Cell wall AB inhibitors (part 2)

Cephalosporins (CPs)

The CPs are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins. CPs 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.

Antibacterial spectrum

CPs have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases.

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 CPs. Agents in this generation also have modest activity against Proteus mirabilis, E. coli, and K. pneumoniae. Most oral cavity anaerobes like Peptostreptococcus are sensitive, but the Bacteroides fragilis group is resistant.

2. **Second generation:** The second-generation CPs display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker. Antimicrobial coverage of the cephamycins (cefotetan and cefoxitin) also includes anaerobes (for example, Bacteroides fragilis). They are the only CPs commercially available with appreciable activity against gram-negative anaerobic bacteria. However, neither drug is first line because of the increasing prevalence of resistance among B. fragilis to both agents.

3. **Third generation:** These CPs have assumed an important role in the treatment of infectious diseases. Although they are less potent than first-generation CPs against MSSA, the third-generation CPs have enhanced activity against gram-negative bacilli, including those mentioned above, as well as most other enteric organisms plus Serratia marcescens.

Ceftriaxone and cefotaxime have become agents of choice in the treatment of meningitis.

Ceftazidime has activity against P. aeruginosa; however, resistance is increasing and use should be evaluated on a case-by-case basis. Third-generation CPs must be used with caution, as they are associated with significant "collateral damage," essentially meaning the induction and spread of antimicrobial resistance. [Note: Fluoroquinolone use is also associated with collateral damage.]

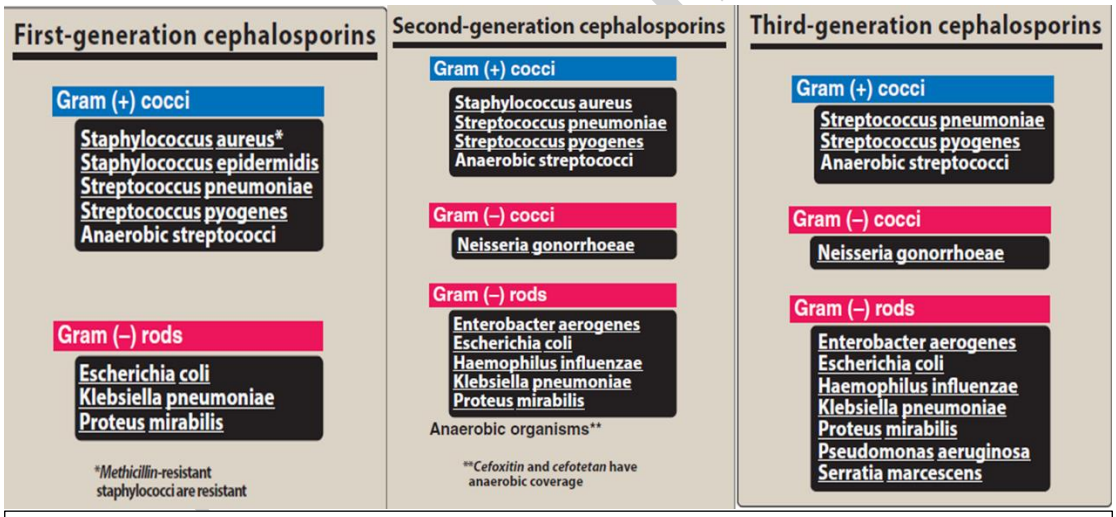
4. Fourth generation: Cefepime is classified as a fourth-generation cephalosporin and must be administered parenterally. Cefepime has a wide antibacterial spectrum,

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. When selecting
an antibiotic that is active against P. aeruginosa, clinicians should refer to their local antibiograms (laboratory testing for the sensitivity of an isolated bacterial strain to different antibiotics) for direction.

5. Advanced generation: Ceftaroline is a broad spectrum, advanced-generation cephalosporin that is administered IV as a prodrug, ceftaroline fosamil. It is the only commercial available β-lactam in the United States with activity against MRSA and is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia.

The unique structure allows ceftaroline to bind to PBP2a found with MRSA. In addition to its broad gram-positive activity, it also has similar gram-negative activity to the third-generation cephalosporin ceftriaxone.

Important gaps in coverage include P. aeruginosa, extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, and Acinetobacter baumannii. The twice-daily dosing regimen also limits use outside of an institutional setting.



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

Figure 1: Summary of therapeutic applications of CPs .

Resistance

Resistance to the cephalosporins is either due to the hydrolysis of the beta-lactam ring by β-lactamases or reduced affinity for PBPs.

Pharmacokinetics

1. Administration: Many of the CPs must be administered IV or IM because of their poor oral absorption.

2. Distribution:

- All CPs distribute very well into body fluids.
- However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few CPs. For example, ceftriaxone and cefotaxime are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae.
- Cefazolin is commonly used as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing Staphylococcus aureus.
- Cefazolin is effective for most surgical procedures, including orthopaedic surgery because of its ability to penetrate bone. All CPs cross the placenta.

3. Elimination:

- CPs are eliminated through tubular secretion and/or glomerular filtration. Therefore, doses must be adjusted in cases of renal dysfunction to guard against accumulation and toxicity.
- One exception is ceftriaxone, which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

An important therapeutic advantage of some cephalosporines are summarised in the figure below.

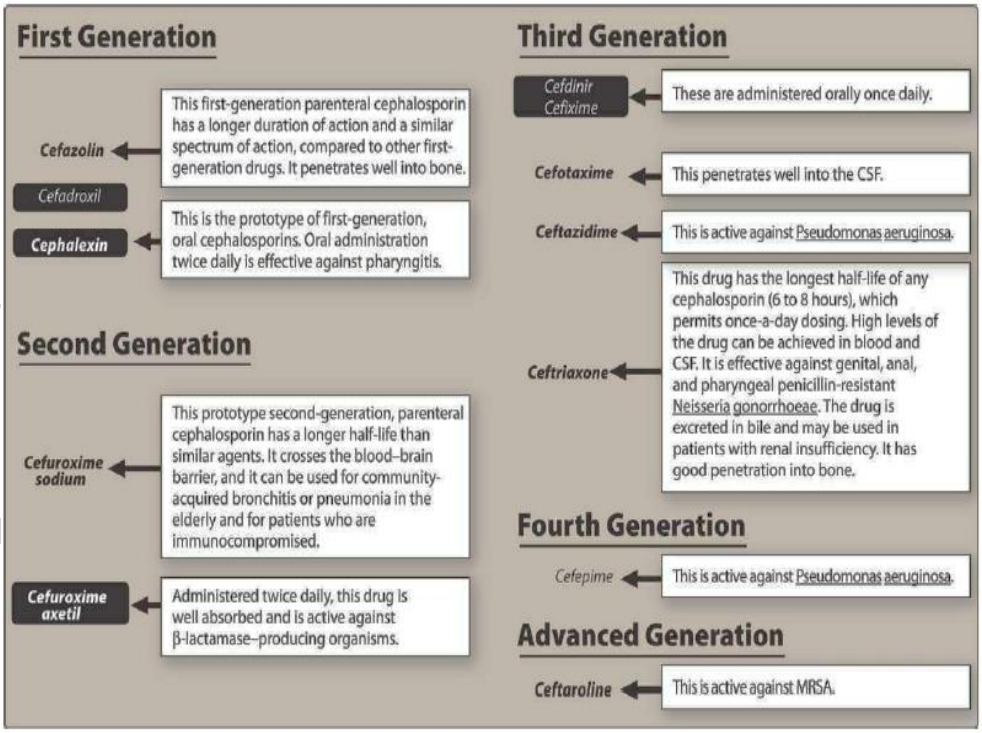


Figure 2: Therapeutic advantages of some clinically useful CPs . [Note: Drugs that can be administered orally are shown in reverse type. More useful drugs shown in bold.]. (CSF = cerebrospinal fluid.)

Adverse effects

- Like the penicillins, the CPs are generally well tolerated. However, allergic reactions are a concern. Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins should not receive CPs.
- CPs should be avoided or used with caution in individuals with penicillin allergy. Current data suggest that the cross-reactivity between penicillin and CPs 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 CPs.

OTHER β-LACTAM ANTIBIOTICS

A. Carbapenems

- Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins. Imipenem, meropenem, doripenem, and ertapenem are the drugs of this group currently available.
- Imipenem is compounded with cilastatin to protect it from metabolism by renal dehydropeptidase.

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 (although other pseudomonal strains are resistant and resistant strains of P. aeruginosa have been reported to arise during therapy).
- Meropenem and doripenem have antibacterial activity similar to that of imipenem.
- Unlike other carbapenems, ertapenem lacks coverage against P. aeruginosa, Enterococcus species, and Acinetobacter species.

Pharmacokinetics:

- Imipenem/cilastatin and meropenem 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.
- They are excreted by glomerular filtration.
- 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.

- Compounding the imipenem with cilastatin protects the parent drug and, thus, prevents the formation of the toxic metabolite.
- The other carbapenems do not require coadministration of cilastatin.
- Ertapenem can be administered via IV or IM injection once daily. [Note: 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. High levels of imipenem may provoke seizures; however, the other carbapenems are less likely to do so.

B. Monobactams

- ❖ The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the β-lactam ring is not fused to another ring.
- ❖ Aztreonam, which is the only commercially available monobactam, has antimicrobial activity directed primarily against gram-negative pathogens, including the Enterobacteriaceae and P. aeruginosa.
- ❖ It lacks activity against gram-positive organisms and anaerobes. Aztreonam is resistant to the action of most β-lactamases, with the exception of the ESBLs.
- ❖ It is administered either IV or IM and can accumulate in patients with renal failure.
- ❖ Aztreonam is relatively nontoxic, but it may cause phlebitis, skin rash and, occasionally, abnormal liver function tests.
- ❖ This drug has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to other penicillins, CPs , or carbapenems.

β-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. Instead, they bind to and inactivate 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.

THE OTHER CELL WALL INHIBITORS ANTIBIOTICS ARE ***VANCOMYCIN AND DAPTOMYCIN WHICH ARE SUMMARISED IN TABLE 1***.

Table 1: Side-by-side comparison of *vancomycin* and *daptomycin*

Parameter	*VANCOMYCIN*	*DAPTOMYCIN*
Mechanism of Action	Inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein
Pharmacodynamics	Time dependent Bactericidal	Concentration dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: Staphylococcus aureus (including MRSA), Streptococcus pyogenes, S. agalactiae, penicillin-resistant S. pneumoniae, *vancomycin*-susceptible Enterococcus faecalis, and E. faecium	
Unique Antibacterial Spectrum	Clostridium difficile (oral only)	*Vancomycin*-resistant E. faecalis and E. faecium (VRE)
Rout	IV/PO	IV
Pharmacokinetics	Renal elimination Normal half-life: 6–10 hrs Dose is adjusted based on renal function	Renal elimination Normal half-life: 7–8 hours Dose is adjusted based on renal function
Unique Adverse Effects	Infusion related reactions due to histamine release: Fever, chills, phlebitis, flushing (red man syndrome); dose-related ototoxicity and nephrotoxicity	Myalgias, elevated hepatic transaminases and creatine phosphokinases (check weekly), and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while on therapy)
Key Learning Points	Drug of choice for severe MRSA infections; oral form only used for C. diffcile infection; resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules; monitor serum trough concentrations for safety and efficacy	*Daptomycin* is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia