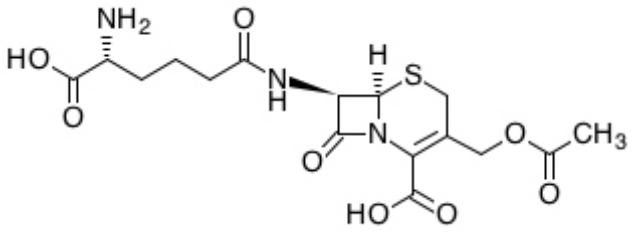
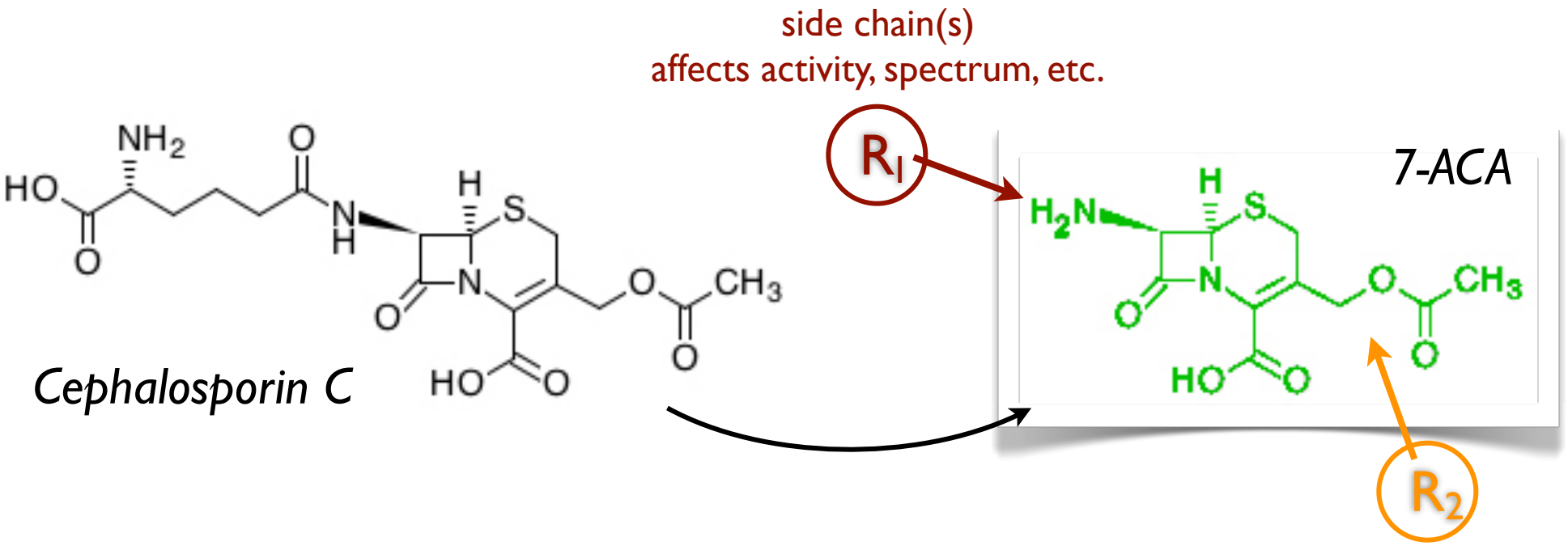
# Cephalosporins




*Cephalosporin C*

- First isolated by Brotzu from *Cephalosporium acremonium* (a mold) from a sewage outfall (and popular swimming spot) in Sardinia. He noticed the *C. acremonium* cultures inhibited the growth of *Salmonella enterica (typhi)*, a Gram- bug that produces a penicillinase
- M.O.A. same as penicillins, to inhibit synthesis and maintenance of bacterial peptidoglycan
- Slightly different nucleus shape made them more resistant to penicillinases

# Semi-synthetic cephalosporins



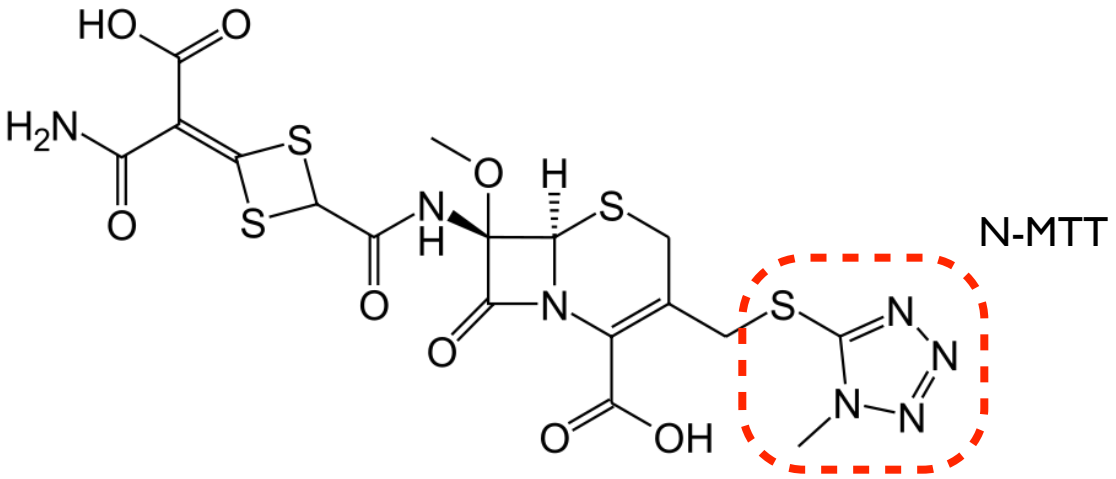

- Cephalosporin C had poor bioavailability, rapidly cleared
- Cleave off natural sidechain to yield 7-aminocephalosporanic acid (7-ACA) core, which then could be synthetically substituted with other sidechains.
  - Alter the spectrum, stability, bioavailability, resistance to beta-lactamases
  - All cephalosporins in use are of the semi-synthetic variety, no equivalents to Pen G and V in use.

# Cephalosporins general features

- Generally broader spectrum coverage than penicillins
  - Whereas original penicillins had primarily Gram+ coverage, most cephalosporins also cover some Gram-
  - Better resistance to beta-lactamases, but susceptible to AmpC, ESBL (if bug makes ESBL or AmpC, typically go to carbapenems instead).
- Cleared renally with ~5-30% metabolic breakdown, much active drug excreted in urine
  - Exceptions: cetriaxone, significant biliary elimination
- Low toxicity:
  - Generally lower allergenicity than penicillins though still some due to beta-lactam ring opening (10% cross-reactivity with penicillins)
  - Diarrhea: the broader the spectrum, the more likely of disruption of gut flora and diarrhea, which can lead to significant problems

# Cephalosporins general features

- Other adverse drug reactions from cephalosporins containing N-MTT or N-MTD moieties:
  - Example: cefotetan has an N-methylthiotetrazole (N-MTT) moiety that is released as a metabolic byproduct. This can cause hypoprothrombinemia, which manifests as bleeding due to combination of effects: 1) altered vitamin K production, 2) direct interaction of N-MTT with prothrombin, 3) platelet dysfunction. First noted with moxalactam (2-3% fatalities; off market); much higher N-MTT levels than cefotetan.
  - N-MTT also can inhibit aldehyde degydrogenase, giving rise to a disulfram-like reaction following alcohol consumption. Intense hang-over feeling, hyper-sensitivity to alcohol.




*Cefotetan*

# Cephalosporins general features

- Cephalosporin "generations": generally get broader, more Gm- coverage with later generations
  - Generation 1: Generally had better Gram+ than Gram- activity; susceptible to many Gram- beta-lactamases
    - Examples: Cephalexin, Cefazolin
  - Generation 2: Better resilience to Gram- beta-lactamases, Gram- coverage
    - Examples: Cefuroxime
  - Generation 3: More potent, better Gram- beta-lactamase stability, better penetration; pick up some anti-*Pseudomonal* activity, give up some Gram+ coverage
    - Examples: Cefpodoxime, Cefdinir, Cefixime, Cefotaxime, Ceftriaxone, Ceftazidime,
  - Generation 4: Very broad spectrum (Gm- and Gm+)
    - Example: Cefepime
  - Generation 5: MRSA and PRSP coverage
    - Example: Ceftaroline

# Cephalosporins general features

- Some penetrate to the CNS:
  - *Cefuroxime*
  - *Cefotaxime*
  - *Ceftazidime*
  - *Ceftriaxone*

# Oral cephalosporins

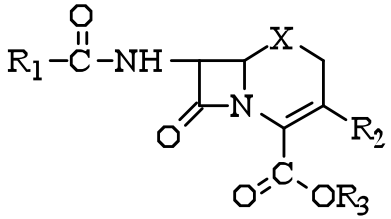
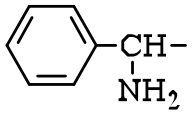
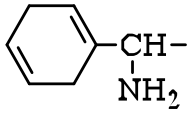
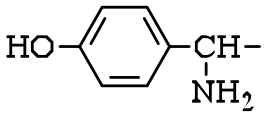
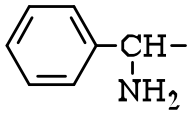
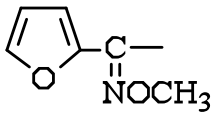
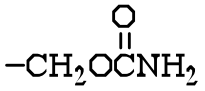
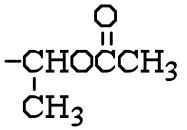
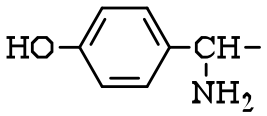
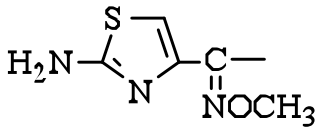
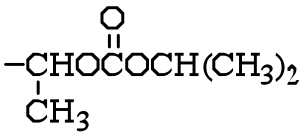
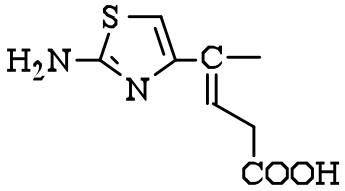
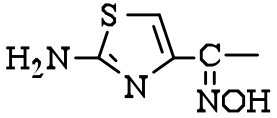
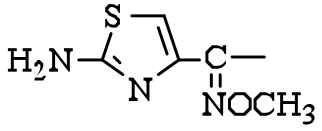
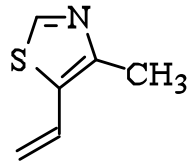


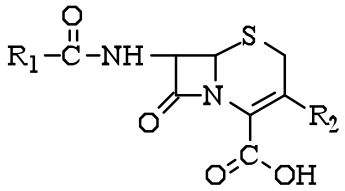
Table - Oral Cephalosporins

| generation | name | brand name | structure | | | | dose |
|---|---|---|---|---|---|---|---|
| | | | $R_1$ | $R_2$ | $R_3$ | X | |
| 1 | cephalexin | generic |  | $-CH_3$ | —H | —S— | QID |
| 1 | cephradine | generic |  | $-CH_3$ | —H | —S— | BID |
| 1 | cefadroxil | generic |  | $-CH_3$ | —H | —S— | BID |
| 2 | cefaclor | generic |  | $-Cl$ | —H | —S— | TID |
| 2 | cefuroxime axetil | generic |  |  |  | —S— | BID |
| 2 | cefprozil | generic |  | $-CH=CHCH_3$ | —H | —S— | BID |

# Oral cephalosporins (cont.)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 3 | cefpodoxime proxetil | generic |  | $-CH_2OCH_3$ |  | $-CH_2-$ | BID |
| 3 | ceftibutin | Cedax® |  | | —H | —S— | qd |
| 3 | cefdinir | generic |  | $-CH=CH_2$ | —H | —S— | BID |
| 3 | cefditoren pivoxil | generic |  |  | $-CH_2OCOC(CH_3)_3$ | —S— | BID |
| 3 | cefixime | Suprax® | ---- | ---- | ---- | ---- | qd |

# Parenteral cephalosporins/cephamycins



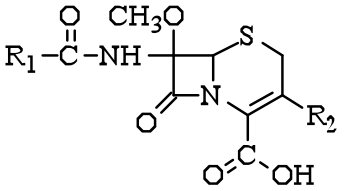
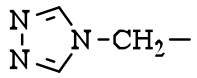
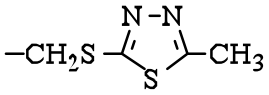
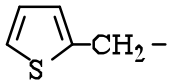
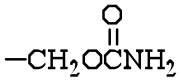
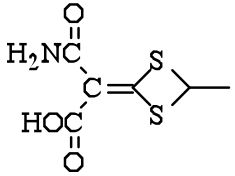
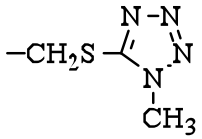
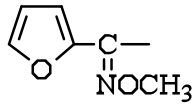
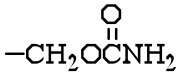
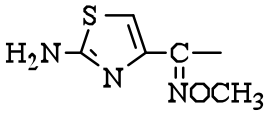
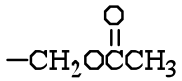
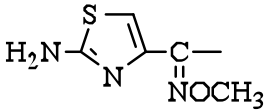
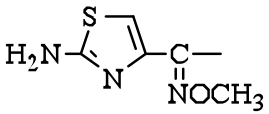
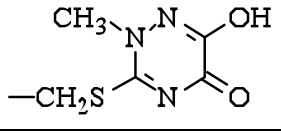
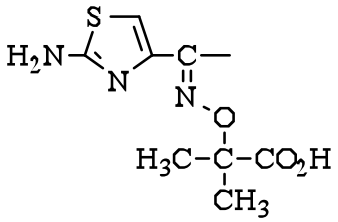
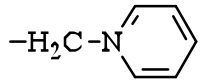
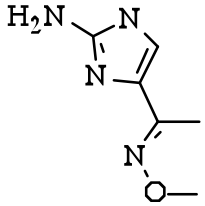
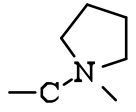


Table - Parenteral Cephalosporins and Cephamycins  Cephalosporin  *Cephamycin

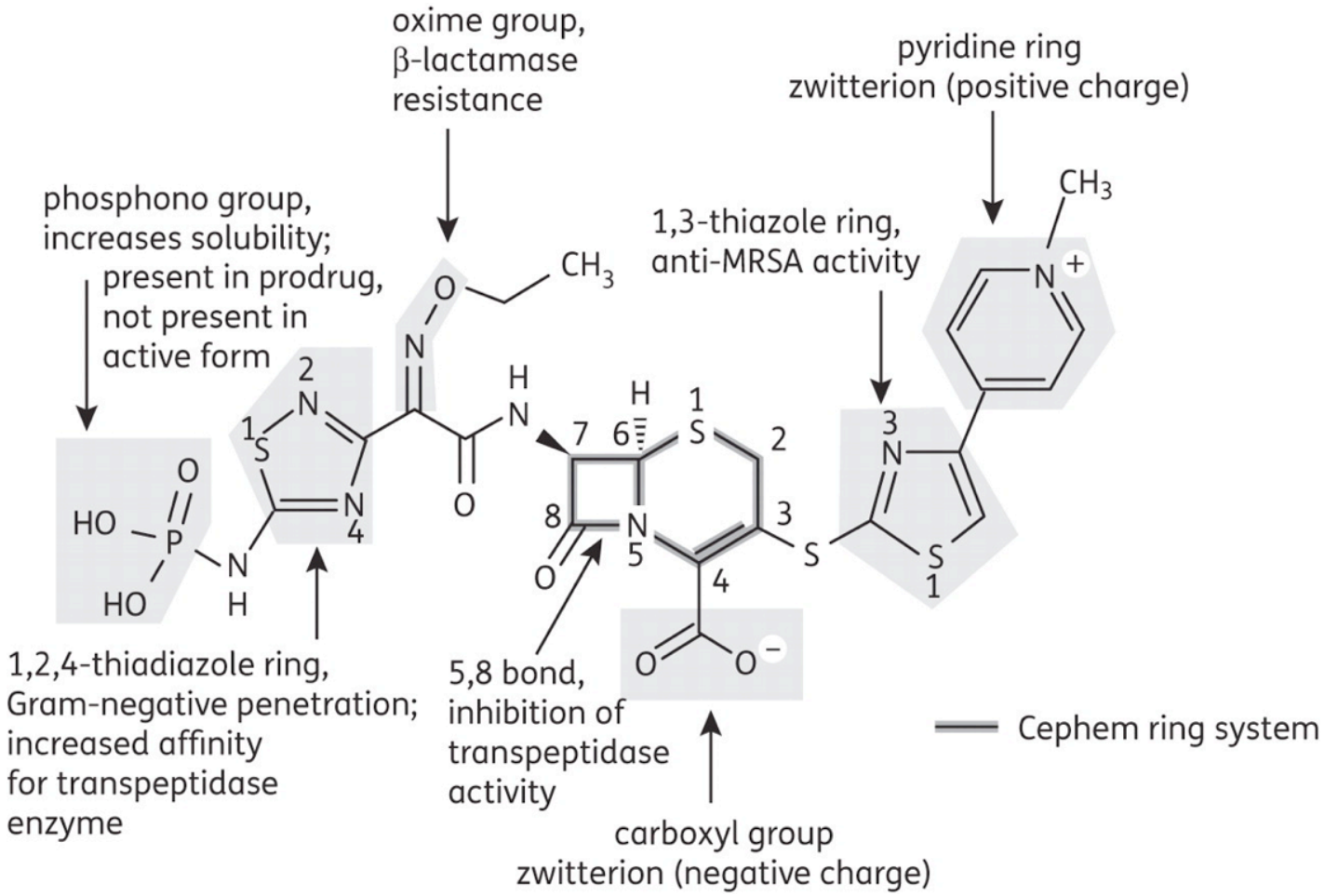
| generation | name | brand name | structure | | dose |
|---|---|---|---|---|---|
| | | | $R_1$ | $R_2$ | |
| 1 | cefazolin | generic |  |  | TID |
| 2 | cefoxitin* | generic |  |  | QID |
| 2 | cefotetan* | generic |  |  | BID |
| 2 | cefuroxime | generic |  |  | TID |
| 3 | cefotaxime | generic |  |  | TID |
| 3 | ceftizoxime | Cefizox® |  | —H | TID |
| 3 | ceftriaxone | generic |  |  | qd |

# Parenteral cephalosporins/cephamycins (cont.)

| | | | | | |
|---|---|---|---|---|---|
| 3 | ceftazidime | generic |  |  | TID |
| 4 | cefepime | generic |  |  | BID |

# Anatomy of a cephalosporin

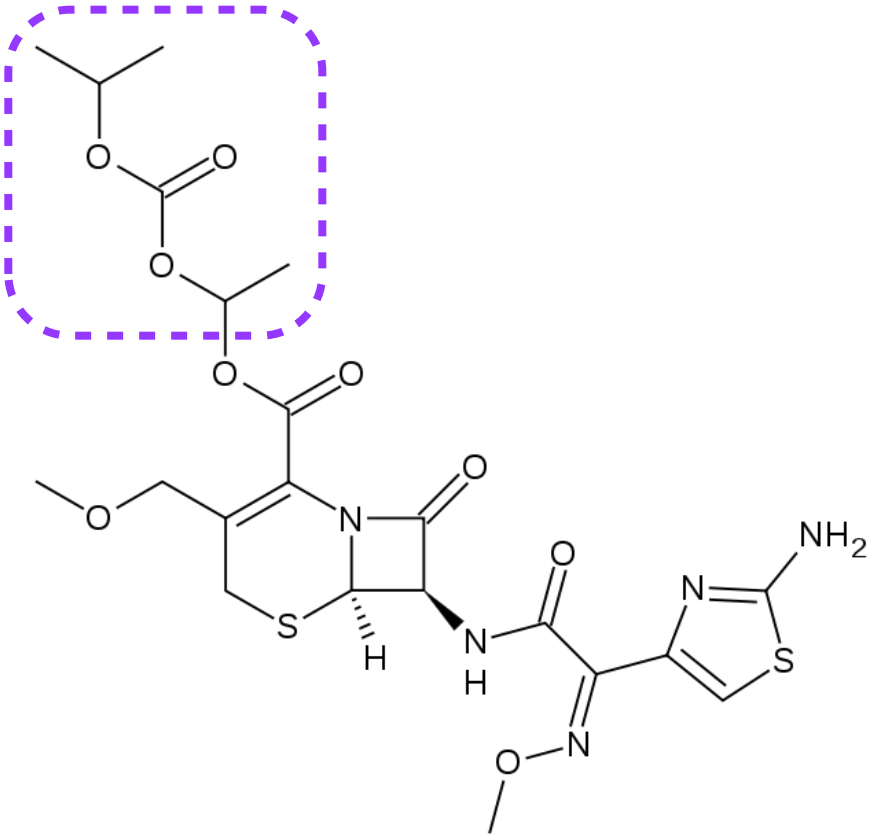
Example: ceftaroline (a gen-5 ceph)



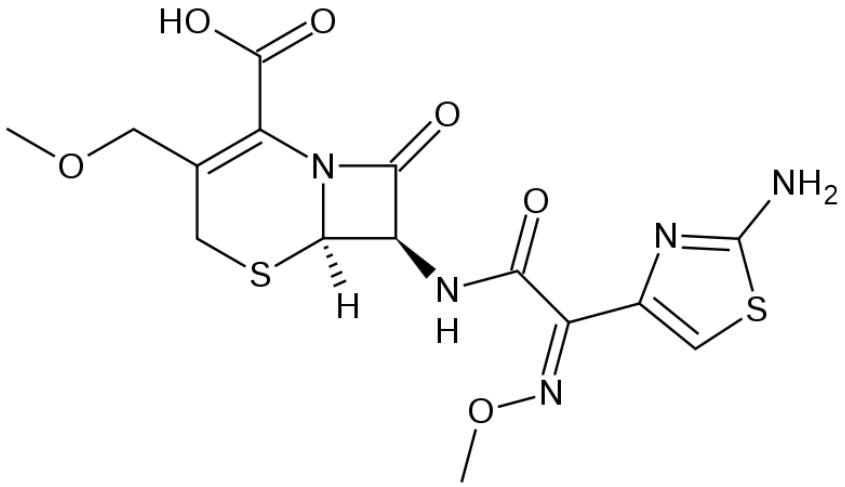

Laudano JB, J. Antimicrob. Chemother. 2011;66:iii11-iii18

# Some cephalosporins are prodrugs

- Examples: Cefpodoxime, Cefuroxime, Ceftizoxime, Cefditoren, Cefetamet
  - Metabolized to active drug by intestinal mucosal tissue
  - Sometimes aids in better absorption; e.g. crossing membranes
  - Sometimes aids in better solubility

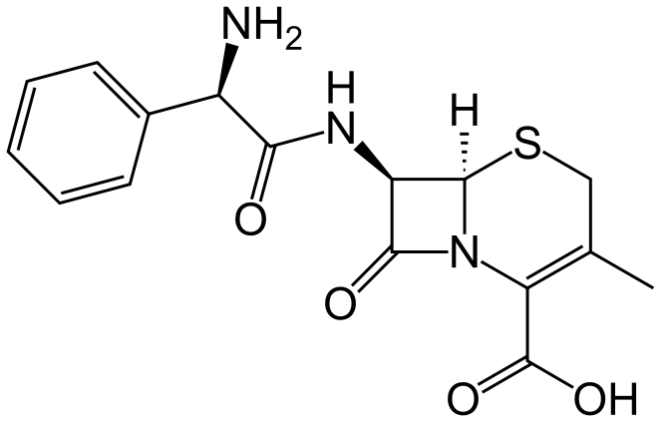


*cefpodoxime proxetil*



*cefpodoxime*

# Cephalexin (Gen1, PO)




- Keflex ® (Eli Lilly), and generics
- Up to 90% excreted unmodified in urine.
- Indications:
  - Skin infections: *S. aureus* (*MSSA* even w/ penicillinase, not *MRSA*), *S. pyogenes*
  - Respiratory infections: *S. pneumoniae* (not PRSP), *S. pyogenes*
  - Otitis media: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*
    - *H. influenzae* and *M. catarrhalis* may have resistance due to beta-lactamases
  - Urogenital: *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*
  - Bone: *S. aureus*, *P. mirabilis*

# Cephalexin (Gen1, PO)

Indicated spectrum for cephalexin (Gen1, oral):

## Aerobic gram-positive microorganisms:

*Staphylococcus aureus* (including penicillinase-producing strains)
*Streptococcus pneumoniae* (only penicillin-sensitive strains)
*Streptococcus pyogenes*

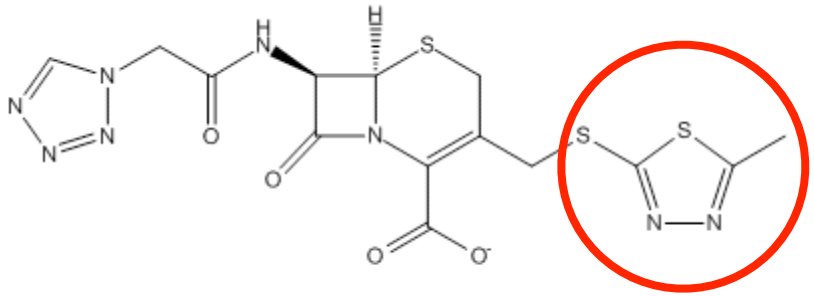
### Resistant Gm+ bacteria, not covered:

MRSA
PRSP
Most strains of *enterococci* (*E. faecalis*) are resistant to cephalosporins, including Cephalexin.
*Enterobacter spp.*
*Morganella morganii*
*Proteus vulgaris*
*Pseudomonas spp.*
*Acinetobacter calcoaceticus*

## Aerobic gram-negative microorganisms:

*Escherichia coli*
*Haemophilus influenzae*
*Klebsiella pneumoniae*
*Moraxella catarrhalis*
*Proteus mirabilis*

# Cefazolin (Gen1, Parenteral IV/IM)



N-MTD
(N-methylthiodiazole)

- Ancef ® (GSKB), and generics
- Up to 80% excreted unmodified in urine.
- For Gm+ *Staphylococci* including *Staph. aureus* (not *MRSA*), *Streptococci* including *Strep. pyogenes, Strep. pneumoniae* (not *PRSP*)
  - Respiratory tract infections (*Staph., Strep.*)
  - Uncomplicated skin infections
  - Osteomyelitis: bone and joint
- Some Gram- coverage: *E. coli*, *H. influenzae* (some resistance), P. *mirabilis,*
  - Urogenitial
- Like N-MTT, N-MTD sidechain, potential for bleeding and disulfram-like alcohol side effects
  - Co-administration with parenteral vitamin K may counter bleeding

# Cefazolin (Gen1, Parenteral IV/IM)

Indicated spectrum for cefazolin (Gen1, parenteral):

Aerobic gram-positive microorganisms:

- *Staphylococcus aureus* (including penicillinase-producing strains; not MRSA)
- *Staph. epidermidis*
- *Strep. pneumoniae* (only penicillin-sensitive strains; not PRSP)
- *Strep. pyogenes*
- *Strep. agalactiae*

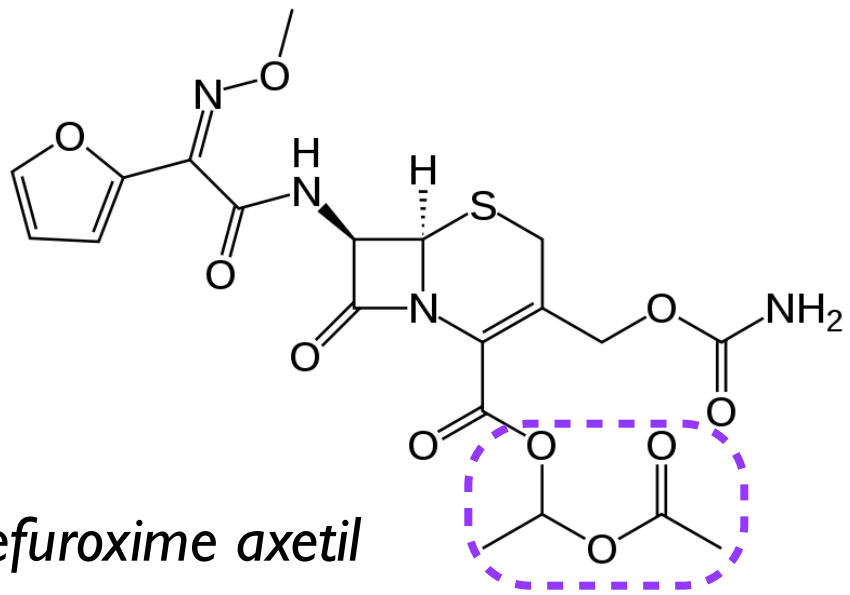
Resistant Gm+ bacteria, not covered:

- MRSA
- PRSP
- *Enterococci* (*E. faecalis*)

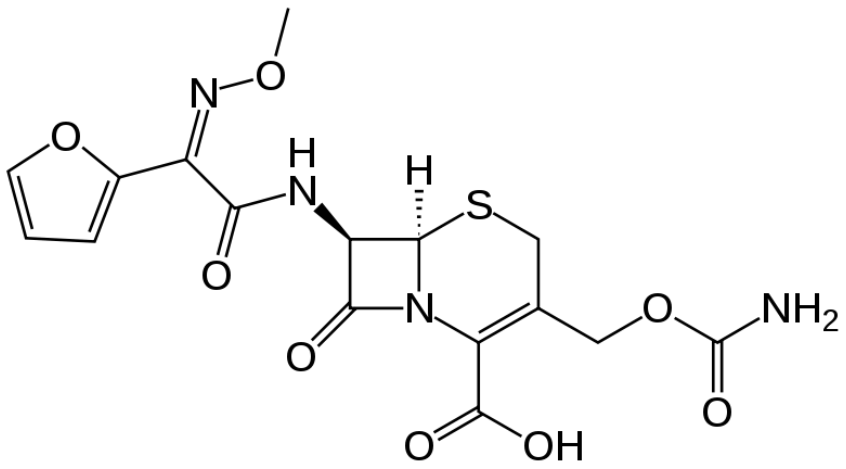
Aerobic gram-negative microorganisms:

- *Escherichia coli*
- *Proteus mirabilis*

# Cefuroxime axetil (Gen2, PO)



*cefuroxime axetil*

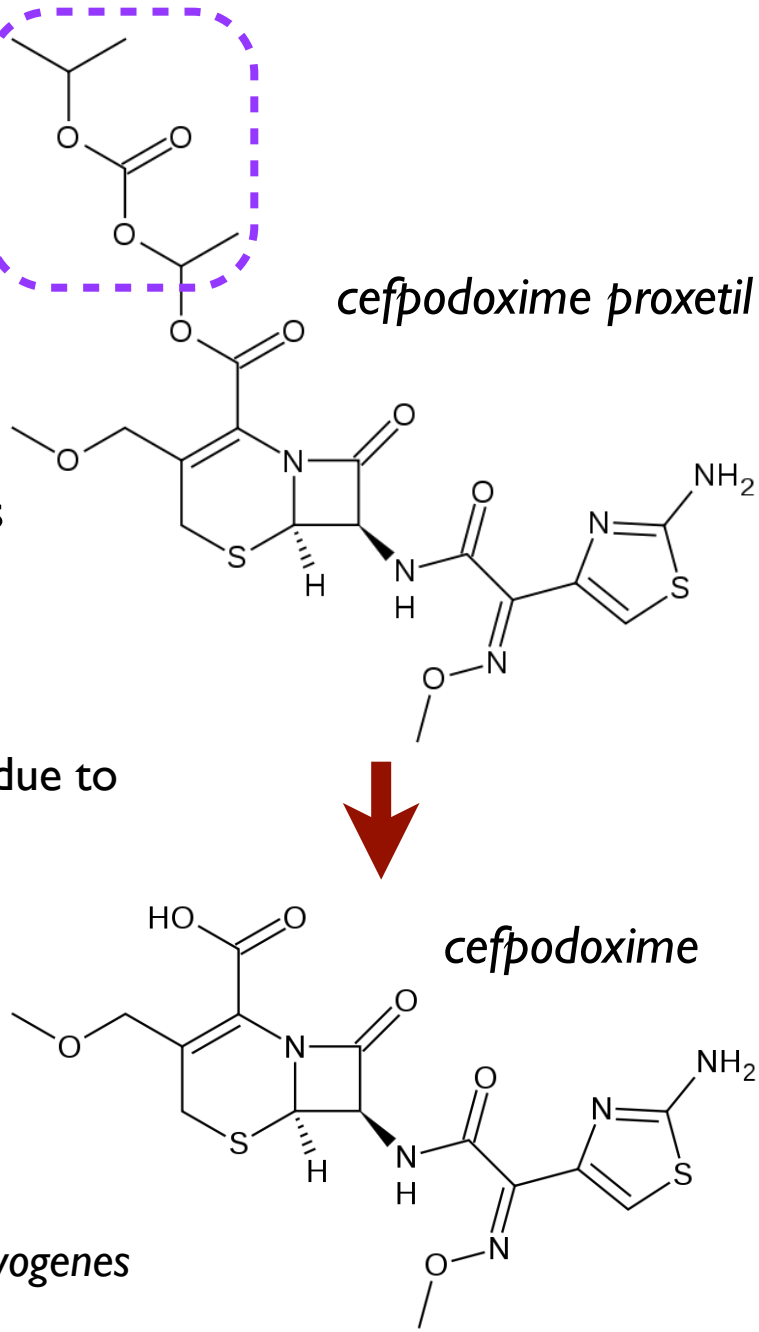


*cefuroxime*

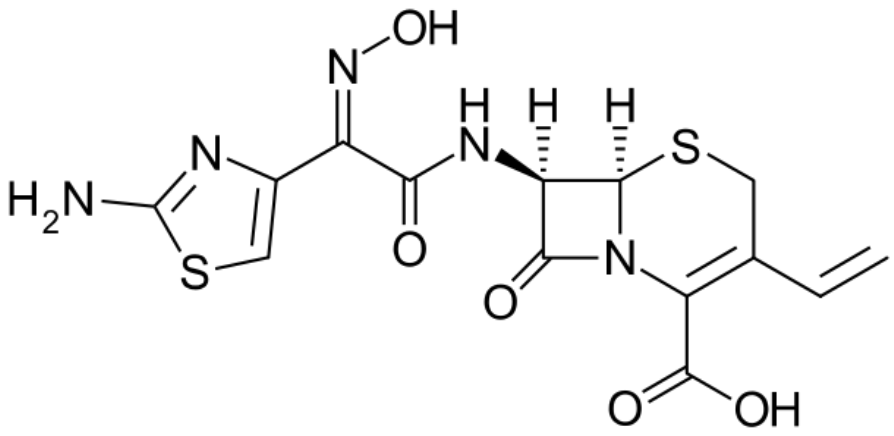
- Ceftin ® (GSKB) and generics
- Prodrug: cefuroxime axetil converted to cefuroxime (also IV, not as prodrug)
- Indications:
  - Pharyngitis, Tonsollitis, Otitis media, sinusitis, bronchitis (*H. flu*, *S. pneumo*, *M. cat*)
  - Skin infections *(S. pyogenes, MSSA)*
  - UTI (*E. coli, Klebsiella*)
  - *N. gonorrhoeae* including penicillinase-producing
  - Early Lyme disease *Borrelia Burgdorferi* (amoxicillin, doxycycline also)
- <u>Penetrates to CNS</u>: meningitis (*N. meningitidis*, *H. influenzae*, *S. pneumoniae*)

# Cefpodoxime proxetil (Gen3, PO)

- Vantin ® (Pharmacia), and generics
- Prodrug
- Good Gram- and Gram+ coverage
  - not *Pseudomonas*, *Enterococci, B. fragilis*
- Indications: big for otitis media, pharyngitis, sinusitis
  - Community Acquired Pneumonia (CAP):
    - *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*
    - *H. influenzae* and *M. catarrhalis* may have resistance due to beta-lactamases
  - *N. gonorrhoeae*: single 200mg dose
  - UTI
  - Otitis media:
    - *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*
  - Uncomplicated skin infections: *S. aureus* (not MRSA), *S. pyogenes*



# Cefdinir (Gen3, PO)




- Omnicef ® (Abbot) and generics
- Similar coverage to cefpodoxime, but tastes better (important for children)
- Best selling cephalosporin, often prescribed for AOM (acute otitis media) if infection not responding to amoxicillin

# Relative tastiness of cephalosporins

**TABLE 2**
**Taste Ratings for Oral Cephalosporin Suspensions***

| Antibiotic | Rating |
|---|---|
| Loracarbef | ++++ |
| Cefdinir | ++++ |
| Cefixime | +++ |
| Cephalexin | +++ |
| Cefaclor | +++ |
| Amoxicillin⁺ | +++ |
| Trimethoprim-sulfamethoxazole⁺ | ++ |
| Cefprozil | ++ |
| Amoxicillin/clavulanate⁺ | ++ |
| Cefpodoxime | + |
| Cefuroxime axetil | + |

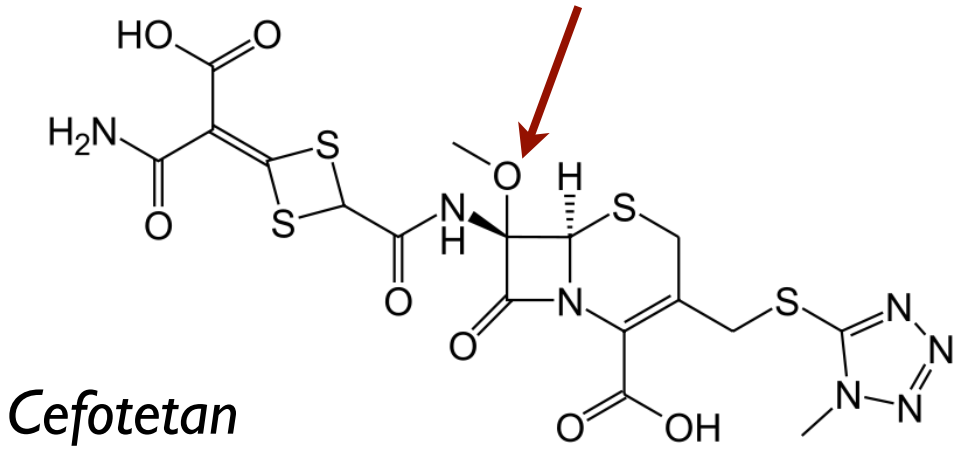
* Data modified from references 9-11

⁺ Comparative commonly prescribed agent in pediatric patients

++++, best overall taste; +++ above average;
++, below average; + poorly palatable

National Foundation for Infectious Diseases
http://www.nfid.org/pdf/pediatric_archive/cephalosporinsupdate.pdf

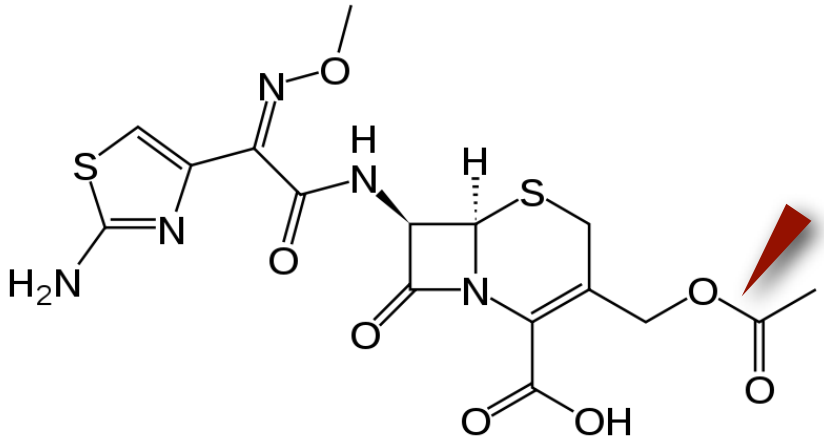
# Cefotetan (Gen2, IV), a “cephamycin”




*Cefotetan*

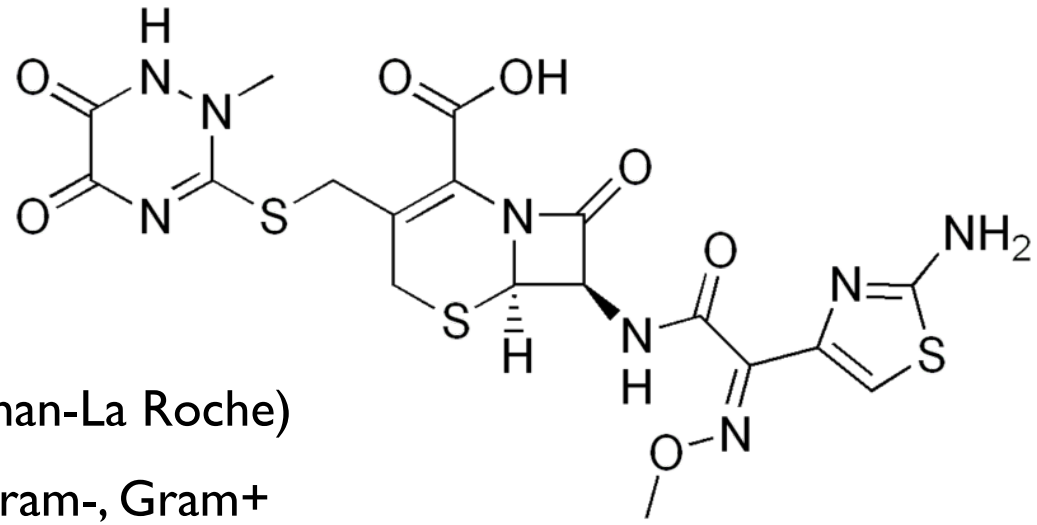
- Originally isolated from *Streptomyces*; now semi-synthetic derivatives
- Cephamycins have an O-methylated beta-lactam ring (→)
- Good anaerobic activity over other Gen2 cephalosporins

# Cefotaxime (Gen3, Parenteral IV/IM)



- Claforan® (Sanofi Aventis)
- Cefotaxime becomes deacetylated, resulting desacetylcefotaxime also active
- Broad spectrum; Gram-, Gram+
  - Activity against PRSP, but used in combination with other antimicrobials
  - Notable Gm+ exceptions: *Enterococci*
  - Notable Gm- exceptions: *Pseudomonas*
- Lower respiratory tract infections, bone and joints, skin, urogenital infection, septicemia
- Intra-abdominal including use as pre-surgery prophylaxis
- Penetrates to CNS: meningitis

# Ceftriaxone (Gen3, Parenteral IV/IM)



- Rocephin ® (Hoffman-La Roche)
- Broad spectrum; Gram-, Gram+
  - Can be used for Penicillin-resistant *Strep. Pneumoniae* (PRSP)
  - Highly active against *N. gonorrhoeae*: 250mg single IM dose
  - Some activity against *Pseudomonas aeruginosa*, but not the most potent
- Very long half-life ~6-8h (vs e.g. 1h for cefotaxime); less frequent dosing
- Penetrates the CNS
- Often used in combination w/ aminoglycoside or macrolide
  - *E.g.* w/ azithromycin for *Chlamydia tracomatis*
- Do not co-administer or dilute with calcium-containing compounds/solutions
  - *Ceftriaxone* precipitates with calcium

# Ceftriaxone (Gen3, Parenteral IV/IM)

## Aerobic gram-negative microorganisms:

*Acinetobacter calcoaceticus*
*Enterobacter aerogenes*
*Enterobacter cloacae*
*Escherichia coli*
*Haemophilus influenzae* (including ampicillin-resistant and beta-lactamase producing strains)
*Haemophilus parainfluenzae*
*Klebsiella oxytoca*
*Klebsiella pneumoniae*
*Moraxella catarrhalis* (including beta-lactamase producing strains)
*Morganella morganii*
*Neisseria gonorrhoeae* (including penicillinase- and nonpenicillinase-producing strains)
*Neisseria meningitidis*
*Proteus mirabilis*
*Proteus vulgaris*
*Serratia marcescens*
*Pseudomonas aeruginosa*

## Aerobic gram-positive microorganisms:

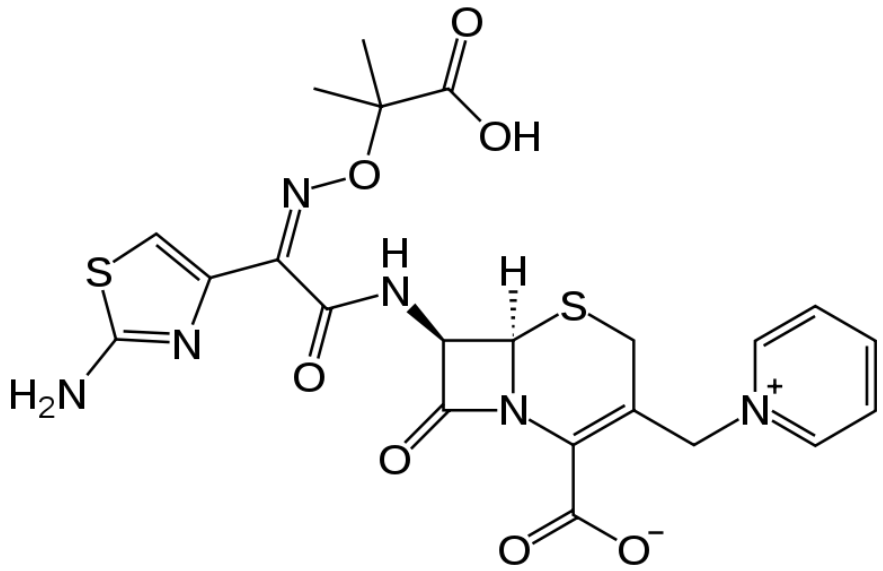
*Staphylococcus aureus* (including penicillinase-producing strains, not MRSA)
*Staphylococcus epidermidis*
*Streptococcus pneumoniae* (active for PRSP)
*Streptococcus pyogenes*
*Viridans group streptococci*

NOTE: MRSA resistant to most cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, eg, *Enterococcus faecalis*, are resistant.

## Anaerobic microorganisms:

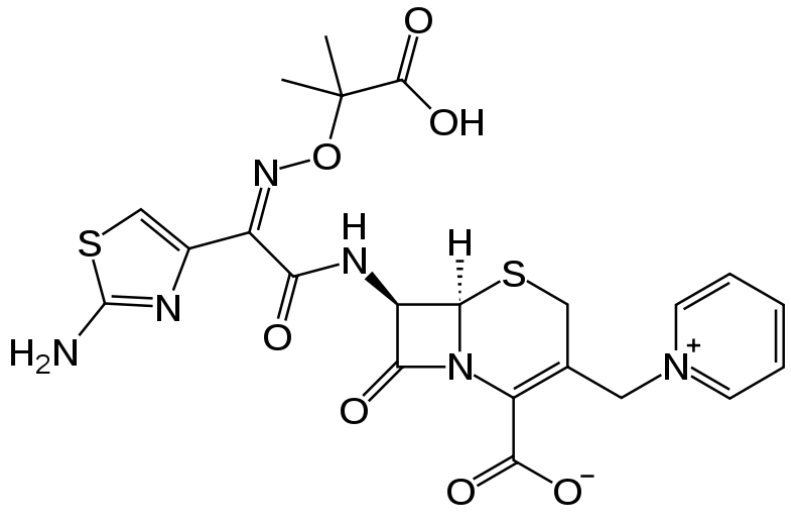
*Bacteroides fragilis*
*Clostridium species* (NOTE: Most strains of *Clostridium difficile* are resistant)
*Peptostreptococcus species*

# Ceftazidime (Gen3, Parenteral IV/IM)



- Tazidime ® (Eli Lilly), Fortum ® (GSK)
- Broad spectrum; Gram-, weak Gram+
  - Activity against *Pseudomonas aeruginosa*, ~85-90% sensitive (only ~68% for CF patients)
  - Poorer against Gm+, not generally used
- CNS penetration in meningitis

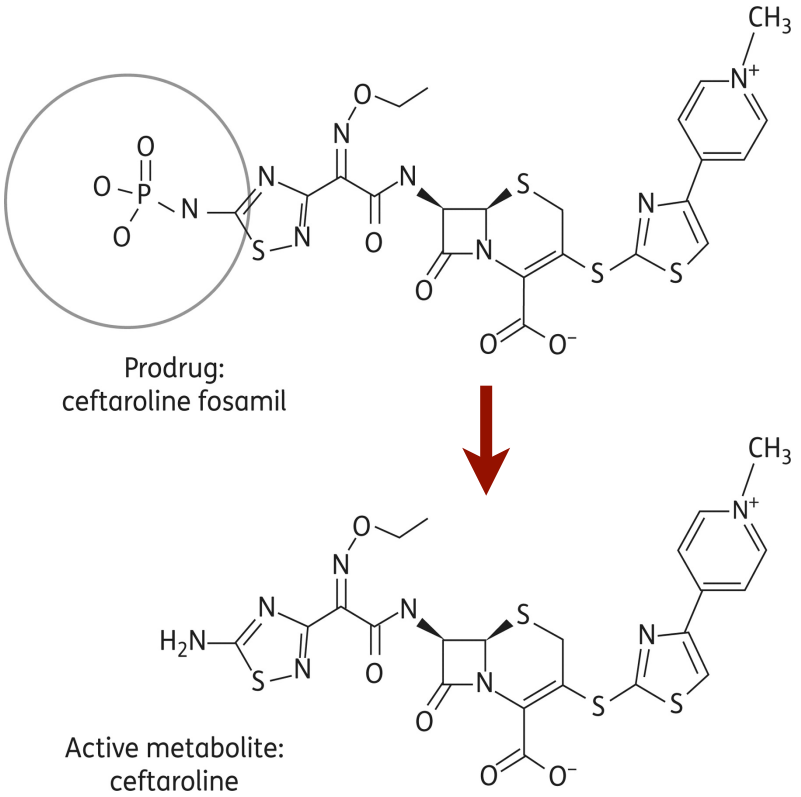
# Cefepime (Gen4, Parenteral IV/IM)



- Maxipime ® (Elan)
- Even more resistant to beta-lactamases binds tightly to PBPs
- Better penetration of Gram- outer membranes
- Broad spectrum: Gram- and Gram+
  - Activity against PRSP
  - *Pseudomonas aeruginosa* coverage (90% sensitive for non-CF patients, only 50% for CF)
  - *Enterobacteriaceae*
  - Not anaerobes
- Empiric therapy: used to suppress infection, then switch to another cephalosporin
  - Does not induce the expression of chromosomal beta-lactamases;
- FDA precaution for neurotoxicity (encephalopathy, myoclonus, seizures)

# Ceftaroline fosamil (Gen5, Parenteral IV/IM)

- Teflaro® (Cerexa, Forest Labs); FDA approved fall, 2010.
- *Ceftaroline fosamil* prodrug becomes dephosphonated in the blood to *ceftaroline*
- Similar spectrum to ceftriaxone, but gain increased Gram+ coverage including *MRSA* and *PRSP* due to increased affinity for *MRSA*'s PBP2a and pen. resistant *S. pneumoniae*'s PBP2x, which confers resistance to most beta-lactams.
  - *MRSA and VRSA*
  - *PRSP*
  - *H. influenzae*
  - *M. catarrhalis*
  - *S. pyogenes*
  - *S. viridans* group
  - *E. faecalis*
  - *K. pneumoniae*
  - *Shigella*
  - NOT for *P. aeruginosa,* beta-lactamase (ESBL, AmpC) producing *Enterobacteriaceae, Bacteriodes, C. difficile*
- Indicated uses
  - Complicated skin infection
  - Community associated pneumonia (CAP)



# Ceftaroline fosamil (Gen5, Parenteral IV/IM)

**Table 1.** *In vitro* activity of ceftaroline against common Gram-positive and Gram-negative bacteria[25]

| Organism (number of isolates) | MIC (mg/L) range | 50% | 90% |
|---|---|---|---|
| **Gram-positive** | | | |
| *Staphylococcus aureus* | | | |
| MSSA (102) | 0.03–0.5 | 0.25 | 0.25 |
| MRSA (105) | 0.5–2 | 0.5 | 1 |
| vancomycin reduced susceptibility (47) | 0.25–2 | 1 | 2 |
| linezolid non-susceptible (13) | 0.5–2 | 1 | 2 |
| *Streptococcus pyogenes* (102) | ≤0.008–0.015 | ≤0.008 | ≤0.008 |
| *Streptococcus agalactiae* (104) | ≤0.008–0.03 | 0.015 | 0.03 |
| *Enterococcus faecalis* | | | |
| vancomycin susceptible (102) | 0.25–16 | 2 | 4 |
| vancomycin resistant (108) | 0.5–16 | 4 | 8 |
| *Streptococcus pneumoniae* | | | |
| penicillin susceptible (MIC ≤ 0.06 mg/L) (102) | ≤0.008–0.06 | ≤0.008 | 0.03 |
| penicillin intermediate (MIC 0.12–1 mg/L) (102) | ≤0.008–0.12 | 0.03 | 0.06 |
| penicillin resistant (MIC ≥ 2 mg/L) (100) | 0.03–0.5 | 0.12 | 0.25 |
| penicillin high-level resistant (MIC ≥ 8 mg/L) (40) | 0.06–0.5 | 0.25 | 0.5 |
| levofloxacin non-susceptible (53) | ≤0.008–0.5 | 0.015 | 0.12 |
| multidrug resistant (≥2 classes) (127) | ≤0.008–0.5 | 0.12 | 0.25 |
| **Gram-negative** | | | |
| *Escherichia coli* | | | |
| ceftazidime susceptible (102) | 0.015–8 | 0.12 | 0.25 |
| *Klebsiella pneumoniae* | | | |
| ceftazidime susceptible (102) | 0.015–1 | 0.06 | 0.5 |
| *Haemophilus influenzae* | | | |
| β-lactamase negative (110) | ≤0.008–0.25 | ≤0.008 | 0.015 |
| β-lactamase positive (101) | ≤0.008–0.12 | ≤0.008 | 0.03 |
| *Pseudomonas aeruginosa* (101) | 4 to >16 | >16 | >16 |
| *Acinetobacter baumannii* (101) | 2 to >16 | >16 | >16 |

D. Biek et al., *J. Antimicrob. Chemo.* (2010) **65** supplement 4: iv9-16

# Ceftaroline fosamil (Gen5, Parenteral IV/IM)

**Table 2.** Activity of ceftaroline and comparator agents against Gram-positive clinical isolates of skin pathogens from US and European medical centres in 2008[26]

| Organism | Antimicrobial agent | MIC (mg/L) range | MIC (mg/L) 50% | MIC (mg/L) 90% | Susceptible (%) |
|---|---|---|---|---|---|
| *Staphylococcus aureus* | | | | | |
| methicillin susceptible (1554) | ceftaroline | ≤0.008–1 | 0.25 | 0.25 | — |
| | ceftriaxone | 1–32 | 4 | 4 | 99.7 |
| | vancomycin | 0.25–2 | 1 | 1 | 100 |
| | linezolid | 0.25–2 | 2 | 2 | 100 |
| methicillin resistant (1237) | ceftaroline | 0.25–2 | 1 | 1 | — |
| | ceftriaxone | 1 to >32 | 32 | >32 | 0 |
| | vancomycin | 0.25–2 | 1 | 1 | 100 |
| | linezolid | 0.25–2 | 2 | 2 | 100 |
| Coagulase-negative staphylococci | | | | | |
| all isolates (641) | ceftaroline | ≤0.008–4 | 0.25 | 1 | — |
| | ceftriaxone | ≤0.25 to >32 | 16 | >32 | 25.3 |
| | vancomycin | ≤0.12–4 | 2 | 2 | 100 |
| | linezolid | 0.12 to >8 | 1 | 1 | 99.2 |
| *Enterococcus faecalis* | | | | | |
| all isolates (613) | ceftaroline | 0.12 to >16 | 2 | 8 | — |
| | ceftriaxone | 1 to >32 | >32 | >32 | — |
| | vancomycin | 0.5 to >16 | 1 | 2 | 95.6 |
| | linezolid | 0.25–2 | 1 | 2 | 100 |
| β-Haemolytic streptococci | | | | | |
| all isolates (596) | ceftaroline | ≤0.008–0.06 | ≤0.008 | 0.015 | — |
| | ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25 | 100 |
| | vancomycin | 0.25–1 | 0.5 | 0.5 | 100 |
| | linezolid | 0.5–2 | 1 | 1 | 100 |
| Viridans group streptococci | | | | | |
| all isolates (190) | ceftaroline | ≤0.008–1 | 0.03 | 0.06 | — |
| | ceftriaxone | ≤0.25–16 | ≤0.25 | 0.5 | 93.7 |
| | vancomycin | 0.25–1 | 0.5 | 0.5 | 100 |
| | linezolid | 0.25–2 | 1 | 1 | 100 |
| penicillin non-susceptible (42) | ceftaroline | ≤0.008–1 | 0.03 | 0.5 | — |
| | ceftriaxone | ≤0.25–16 | ≤0.25 | 8 | 71.4 |
| | vancomycin | 0.25–0.5 | 0.5 | 0.5 | 100 |
| | linezolid | 0.5–1 | 0.5 | 1 | 100 |

D. Biek et al., *J. Antimicrob. Chemo.* (2010) **65** supplement 4: iv9-16

# Cephalosporins Summary

## MOA

- Bind to PBPs (transpeptidase enzymes), disrupting cell wall synthesis
- Bactericidal
- Time-dependent, concentration-independent activity: maintain [drug]>MIC, maximal killing ~4-5xMIC

## Spectrum of activity

- Gen1: Mostly Gram+, less against Gram-
- Gen2,3: generations: More Gram- activity, give up some Gram+ coverage
- Gen4: Broad spectrum, Gram+ and Gram- activity
- Early generation oral drugs: used for less serious community-acquired infections
- Later generation IV/IM drugs: used for hospital-acquired infections, serious infections

## Resistance

- Beta-lactamases
- Altered PBP binding site
- Decreased drug penetration

## Distribution

- Generally good distribution throughout
- Only some have penetration to CSF
- Generally elimination through kidneys

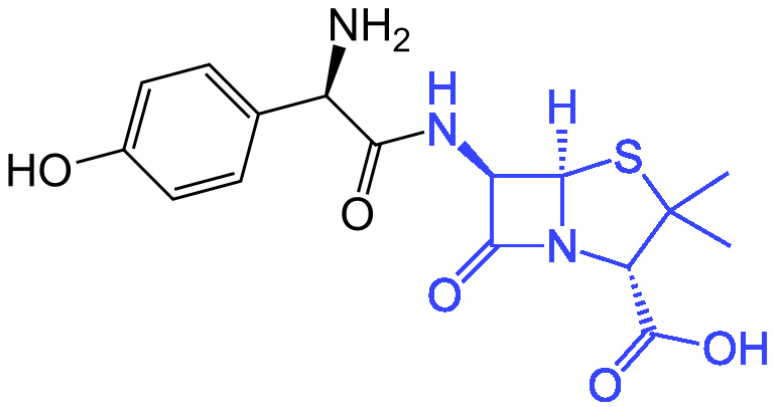
# Cephalosporins Summary

## Adverse reactions

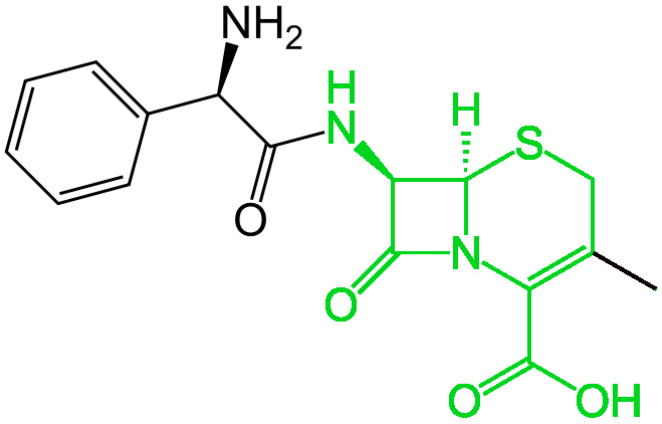
- Hypersensitivity
- <10% cross-reactivity of penicillin-allergic patients with cephalosporins
  - If patient has had an immediate, serious reaction to penicillin, would not give ceph
  - If patient had a delayed, less serious reaction to penicillin, could try ceph with caution; early generations more cross-reactivity, later generations less so
- Those containing N-MTT or N-MTD: bleeding reaction, disulfram-like alcohol hypersensitivity
- Rash
- Diarrhea: broader spectrum, bigger issue

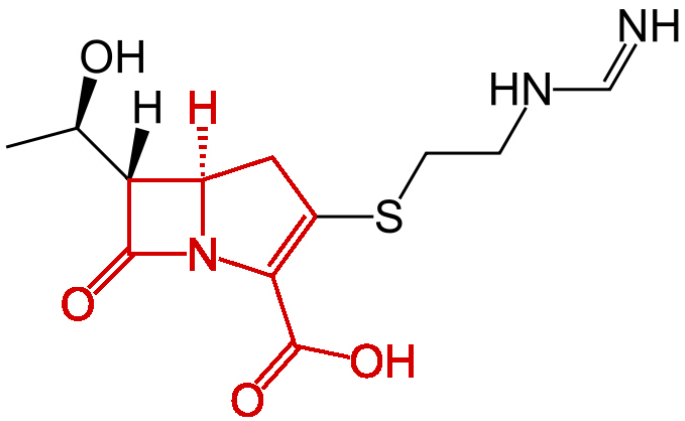
# Beta-lactam antibiotics

*Amoxicillin* (penicillin)

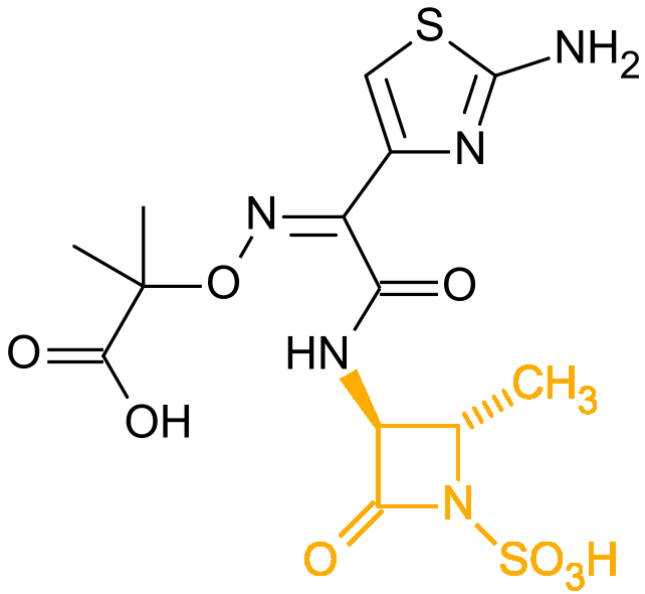



*Cephalexin* (cephalosporin)



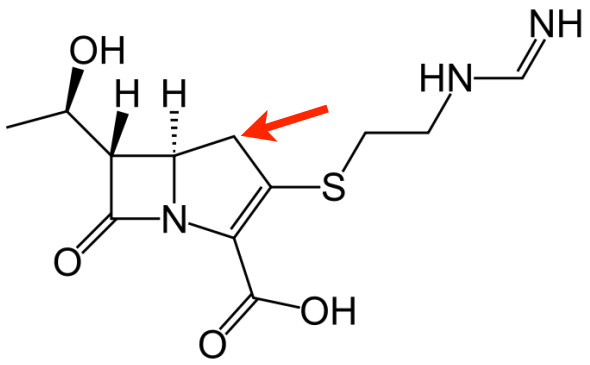




*Imipenem* (carbapenem)

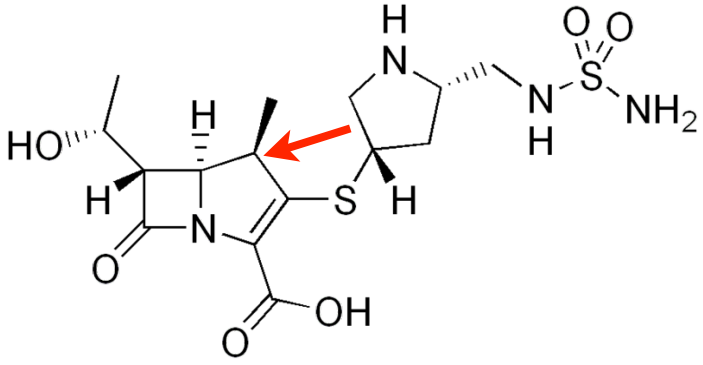



*Aztreonam* (monobactam)

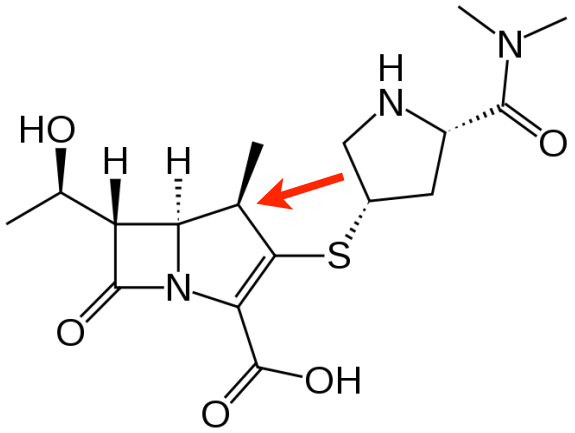
# Beta-lactam antibiotics: Carbapenems



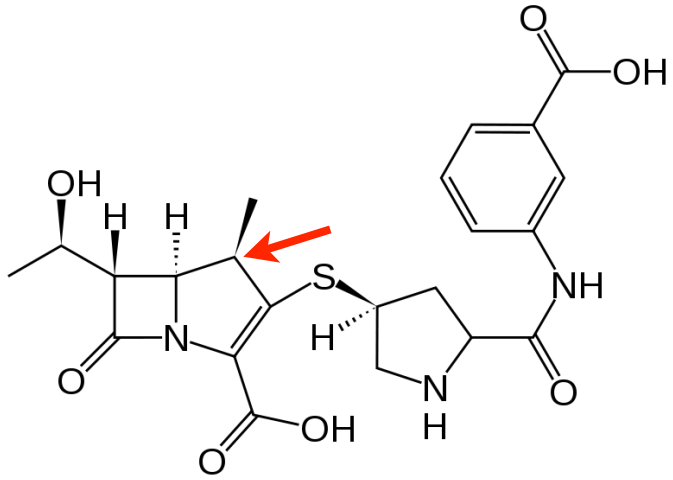
*Imipenem*



*Doripenem*



*Meropenem*



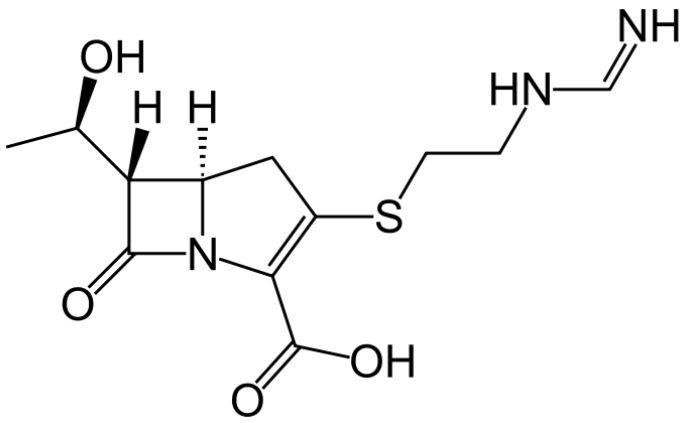
*Ertapenem*

- Carbon instead of sulfur in 5-membered ring (→)
- All are IV products, none oral

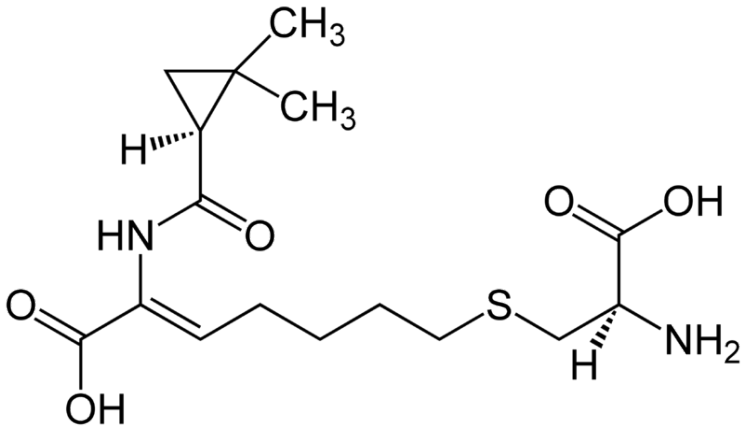
# Carbapenems: general features

- Highly resistant to most beta-lactamases
  - Including to ESBLs and AmpC
  - Carbapenemases are emerging (KPC, VIM, NDM-1)
  - Induce expression of chromosomal beta-lactamases (though not degraded), thus switching to another beta-lactam after carbapenem not advised
- Extremely broad spectrum; broader than penicillins, cephalosporins
  - *Pseudomonas* coverage (not ertapenem), but MICs pretty high (all IV)
  - Not *MRSA*
  - Not *Enterococci*
- Reserved for last line use or complicated cases
  - Used for polymicrobial infections
  - If multi-drug resistance is evident
- Relatively low toxicity

# Carbapenems: Imipenem + Cilastatin




*Imipenem*




*Cilastatin*

- Primaxin ® (Merck)
- Combined with cilastatin because normally imipenem would be hydrolyzed by a renal dihydropeptidase enzyme (DHP-1). Cilastatin inhibits this enzyme.
  - Other carabapenems more stable, do not require DHP-1 inhibitor
- Impipenem unusual in that it actually also inhibits some beta-lactamases
- Risk for seizures (1.5-2%), thus not indicated for meningitis

# Carbapenems: Imipenem + Cilastatin

## ◉ Indicated microbial spectra:

**Gram-positive aerobes:**

Enterococcus faecalis
(NOTE: Imipenem is inactive against Enterococcus faecium)
Staphylococcus aureus including penicillinase-producing strains
(NOTE: **not MRSA**.)
Staphylococcus epidermidis including penicillinase-producing strains
Streptococcus agalactiae (Group B streptococci)
Streptococcus pneumoniae
Streptococcus pyogenes

**Gram-negative aerobes:**

Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Escherichia coli
Gardnerella vaginalis
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella spp.
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Pseudomonas aeruginosa
(NOTE: Imipenem is inactive in vitro against Xanthomonas (Pseudomonas) maltophilia and some strains of P. cepacia.)
Serratia spp., including S. marcescens

**Gram-positive anaerobes:**

Bifidobacterium spp.
Clostridium spp.
Eubacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp.

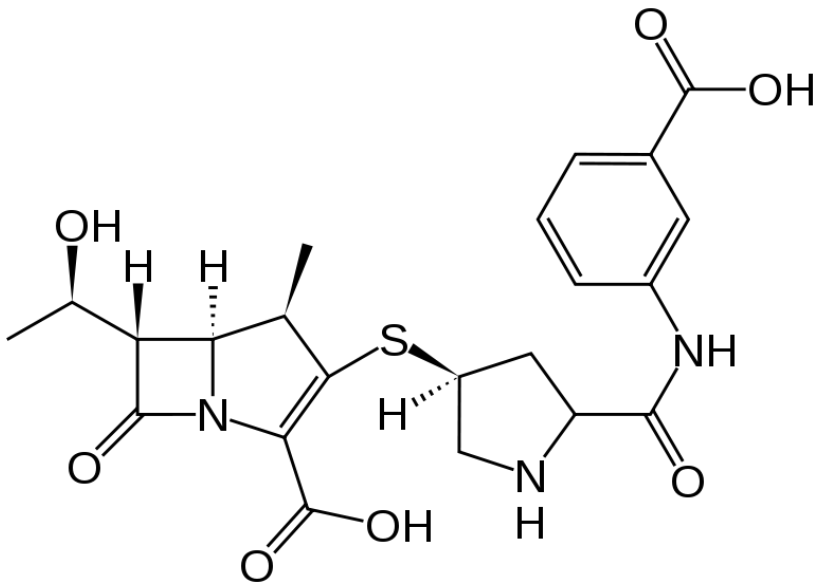
**Gram-negative anaerobes:**

Bacteroides spp., including B. fragilis
Fusobacterium spp.

# Imipenem + Cilastatin: indicated uses

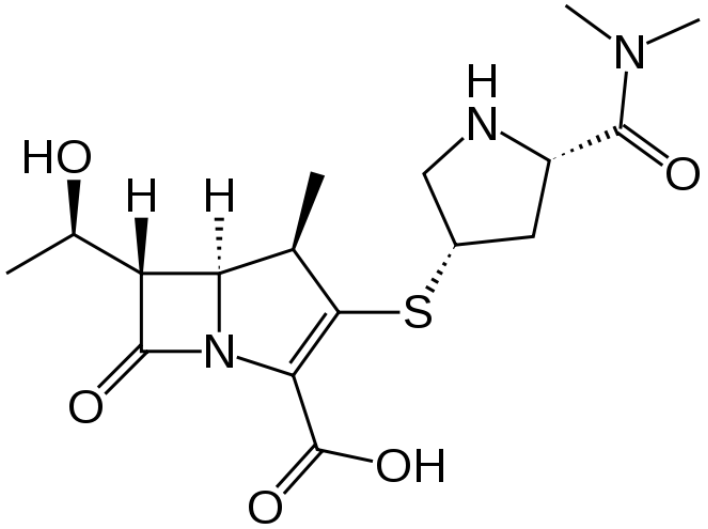
- Lower respiratory tract infections
- UTI, complicated and uncomplicated
- Intra-abdominal infections
- Gynecological infections
- Septicemia
- Osteomyelitis: bone and joint infections
- Skin infections
- Endocarditis
- Polymicrobial infections

# Carbapenems: Meropenem



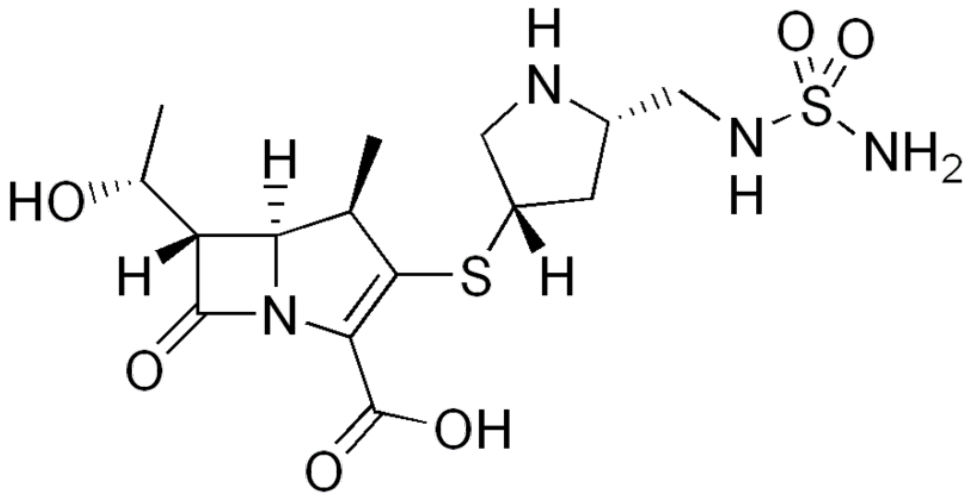

- Merrem ® (AstraZeneca)
- Lower seizure risk (0.4%) than imipenem. Penetrates to CSF. Inidicated use for meningitis caused by *S. pneumoniae, H. influenzae, N. meningiditis*
- Other indicated uses:
  - Intra-abdominal infections caused by *Strep. viridans, E. coli, Klebsiella pneumoniae, P. aeruginosa, B. fragilis*
  - Complicated skin infections (not MRSA)

# Carbapenems: Ertapenem



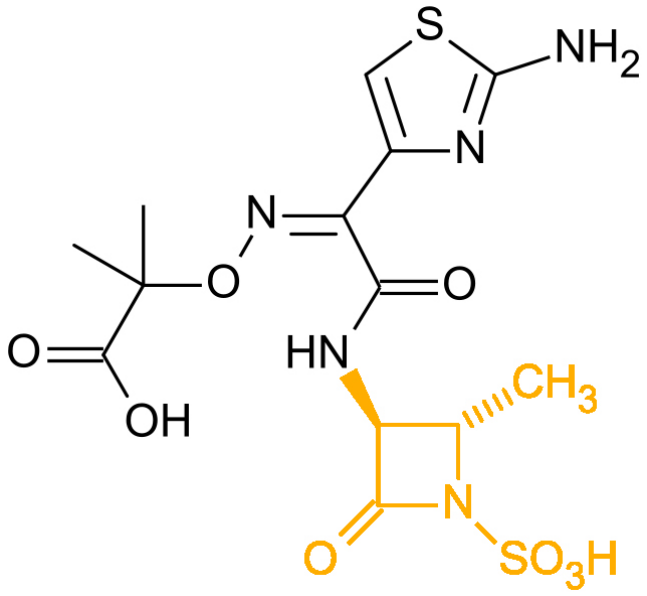

- Invanz ® (Merck)
- Possibly more susceptible to ESBL and AmpC than other carbapenems
- Very broad spectrum, thus good for polymicrobial infections
  - But not covering *PRSP*, not *MRSA*, not *Pseudomonas*
- Other indicated uses:
  - Complicated intra-abdominal infections
  - Complicated skin infections (not MRSA)
  - Complicated UTI
  - Pelvic infections
  - CAP (not involving PRSP)

# Carbapenems: Doripenem




- Doxibax ® (Ortho-McNeil)
- Very good activity against Gram-, including *Pseudomonas* and anaerobes
- Other indicated uses:
  - Complicated intra-abdominal infections
  - Complicated skin infections (not MRSA)
  - Complicated UTI
  - Pelvic infections
  - CAP (not involving PRSP)

# Monobactam: Aztreonam (IV, inhaled)




- Azactam® (Squibb), Cayston® (Gilead) and generics
- Natural product, but now produced synthetically
- Gram- spectrum, similar to aminoglycosides; (minimal Gram+ and anaerobe)
  - Activity against *Pseudomonas* (Cayston inhaled formulation: indicated for *P. aeruginosa* CF patient)
- Resistant to most beta-lactamases but not ESBL
- No penicillin allergy cross-reactivity

# Beta-lactamases

- Penicillinases (e.g. *S. aureus*)
  - Degrade penicillins (not penicillin-resistant penicillins)
- AmpC
  - Degrade penicillins, cephalosporins (possibly not cefepime)
  - Gram- bacteria: *P. aeruginosa*, *Citrobacter*, *Enterobacter*, *Serratia*, *E. coli* (not inducible)
  - Not inhibited by beta-lactamase inhibitors
- Extended Spectrum Beta-lactamases (ESBL)
  - Degrade cephalosporins, aztreonam (monobactam)
  - Mostly in *Enterobacteriaceae: Klebsiella*, *E. coli*, *Citrobacter*, *Proteus*, *Serratia*, *Salmonella, Morganella*
  - Susceptible to beta-lactamase inhibitors, but lactamase production may overwhelm
  - Often plasmid-encoded alongside other drug-resistance genes
- Carbapenemases
  - Notable examples: KPC, VIM, NDM-1

# Emergence of carbapenemases

TABLE 4. Substrate and inhibition profiles of the carbapenemases

| Molecular class | Functional group | Enzyme | Hydrolysis profile[a] | | | | | Inhibition profile[b] | | Reference(s) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Penicillins | Early cephalosporins | Extended-spectrum cephalosporins | Aztreonam | Carbapenems | EDTA | Clavulanic acid | |
| A | 2f | NMC | + | + | + | + | + | − | + | 124 |
| | | IMI | + | + | + | + | + | − | + | 183 |
| | | SME | + | + | ± | + | + | − | + | 179 |
| | | KPC | + | + | + | + | + | − | + | 4 |
| | | GES | + | + | + | − | ± | − | + | 174, 219 |
| B1 | 3 | IMP | + | + | + | − | + | + | − | 224 |
| | | VIM | + | + | + | − | + | + | − | 224 |
| | | GIM | + | + | + | − | + | + | − | 224 |
| | | SPM | + | + | + | − | + | + | − | 224 |
| D | 2d | OXA | + | + | ± | − | ± | − | ± | 225 |

[a] Symbols: +, strong hydrolysis (generally, $k_{cat}$ of >2 $s^{-1}$); ±, weak hydrolysis (generally, $k_{cat}$ of 0.5 to 2 $s^{-1}$); −, no measurable hydrolysis reported (generally, $k_{cat}$ of <0.5 $s^{-1}$).
[b] Symbols: +, reported inhibition; ±, variable inhibition among β-lactamase family members; −, no inhibition reported.

- KPC: *Klebsiella pneumonia carbapenemase*
  - A group 2f carbapenemase encoded on plasmids
  - *K. pneumoniae*, now broader spectrum of *Enterobacteriaceae*
- NDM: *New Dehli Metallo-beta lactamase* (a carbapenemase)
  - A group 3 metallo-beta lactamase encoded on plasmids
  - *K. pneumoniae*, *Acinetobacter baumanii*, now *E. coli*

AM Queenan and K Bush, *Clinical Microbiol. Rev.* (2007) **20:** 440

# NDM-1

- 2008 man hospitalized in Sweden presents *K. pneumoniae* showing an unprecedented level of multi-drug resistance including to carbapenems. Only colistin effective.
  - Infection acquired in New Dehli where the man had travelled before returning to Sweden.
- 2009 one NDM-1 case in Austria has tie to Southeast Asia, one has no such link suggesting a local source
- 2009 Canada: woman while spending 3.5 months in India developed diarrhea, persists for a month, hospitalized as health worsens, develops UTI, encephalitis, evacuated to Canada.
  - Treated unsuccessfully with vancomycin, imipenem
  - NDM-1 identified, but not from *Klebsiella*, from *E. coli*
- 2010 USA: 3 cases with links to medical treatment in India
- 2011 survey of 50 street taps in India, 2 harbor bacteria with NDM-1 gene; of 171 street water, 51 harbor bacteria with NDM-1 gene. Suggests NDM-1 carbapenemase is out of nosicomial environment

**Antibiotic Susceptibility of *Klebsiella pneumoniae* (ATCC® BAA-2146™)**

| Antimicrobial | MIC[a] | Interpretation[b] |
|---|---|---|
| Amikacin | ≥64 | R |
| Amoxicillin / Clavulanic Acid | ≥32 | R |
| Ampicillin | ≥32 | R |
| Ampicillin / Sulbactam | ≥32 | R |
| Aztreonam | ≥64 | R |
| Cefalotin | ≥64 | R |
| Cefazolin | ≥64 | R |
| Cefepime | ≥64 | R |
| Cefotaxime | ≥64 | R |
| Cefotetan | ≥64 | R |
| Cefoxitin | ≥64 | R |
| Cefpodoxime | ≥8 | R |
| Ceftazidime | ≥64 | R |
| Ceftizoxime | ≥64 | R |
| Ceftriaxone | ≥64 | R |
| Cefuroxime | ≥64 | R |
| Cefuroxime Axetil | ≥64 | R |
| Ciprofloxacin | ≥4 | R |
| Gentamicin | ≥16 | R |
| Imipenem | ≥16 | R |
| Levofloxacin | ≥8 | R |
| Meropenum | ≥16 | R |
| Moxifloxacin | ≥8 | R |
| Nalidixic Acid | ≥32 | R |
| Nitrofurantoin | ≥512 | R |
| Norfloxacin | ≥16 | R |
| Piperacillin | ≥128 | R |
| Piperacillin / Tazobactam | ≥128 | R |
| Tetracycline | ≥16 | R |
| Tecarcillin | ≥128 | R |
| Ticarcillin / Clavulanic Acid | ≥128 | R |
| Tigecycline | ≥8 | R |
| Tobramycin | ≥16 | R |
| Trimethoprim / Sulfamethoxazole | ≥320 | R |

a. Antibiotic susceptibility was obtained using Vitek® 2 AST-GN24 and AST-EXN7 cards
b. Parameter Set: MIC Interpretation Guideline: CLSI M100-S16 (2006)
Therapeutic Interpretation Guideline: Natural Resistance

https://www.atcc.org/CulturesandProducts/Microbiology/FeaturedCultures/tabid/1788/Default.aspx