaction
2. Diarrhea
3. Nephritis
4. Neurotoxicity
5. Hematologic toxicities



CONTRAINDICATIONS AND WARNINGS

- Cephalosporins are contraindicated in patients who are allergic to them or to penicillins or other beta lactams.
- Cefaclor: may cause serum sickness like reaction mainly in children < 5 years with symptoms of fever, rash, erythema multiforme and arthralgia often during second or third exposure.
- Cefditoren: Hypersensitivity milk protein, C/I in carnitine deficiency or inborn errors of metabolism that may result in clinically significant carnitine deficiency.



- Ceftriaxone: C/I in hyperbilirubinemic neonates (<28 days), because it displaces bilirubin from albumin binding sites, concomitant use with IV calcium-containing solutions/products in neonates (≤ 28 days), IV use of ceftriaxone solutions containing lidocaine and in neonates <41 weeks postmenstrual age.



○ **Pregnancy category:**

- Category B (all cephalosporins cross the placenta)

○ **Renal dose adjustment:**

All of the cephalosporins except ceftriaxone need renal dose adjustment.

○ **No hepatic dose adjustment is needed**



Renal dose adjustment

Antibiotic	CrCl	Antibiotic	CrCl
Cefazolin	<55 ml/min	Ceftazidime	≤ 50 ml/min
Cefadroxil	≤50 ml/min	Ceftibuten	<50 ml/min
Cephalexin	<30 ml/min	Cefepime	≤ 60 ml/min
Cefotetan	≤30 ml/min	Ceftaroline	≤ 50 ml/min
Cefoxitin	≤ 50 ml/min	Ceftobiprole	< 50 ml/min
Cefprozil	< 30 ml/min	Ceftolozane/tazobactam	≤ 50 ml/min
Cefuroxime	< 30 ml/min	Cefpodoxime	< 30 ml/min
Cefdinir	< 30 ml/min	Cefotaxime	< 20 ml/min
Cefditoren	< 50 ml/min	Cefixime	< 60 ml/min

VANCOMYCIN



MECHANISM OF ACTION

- Tricyclic glycopeptide.
- Inhibits bacterial cell wall synthesis by blocking glycopeptide polymerization through binding tightly to D-alanyl-D-alanine portion of cell wall precursor.



○ Mechanism of resistance:

Can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of vancomycin to receptor molecules (D-ala is replaced by D-lactate in the receptor).

○ Antimicrobial properties:

- Bactericidal
- Time dependent killing
- Administered PO, IV, intrathecal and intravitreal.
- Pregnancy Category: B if oral, C if IV (fda)



COVERAGE

- Narrow spectrum - ONLY Gram positives:
 - Aerobes: *Staphylococci* (MRSA, MSSA, CNST), *Enterococci* (*E. faecalis* & *E. faecium*)
 - Anaerobes: *C. difficile*, *Propionibacterium* spp.
- Useful for: gram positive infections (MRSA, *E. faecium*)
- Not useful for: any gram negative, VRE



o **Hepatic or renal adjustment**

- There is no need for hepatic dosage adjustment .
- Oral: no adjustment needed
- IV: adjust in based on renal function and trough serum concentrations.

o **Contraindications:**

- Hypersensitivity to vancomycin.



SIDE EFFECTS:

- Orally: GI SE.
- Fever
- Phlebitis.

- Nephrotoxicity: usually reversible, Risk factors
Preexisting renal impairment, Concomitant nephrotoxic medication, Advanced age and Dehydration. if multiple sequential (≥ 2) SCr demonstrate an increase of 0.5 mg/dl or $\geq 50\%$ increase from baseline (whichever is greater) in the absence of an alternative explanation, the patient should be identified as having vancomycin-induced nephrotoxicity (DC if nephrotoxicity signs occur).



- Ototoxicity: transient or permanent, DC if occurred.

- Infusion reaction (red man syndrome): rapid IV administration (<1 hour) may result in hypotension, flushing, erythema, urticaria and pruritus.

- **Management of red man syndrome:**
 - Slow infusion rate (1½ to 2 hours)
 - Increase the dilution volume
 - Administration of antihistamine.



MONITORING

- Trough is monitored before the fourth dose (within 30min to 1 hour) (steady state)
- Trough level: 10-15 mg/dl: skin and soft tissue infections, surgical site infections.
- 15-20mcg/ml : bacteremia, brain abscess, CSF shunt infection, endocarditis, intra-abdominal infections, meningitis, osteomyelitis, peritonitis, pneumonia, sepsis and septic shock, septic arthritis, toxic shock syndrome.



- Drawing >1 trough concentration prior to the fourth dose for short course (<3 days) or lower intensity dosing (target trough concentrations <15 mcg/mL) is not recommended. For patients with uncomplicated skin and soft tissue infections who are not obese and have normal renal function, serum trough monitoring is generally not needed



- *Hemodynamically stable patients*: Draw trough concentrations at least once-weekly.
- *Hemodynamically unstable patients*: Draw trough concentrations more frequently or in some instances daily.
- *Prolonged courses (>3 to 5 days)*: Draw at least one steady-state trough concentration; repeat as clinically appropriate.
- No monitoring needed when given orally



POLYMYXIN E AND B



o **Mechanism of action:**

- Binds to phospholipids alter permeability and damages the bacterial cytoplasmic membrane permitting leakage of intracellular constituents.
- Polymyxin E (Colistimethane) is the inactive prodrug that is hydrolyzed to colistin.



COVERAGE

- Narrow spectrum: aerobic Gram negatives
- Reliable activity against: ESBLs, CREs, *Pseudomonas*, *Acinetobacter*
- Useful for: highly resistant aerobic gram negative infections where there are no other options
- Not useful for: Gram positives



○ **Antimicrobial properties:**

- Bactericidal
- Concentration-dependent killing
- Route of administration: IV, IM, nebulizer and intrathecal.

○ **Side effects:**

1. Respiratory distress
2. Dose dependent Nephrotoxicity (risk factors: preexisting renal impairment, advanced age and dehydration)
3. Neurotoxicity manifest as neuromuscular blockade.



- Both need renal dose adjustment
- No hepatic dose adjustment
- pregnancy category C
- Contraindications: With known hypersensitivity to the drug
- Resistance Mechanism: efflux pumps, the formation of capsules and overexpression of the outer membrane protein, modification of the lipid A component of lipopolysaccharide and mcr-1 gene appearance



THEY HAVE VERY DIFFERENT PHARMACOKINETICS AND PHARMACODYNAMICS

Polymyxin B	Polymyxin E
Active	Prodrug
Time to peak ~2hr	Time to peak ~7hr
May not require LD	Require LD
	Excreted primarily in urine



Tetracyclines



- **Members of group:** Tetracycline, Doxycycline, Minocycline.
- **MOA:** binds reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mRNA-ribosome complex, thereby inhibiting bacterial protein synthesis.



COVERAGE:

- Broad-spectrum
 - Aerobic Gram positives: Streptococci, Staphylococci (including MRSA!), Listeria
 - Aerobic Gram negatives: easy to kill (E.coli, Klebsiella), N. meningitidis, Brucella spp.
 - Atypicals
 - Others: P. acnes, Vibrio, Treponema pallidum, H. pylori, Plasmodium spp. (malaria), Bartonella spp., Rickettsiae
- Niches: MRSA, atypicals, Rickettsiae, Bartonella
- If have a highly resistant organism, consider a Tetracycline!



○ **Antimicrobial properties:**

- Bacteriostatic effect
- Concentration– dependent killing

○ Pregnancy category D.

○ Route of administration: Tetracycline (PO), Doxycycline (PO, IV), Minocycline (PO, IV).



