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.
- Slightly different nucleus shape made them more resistant to penicillinases.
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: ceftriaxone, 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
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 dehydrogenase, giving rise to a disulfram-like reaction following alcohol consumption. Intense hang-over feeling, hyper-sensitivity to alcohol.
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
Some penetrate to the CNS:

- Cefuroxime
- Cefotaxime
- Ceftazidime
- Ceftriaxone
### Oral cephalosporins

![Chemical structure of cephalosporins]

### Table - Oral Cephalosporins

<table>
<thead>
<tr>
<th>generation</th>
<th>name</th>
<th>brand name</th>
<th>structure</th>
<th>dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cephalaxin</td>
<td>generic</td>
<td><img src="image" alt="Structure" /></td>
<td>-CH₃</td>
</tr>
<tr>
<td>1</td>
<td>cephradine</td>
<td>generic</td>
<td><img src="image" alt="Structure" /></td>
<td>-CH₃</td>
</tr>
<tr>
<td>1</td>
<td>cefadroxil</td>
<td>generic</td>
<td><img src="image" alt="Structure" /></td>
<td>-CH₃</td>
</tr>
<tr>
<td>2</td>
<td>cefaclor</td>
<td>generic</td>
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<td>-Cl</td>
</tr>
<tr>
<td>2</td>
<td>cefuroxime</td>
<td>generic</td>
<td><img src="image" alt="Structure" /></td>
<td>CH₂OCHNH₂</td>
</tr>
<tr>
<td>2</td>
<td>cefprozil</td>
<td>generic</td>
<td><img src="image" alt="Structure" /></td>
<td>-CH=CHCH₃</td>
</tr>
<tr>
<td>3</td>
<td>Cephalosporin</td>
<td>Brand Name</td>
<td>Structure</td>
<td>Function</td>
</tr>
<tr>
<td>----</td>
<td>----------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>3</td>
<td>cefpodoxime proxetil</td>
<td>generic</td>
<td><img src="image" alt="Structure of cefpodoxime proxetil" /></td>
<td>-CH₂OCH₃</td>
</tr>
<tr>
<td>3</td>
<td>ceftibutin</td>
<td>Cedax®</td>
<td><img src="image" alt="Structure of ceftibutin" /></td>
<td>-H</td>
</tr>
<tr>
<td>3</td>
<td>cefdinir</td>
<td>generic</td>
<td><img src="image" alt="Structure of cefdinir" /></td>
<td>-CH=CH₂</td>
</tr>
<tr>
<td>3</td>
<td>cefditoren pivoxil</td>
<td>generic</td>
<td><img src="image" alt="Structure of cefditoren pivoxil" /></td>
<td>-CH₂OCOC(CH₃)₃</td>
</tr>
<tr>
<td>3</td>
<td>cefixime</td>
<td>Suprax®</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>
## Parenteral cephalosporins/cephamycins

### Table - Parenteral Cephalosporins and Cephamycins

<table>
<thead>
<tr>
<th>Generation</th>
<th>Name</th>
<th>Brand Name</th>
<th>Structure</th>
<th>Cephamycin Structure</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cefazolin</td>
<td>Generic</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Cephamycin Structure" /></td>
<td>TID</td>
</tr>
<tr>
<td>2</td>
<td>Cefoxitin*</td>
<td>Generic</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Cephamycin Structure" /></td>
<td>QID</td>
</tr>
<tr>
<td>2</td>
<td>Cefotetan*</td>
<td>Generic</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Cephamycin Structure" /></td>
<td>BID</td>
</tr>
<tr>
<td>2</td>
<td>Cefuroxime</td>
<td>Generic</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Cephamycin Structure" /></td>
<td>TID</td>
</tr>
<tr>
<td>3</td>
<td>Cefotaxime</td>
<td>Generic</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Cephamycin Structure" /></td>
<td>TID</td>
</tr>
<tr>
<td>3</td>
<td>Ceftizoxime</td>
<td>Cefizox®</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Cephamycin Structure" /></td>
<td>TID</td>
</tr>
<tr>
<td>3</td>
<td>Ceftriaxone</td>
<td>Generic</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Cephamycin Structure" /></td>
<td>qd</td>
</tr>
</tbody>
</table>
**Parenteral cephalosporins/cephamycins (cont.)**

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Form</th>
<th>Chemical Structure</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ceftazidime</td>
<td>generic</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>TID</td>
</tr>
<tr>
<td>4</td>
<td>cefepime</td>
<td>generic</td>
<td><img src="" alt="Chemical Structure" /></td>
<td>BID</td>
</tr>
</tbody>
</table>
Example: ceftaroline (a gen-5 ceph)

1,2,4-thiadiazole ring, Gram-negative penetration; increased affinity for transpeptidase enzyme

1,3-thiazole ring, anti-MRSA activity

phosphono group, increases solubility; present in prodrug, not present in active form

oxime group, β-lactamase resistance

pyridine ring zwitterion (positive charge)

carboxyl group zwitterion (negative charge)

Cephem ring system

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

\[
\text{cefpodoxime proxetil} \quad \text{cefpodoxime}
\]
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*
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
  - Osteomyelitis: 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
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)

- 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
Taste Ratings for Oral Cephalosporin Suspensions*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loracarbef</td>
<td>++++</td>
</tr>
<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>
</tr>
<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
Cefotetan (Gen2, IV), a “cephamycin”

- 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)
inhibitory acyl-enzyme intermediate. A deacylation constant ($k_3$ value) could not be determined for the ceftaroline E$_2$I complex, which was essentially irreversible. In the presence of increasing concentrations of the cell wall surrogate, $k_2/K_d$ increased significantly for nitrocefin and imipenem, indicating enhanced formation of the open form of the active site. In contrast, the effect of the cell wall surrogate on the activity of ceftaroline was minimal, suggesting that only ceftaroline had the ability to efficiently bind to the allosteric site of PBP 2a, facilitating its access to the catalytic site where it inhibits transpeptidase activity.  

**In vitro microbiological activity**

Ceftaroline is a broad-spectrum cephalosporin with activity against clinically important Gram-positive bacteria, including many contemporary resistance phenotypes, as well as common Gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*. As shown in Table 1.

**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 50% 90%</td>
</tr>
<tr>
<td><strong>Gram-positive</strong></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>MSSA (102)</td>
<td>0.03–0.5 0.25 0.25</td>
</tr>
<tr>
<td>MRSA (105)</td>
<td>0.5–2 0.5 1</td>
</tr>
<tr>
<td>vancomycin reduced susceptibility (47)</td>
<td>0.25–2 1 2</td>
</tr>
<tr>
<td>linezolid non-susceptible (13)</td>
<td>0.5–2 1 2</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em> (102)</td>
<td>≤0.008–0.015 ≤0.008 ≤0.008</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> (104)</td>
<td>≤0.008–0.03 0.015 0.03</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td></td>
</tr>
<tr>
<td>vancomycin susceptible (102)</td>
<td>0.25–16 2 4</td>
</tr>
<tr>
<td>vancomycin resistant (108)</td>
<td>0.5–16 4 8</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>penicillin susceptible (MIC ≤0.06 mg/L) (102)</td>
<td>≤0.008–0.06 ≤0.008 0.03</td>
</tr>
<tr>
<td>penicillin intermediate (MIC 0.12–1 mg/L) (102)</td>
<td>≤0.008–0.12 0.03 0.06</td>
</tr>
<tr>
<td>penicillin resistant (MIC ≥2 mg/L) (100)</td>
<td>0.03–0.5 0.12 0.25</td>
</tr>
<tr>
<td>penicillin high-level resistant (MIC ≥8 mg/L) (40)</td>
<td>0.06–0.5 0.25 0.5</td>
</tr>
<tr>
<td>levofoxacin non-susceptible (53)</td>
<td>≤0.008–0.5 0.015 0.12</td>
</tr>
<tr>
<td>multidrug resistant (≥2 classes) (127)</td>
<td>≤0.008–0.5 0.12 0.25</td>
</tr>
<tr>
<td><strong>Gram-negative</strong></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td></td>
</tr>
<tr>
<td>ceftazidime susceptible (102)</td>
<td>0.015–8 0.12 0.25</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>ceftazidime susceptible (102)</td>
<td>0.015–1 0.06 0.5</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
</tr>
<tr>
<td>β-lactamase negative (110)</td>
<td>≤0.008–0.25 ≤0.008 0.015</td>
</tr>
<tr>
<td>β-lactamase positive (101)</td>
<td>≤0.008–0.12 ≤0.008 0.03</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> (101)</td>
<td>4 to &gt;16 &gt;16 &gt;16</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em> (101)</td>
<td>2 to &gt;16 &gt;16 &gt;16</td>
</tr>
</tbody>
</table>
respectively) and b-lactamase-positive and -negative isolates of *Haemophilus influenzae* (MIC$_{90}$s, 0.03 and 0.015 mg/L, respectively) (Table 1). Ceftaroline is inactive against extended-spectrum b-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$_{90}$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 b-haemolytic streptococci (Table 2). For MRSA, MIC$_{90}$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$_{90}$, 0.5 mg/L) compared with ceftriaxone, which was less active (MIC$_{90}$, 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 iv.

### 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>MIC (mg/L)</th>
<th>Susceptible (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>range</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methicillin susceptible (1554)</td>
<td>ceftaroline</td>
<td>$\leq 0.008$ – 1</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>1 – 32</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25 – 2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.25 – 2</td>
<td>2</td>
</tr>
<tr>
<td>methicillin resistant (1237)</td>
<td>ceftaroline</td>
<td>0.25 – 2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>1 to $&gt;32$</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25 – 2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.25 – 2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Coagulase-negative staphylococci</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all isolates (641)</td>
<td>ceftaroline</td>
<td>$\leq 0.008$ – 4</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>$\leq 0.25$ to $&gt;32$</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>$\leq 0.12$ – 4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.12 to $&gt;8$</td>
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</tr>
<tr>
<td><strong>Enterococcus faecalis</strong></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>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>1 to $&gt;32$</td>
<td>$&gt;32$</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.5 to $&gt;16$</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.25 – 2</td>
<td>1</td>
</tr>
<tr>
<td><strong>β-Haemolytic streptococci</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all isolates (596)</td>
<td>ceftaroline</td>
<td>$\leq 0.008$ – 0.06</td>
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<tr>
<td></td>
<td>ceftriaxone</td>
<td>$\leq 0.25$</td>
<td>$\leq 0.25$</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25 – 2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.5 – 2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Viridans group streptococci</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all isolates (190)</td>
<td>ceftaroline</td>
<td>$\leq 0.008$ – 1</td>
<td>0.03</td>
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<tr>
<td></td>
<td>ceftriaxone</td>
<td>$\leq 0.25$ – 16</td>
<td>$\leq 0.25$</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25 – 2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.25 – 2</td>
<td>1</td>
</tr>
<tr>
<td>penicillin non-susceptible (42)</td>
<td>ceftaroline</td>
<td>$\leq 0.008$ – 1</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>$\leq 0.25$ – 16</td>
<td>$\leq 0.25$</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>0.25 – 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>0.5 – 1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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
- Gen 1: Mostly Gram+, less against Gram-
- Gen 2, 3: More Gram- activity, give up some Gram+ coverage
- Gen 4: 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**
- **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 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
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) malthophilia 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. Indicated 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 cepfime)
- 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

<table>
<thead>
<tr>
<th>Molecular class</th>
<th>Functional group</th>
<th>Enzyme</th>
<th>Hydrolysis profile&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Inhibition profile&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Penicillins</td>
<td>Early cephalosporins</td>
<td>Extended-spectrum cephalosporins</td>
</tr>
<tr>
<td>A</td>
<td>2f</td>
<td>NMC</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IMI</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SME</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KPC</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GES</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>B1</td>
<td>3</td>
<td>IMP</td>
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<td>+</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td>VIM</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GIM</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SPM</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>D</td>
<td>2d</td>
<td>OXA</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
</tbody>
</table>

<sup>a</sup> Symbols: +, strong hydrolysis (generally, $k_{cat}$ of $>2$ s<sup>−1</sup>); ±, weak hydrolysis (generally, $k_{cat}$ of $0.5$ to $2$ s<sup>−1</sup>); −, no measurable hydrolysis reported (generally, $k_{cat}$ of $<0.5$ s<sup>−1</sup>).

<sup>b</sup> Symbols: +, reported inhibition; ±, variable inhibition among β-lactamase family members; −, no inhibition reported.

**KPC: Klebsiella pneumoniae 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*
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

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

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MICa</th>
<th>Interpretationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≥64</td>
<td>R</td>
</tr>
<tr>
<td>Amoxicillin / Clavulanic Acid</td>
<td>≥32</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≥32</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin / Sulbactam</td>
<td>≥32</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
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<tr>
<td>Cefalotin</td>
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<td>R</td>
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<tr>
<td>Cefazolin</td>
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<td>Cefepime</td>
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<tr>
<td>Cefotaxime</td>
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</tr>
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<td>R</td>
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<tr>
<td>Ciprofloxacin</td>
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<td>Imipenem</td>
<td>≥16</td>
<td>R</td>
</tr>
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<td>Ticarcillin / Clavulanic Acid</td>
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<td>Tobramycin</td>
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<tr>
<td>Trimethoprim / Sulfamethoxazole</td>
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</tbody>
</table>

*Antibiotic susceptibility was obtained using Vitek® 2 AST-GN24 and AST-EXN7 cards. 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