Cephalosporins

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.

Semi-synthetic cephalosporins

- Cephalosporin C had poor bioavailability, rapidly cleared.
- All cephalosporins in use are of the semi-synthetic variety, no equivalents to Pen G and V in use.
- Cleave off natural sidechain to yield 7-aminocephalosporanic acid (7-ACA) core, which then could be synthetically substituted with other sidechains (R1, R2).
- Alter the spectrum, stability, bioavailability, resistance to beta-lactamases.
- More modifications possible than w/ penicillins.
Cephamycin general features

- Cephamycin beta-lactams + cephalosporins = cephems (but we will use “cephalosporin” to refer to both).
- Originally isolated from *Streptomyces*; now semi-synthetic derivatives
- Cephamycins have an O-methylated beta-lactam ring
- Good anaerobic activity

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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
- Low toxicity:
  - Lower allergenicity than penicillins though still some due to beta-lactam ring opening (10% cross-reactivity with penicillins)
Cephalosporins general features

- Other adverse drug reactions:
  - Some such as 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 gut flora changes vitamin K production, 2) direct interaction of N-MTT with prothrombin, 3) platelet dysfunction. First noted with moxalactam (2-3% fatalities; off market).
  - N-MTT also can inhibit aldehyde dehydrogenase, giving rise to a disulfiram-like reaction following alcohol consumption. Intense hang-over feeling, hyper-sensitivity to alcohol.

![Cefotetan](image)

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

Underlined are on UW formulary

<table>
<thead>
<tr>
<th>generation</th>
<th>name</th>
<th>brand name</th>
<th>structure</th>
<th>dose</th>
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<tbody>
<tr>
<td>1</td>
<td>cephalexin</td>
<td>generic</td>
<td><img src="image" alt="structure" /></td>
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<tr>
<td></td>
<td>cephradine</td>
<td>generic</td>
<td><img src="image" alt="structure" /></td>
<td>BID</td>
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<tr>
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<td>cefadroxil</td>
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<td><img src="image" alt="structure" /></td>
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</tr>
<tr>
<td>2</td>
<td>cefaclor</td>
<td>generic</td>
<td><img src="image" alt="structure" /></td>
<td>TID</td>
</tr>
<tr>
<td>2</td>
<td>cefuroxime</td>
<td>generic</td>
<td><img src="image" alt="structure" /></td>
<td>BID</td>
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<tr>
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<td>cefprozil</td>
<td>generic</td>
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Table - Oral Cephalosporins

<table>
<thead>
<tr>
<th>generation</th>
<th>name</th>
<th>brand name</th>
<th>structure</th>
<th>dose</th>
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<tbody>
<tr>
<td>1</td>
<td>cephalexin</td>
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<tr>
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<td>cefprozil</td>
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</table>

Courtesy Prof. Gary Elmer
### Oral cephalosporins (cont.)

<table>
<thead>
<tr>
<th>Generation</th>
<th>Cephalosporin</th>
<th>Brand Name</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>3</td>
<td>cefpodoxime</td>
<td>proxetil</td>
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<tr>
<td>3</td>
<td>ceftibutin</td>
<td>Cedax®</td>
<td>qd</td>
</tr>
<tr>
<td>3</td>
<td>cefdinir</td>
<td>generic</td>
<td>BID</td>
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<tr>
<td>3</td>
<td>cefditoren</td>
<td>pivoxil</td>
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</tr>
<tr>
<td>3</td>
<td>cefixime</td>
<td>Suprax®</td>
<td>qd</td>
</tr>
</tbody>
</table>

### Parenteral cephalosporins/cephamycins

![Parenteral Cephalosporins and Cephamycins](image_url)

<table>
<thead>
<tr>
<th>Generation</th>
<th>Name</th>
<th>Brand Name</th>
<th>Cephalosporin Structure</th>
<th>*Cephamycin Structure</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cefazolin</td>
<td>generic</td>
<td>R_1 -NH_O_N_N_CH_3 -CH_3</td>
<td>O_CH_2_O_CH_3</td>
<td>TID</td>
</tr>
<tr>
<td>2</td>
<td>cefoxitin*</td>
<td>generic</td>
<td>R_1 -NH_O_N_N_CH_3 -CH_3</td>
<td>O_CH_2_O_CH_3</td>
<td>QID</td>
</tr>
<tr>
<td>2</td>
<td>cefotetan*</td>
<td>generic</td>
<td>R_1 -NH_O_N_N_CH_3 -CH_3</td>
<td>O_CH_2_O_CH_3</td>
<td>BID</td>
</tr>
<tr>
<td>2</td>
<td>cefuroxime</td>
<td>generic</td>
<td>R_1 -NH_O_N_N_CH_3 -CH_3</td>
<td>O_CH_2_O_CH_3</td>
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<tr>
<td>3</td>
<td>cefotaxime</td>
<td>generic</td>
<td>R_1 -NH_O_N_N_CH_3 -CH_3</td>
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<tr>
<td>3</td>
<td>ceftizoxime</td>
<td>Cefizox®</td>
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<td>O_CH_2_O_CH_3</td>
<td>TID</td>
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<tr>
<td>3</td>
<td>ceftriaxone</td>
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<td>R_1 -NH_O_N_N_CH_3 -CH_3</td>
<td>O_CH_2_O_CH_3</td>
<td>qd</td>
</tr>
</tbody>
</table>

**Table - Parenteral Cephalosporins and Cephamycins**

*Courtesy Prof. Gary Elmer*
### Formulary Oral Cephalosporins

#### a) General comments:
- Used for follow-up and ambulatory patient therapy, UTI (pen. Allergic), otitis media, staph. URI, LRI

#### b) First Generation
- **Cephalexin Keflex**
- **Dista and generics**
- **Indications:**
  1. Respiratory tract – *Strep. pneumoniae* and *Strep. pyogenes*
  2. Otitis media – *Strep. pneumoniae*, *H. flu*, *M. cat.* (the *H. flu* and *M. cat.* may be resistant)
  4. Bone – *Staph.*, *Proteus mirabilis*
  5. GU – *E. coli*, *Klebsiella*, *Proteus mirabilis*

#### c) Second Generation
- **Cefuroxime Axetil**  
  - **Ceftin® Glaxo Wellcome and generic**
  - Broad spectrum oral cephalosporin that gets into CNS
  - **Indications:**
  1. Pharyngitis and tonsillitis – *Strep. pyogenes*
  2. Otitis media – *Strep. pneumoniae*, *M. cat.*, *H. flu*, including *-lactamase producing*
  3. Sinusitis – *Strep. pneumoniae*, *H. flu*
  4. Exacerbation of chronic bronchitis – *Strep. pneumoniae*, *H. flu*, *H. parainfluenzae*
  5. UTI – *E. coli*, *Klebsiella*, *Proteus*
  7. GU – *E. coli*, *Klebsiella*, *Proteus*
  8. Impetigo – *Staph.*, *Strep.*

#### d) Third Generation
- **Cefpodoxime proxetil**  
  - **Vantin**
  - **Pharmacia and now generic**
  - Broad spectrum, beta lactamase resistant cephalosporin
  - **Indications:**
  2. Chronic bronchitis – *Strep. pneumoniae*, *H. flu*, *M. cat.*
  3. Otitis media
  4. Pharyngitis
  5. STD – *N. gonorrheae*, 200mg stat single dose
  6. Uncomplicated skin infections – *Staph.*, *Strep. pyogenes*
  7. UTI

---

**Some oral cephalosporins are prodrugs**

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

---

<table>
<thead>
<tr>
<th></th>
<th>Cefazidime</th>
<th>Generic</th>
<th>Chemical Structure</th>
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</tr>
</tbody>
</table>

---

*Courtesy Prof. Gary Elmer*
Some parenteral cephalosporins are prodrugs

๏ Anatomy of a cephalosporin: ceftaroline (a gen-5 ceph)


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)

- 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
  - Bone and joint
- Some Gram- coverage: *E. coli*, *H. influenzae* (some resistance), *P. mirabilis*,
  - Urogenital
- 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)
- *Staph. epidermidis*
- *Strep. pneumoniae* (only penicillin-sensitive strains)
- *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)

- Ceftin ® (GSKB) and generics
- Prodrug: cefuroxime axetil converted to cefuroxime (also IV, not as prodrug)
- Indications:
  - Pharyngitis, Tonsillitis, 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)
- **Penetrates to CNS:** 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**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Rating</th>
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<tbody>
<tr>
<td>Loracarbef</td>
<td>+++</td>
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<tr>
<td>Cefdinir</td>
<td>+++</td>
</tr>
<tr>
<td>Cefixime</td>
<td>+++</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>+++</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>+++</td>
</tr>
<tr>
<td>Amoxicillin'</td>
<td>+++</td>
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<tr>
<td>Trimethoprim-sulfamethoxazole'</td>
<td>++</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>++</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate'</td>
<td>++</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>+</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>+</td>
</tr>
</tbody>
</table>

* Data modified from references 9-11

Comparative commonly prescribed agent in pediatric patients

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

Cefotaxime (Gen3, Parenteral IV/IM)

- **Clafon®** (Sanofi Aventis)
- Cefotaxime becomes deacetylated, resulting desacetylcefoxime 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

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)

- Fortum ® (GSK)
- Broad spectrum; Gram-, some 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**
  - 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

<table>
<thead>
<tr>
<th>Organism (number of isolates)</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>range</td>
</tr>
<tr>
<td><strong>Gram-positive</strong></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
</tr>
<tr>
<td>MRSA (102)</td>
<td>0.03–0.5</td>
</tr>
<tr>
<td>MRSA (105)</td>
<td>0.5–2</td>
</tr>
<tr>
<td>vancomycin reduced susceptibility (647)</td>
<td>0.25–2</td>
</tr>
<tr>
<td>linazolid non-susceptible (13)</td>
<td>0.5–2</td>
</tr>
<tr>
<td>Streptococcus pyogenes (102)</td>
<td>≤0.008–0.015</td>
</tr>
<tr>
<td>Streptococcus agalactiae (104)</td>
<td>≤0.008–0.03</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td></td>
</tr>
<tr>
<td>vancomycin susceptible (102)</td>
<td>0.25–16</td>
</tr>
<tr>
<td>vancomycin resistant (108)</td>
<td>0.5–16</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td></td>
</tr>
<tr>
<td>penicillin susceptible (MIC ≤0.06 mg/L) (102)</td>
<td>≤0.008–0.06</td>
</tr>
<tr>
<td>penicillin intermediate (MIC 0.12 – 1 mg/L) (102)</td>
<td>≤0.008–0.12</td>
</tr>
<tr>
<td>penicillin-resistant (MIC ≥ 2 mg/L) (100)</td>
<td>0.03–0.5</td>
</tr>
<tr>
<td>≤0.006–0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>levofloxacin non-susceptible (53)</td>
<td>≤0.008–0.5</td>
</tr>
<tr>
<td>multi-drug resistant (≥ 2 classes) (127)</td>
<td>≤0.008–0.5</td>
</tr>
<tr>
<td><strong>Gram-negative</strong></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td></td>
</tr>
<tr>
<td>ceftazidime susceptible (102)</td>
<td>0.015–8</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td></td>
</tr>
<tr>
<td>ceftazidime susceptible (102)</td>
<td>0.015–1</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td></td>
</tr>
<tr>
<td>β-lactamase negative (130)</td>
<td>≤0.008–0.25</td>
</tr>
<tr>
<td>β-lactamase positive (101)</td>
<td>≤0.008–0.12</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (101)</td>
<td>4 to &gt;16</td>
</tr>
<tr>
<td>Acinetobacter baumannii (101)</td>
<td>2 to &gt;16</td>
</tr>
</tbody>
</table>

---

respectively) and β-lactamase-positive and -negative isolates of *Haemophilus influenzae* (MIC<sub>90</sub>s, 0.03 and 0.015 mg/L, respectively) (Table 1). Ceftaroline is inactive against extended-spectrum β-lactamase (ESBL)-producing or AmpC-overexpressing Enterobacteriaceae (data not shown) and has limited activity against non-fermenting Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, with MIC<sub>90</sub>s of 16 mg/L for both organisms (Table 1).

The spectrum of activity of ceftaroline makes it attractive as a new agent for treating cSSSIs. The activity of ceftaroline against contemporary cSSSI clinical isolates was further explored in a surveillance study conducted in the USA and Europe in 2008.

Ceftaroline exhibited broad-spectrum activity against key skin pathogens, including *S. aureus* and β-haemolytic streptococci (Table 2). For MRSA, MIC<sub>90</sub> s of ceftaroline, vancomycin and linezolid were 1, 1 and 2 mg/L, respectively. Ceftaroline also retained activity against the penicillin-non-susceptible viridans group streptococci (MIC<sub>90</sub>, 0.5 mg/L) compared with ceftriaxone, which was less active (MIC<sub>90</sub>, 8 mg/L).

**Basic PK and PD profile**

Ceftaroline fosamil is a prodrug that is rapidly converted by plasma phosphatases into active ceftaroline following intravenous (iv) administration (Figure 3). Phase III clinical studies have evaluated the efficacy of 600 mg of ceftaroline.

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

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antimicrobial agent</th>
<th>range</th>
<th>50%</th>
<th>90%</th>
<th>Susceptible (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methicillin susceptible (1554)</td>
<td>ceftaroline</td>
<td>≤0.008-1</td>
<td>0.25</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>1-32</td>
<td>4</td>
<td>4</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25-2</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.25-2</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>methicillin resistant (1237)</td>
<td>ceftaroline</td>
<td>0.25-2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>1 to &gt;32</td>
<td>32</td>
<td>&gt;32</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25-2</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.25-2</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all isolates (643)</td>
<td>ceftaroline</td>
<td>≤0.008-4</td>
<td>0.25</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>≥0.25 to &gt;32</td>
<td>16</td>
<td>&gt;32</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>≤0.12-4</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.12 to &gt;8</td>
<td>1</td>
<td>1</td>
<td>99.2</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all isolates (613)</td>
<td>ceftaroline</td>
<td>0.12 to &gt;16</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>1 to &gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.5 to &gt;16</td>
<td>1</td>
<td>2</td>
<td>95.6</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.25-2</td>
<td>1</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>β-Haemolytic streptococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all isolates (596)</td>
<td>ceftaroline</td>
<td>≤0.008-0.06</td>
<td>≤0.008</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>≤0.25</td>
<td>≤0.25</td>
<td>≤0.25</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25-1</td>
<td>0.5</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.5-2</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Viridans group streptococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all isolates (190)</td>
<td>ceftaroline</td>
<td>≤0.008-1</td>
<td>0.03</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>≤0.25-16</td>
<td>≤0.25</td>
<td>0.5</td>
<td>93.7</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25-1</td>
<td>0.5</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.25-2</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>penicillin non-susceptible (42)</td>
<td>ceftaroline</td>
<td>≤0.008-1</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>≤0.25-16</td>
<td>≤0.25</td>
<td>0.5</td>
<td>71.4</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25-0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.5-1</td>
<td>0.5</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>
Beta-lactam antibiotics: Carbapenems

- **Imipenem**
- **Meropenem**
- **Doripenem**
- **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

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

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-positive anaerobes:**
- Bifidobacterium spp.
- Clostridium spp.
- Eubacterium spp.
- Peptococcus spp.
- Peptostreptococcus spp.
- Propionibacterium spp.

**Gram-negative anaerobes:**
- Bacteroides spp., including B. fragilis
- Fusobacterium spp.

**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
Imipenem + Cilastatin: indicated uses

- Lower respiratory tract infections
- UTI, complicated and uncomplicated
- Intra-abdominal infections
- Gynecological infections
- Septicemia
- Bone and Joint infections
- Skin infections
- Endocarditis
- Polymicrobial infections

Carbapenems: Meropenem

- Merrem ® (AstraZeneca)
- Lower seizure risk (0.4%) than imipenem. Indicated use for meningitis caused by *S. pneumoniae, H. influenzae, N. meningitidis*

  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)
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