The Cephalosporins

I. CHEMISTRY AND MECHANISM OF ACTION

Cephalosporins are β-lactam antibiotics that differ from the penicillins in that the B ring is a 6-membered dihydrothiazine ring. Variations among the cephalosporins are made on either the acyl side chain at the 7-position to change antibacterial activity or at the 3-position to alter the pharmacokinetic profile. Cephalosporin C was first isolated in 1948 by Dr. Abraham from a fungus, *Cephalosporium acremonium*, collected in seawater near a sewage outlet in Sardinia by Professor Giuseppe Brotzu in 1945.

![General structure of the Cephalosporins](image)

- Similar mechanism of action to penicillins.
- Bind to penicillin binding proteins (transpeptidases, endopeptidases, and carboxypeptidases) and inhibit cell wall biosynthesis in both Gm + and Gm – bacteria.
- However, degree and extent of binding to different PBPs may be different for the cephalosporins than for penicillins. For example, cephalothin causes lysis of *Staph. aureus*, whereas cephalexin produces long filamentous forms in *E. coli*.
- In general, cephalosporins are less susceptible to β-lactamases compared to penicillins.
Table 18. Structures of Representative Cephalosporins

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>N=N</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>H</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-O-CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-O-CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-O-CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-S-N=N</td>
<td>H</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-O-C-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>N=O</td>
<td>-H&lt;sub&gt;2&lt;/sub&gt;C-S-N=N</td>
<td>H</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-N=C=CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
</tr>
</tbody>
</table>
## II. CLASSIFICATION OF THE CEPHALOSPORINS

### Table 19. Classification, Route of Administration, and Trade Names of Cephalosporins

<table>
<thead>
<tr>
<th>Type and Generic Name</th>
<th>Route of Administration</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>IM, IV</td>
<td>Ancef (Glaxo SK) Kefzol (Lilly)</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>IM, IV</td>
<td>Keflin (Lilly)</td>
</tr>
<tr>
<td>Cephapirin</td>
<td>IM, IV</td>
<td>Cefadyl (Apothecon)</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>IV, PO</td>
<td>Duricef (Bristol-Myers Squibb)</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>PO</td>
<td>Keflex &amp; Keflet (Lilly) Cefanex (Apothecon)</td>
</tr>
<tr>
<td>Cephradine</td>
<td>PO</td>
<td>Velosef (Apothecon)</td>
</tr>
<tr>
<td><strong>Second Generation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>IM, IV</td>
<td>Zinacef (Glaxo-SK), Kefurox (Lilly)</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>IM, IV</td>
<td>Mandol (Lilly)</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>IM, IV</td>
<td>Mefoxin (Merck)</td>
</tr>
<tr>
<td>Cefonicid</td>
<td>IM, IV</td>
<td>Monocid (Glaxo-SK)</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>IM, IV</td>
<td>Cefotan (Stuart)</td>
</tr>
<tr>
<td>Cefmetazol</td>
<td>IV</td>
<td>Zefazone (Pharmacia/Pfizer)</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>PO</td>
<td>Ceftin (Glaxo-SK)</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>PO</td>
<td>Ceclor (Lilly)</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>PO</td>
<td>Omnicef (Pfizer)</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>PO</td>
<td>Cefzil (Bristol-Myers Squibb)</td>
</tr>
<tr>
<td>Loracarbef</td>
<td>PO</td>
<td>Lorabid (Lilly)</td>
</tr>
<tr>
<td><strong>Third Generation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>IM, IV</td>
<td>Claforan (Hoechst-Roussel)</td>
</tr>
<tr>
<td>Ceftizoxime</td>
<td>IM, IV</td>
<td>Cefizox (Fujisawa)</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>IM, IV</td>
<td>Rocephin (Roche)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>IM, IV</td>
<td>Fortaz &amp; Ceptaz (Glaxo SK), Tazidime (Lilly), Tazicef (Glaxo SK)</td>
</tr>
<tr>
<td>Ceftoperazone</td>
<td>IM, IV</td>
<td>Cefobid (Roerig)</td>
</tr>
<tr>
<td>Cefixime</td>
<td>PO</td>
<td>Suprax (Lederle)</td>
</tr>
<tr>
<td>Ceftibuten</td>
<td>PO</td>
<td>Cedax (Schering Plough)</td>
</tr>
<tr>
<td>Cefpodoxime axetil</td>
<td>PO</td>
<td>Vantin (Pharmacia/Pfizer)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>IM, IV</td>
<td>Maxipime (Bristol-Myers Squibb)</td>
</tr>
</tbody>
</table>

## III. MECHANISMS OF RESISTANCE (see Penicillin section III)

A. Production of [-lactamases (see penicillin section III)

1. In general, cephalosporins are much more resistant to [-lactamases

2. First and Second Generation cephalosporins are still susceptible to Richmond-Sykes Type I [-lactamases.
IV. SPECTRUM & USES

A. First Generation Cephalosporins - Spectrum

Prototype Drugs are CEFAZOLIN (for IV use) and CEPHALEXIN (oral use).

1. *Staph. aureus* - excellent activity against β-lactamase-producing strains
   Not effective against methicillin-resistant *Staph. aureus* & *epidermidis*

2. Streptococci - excellent activity versus *Streptococcus sp*.
   Not effective against penicillin-resistant *Strep. pneumoniae*

3. Other Gm + bacteria - excellent activity except for *Enterococcus sp*.

4. Moderate activity against gram negative bacteria.
   *Caution: resistance may occur in all cases.*

Susceptible organisms include:

- *E. coli*
- *Proteus mirabilis*
- Indole + *Proteus sp* (many strains resistant)
- *Haemophilus influenzae* (some strains resistant)
- *Neisseria sp* (some gonococci resistant)

B. First Generation Cephalosporins - Uses

1. Upper respiratory tract infections due to *Staph.* and *Strep.*

2. Lower respiratory tract infections due to susceptible bacteria e.g. *Strep. pneumoniae* in penicillin-allergic patient (previous rash)

3. Uncomplicated urinary tract infections (Cephalexin)

4. Surgical prophylaxis for orthopedic and cardiovascular operations
   (cefazolin preferred because of longer half-life)

5. Staphylococcal infections of skin and skin structure

### TABLE 20. COMMENTS ON INDIVIDUAL 1st GENERATION CEPHALOSPORINS

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalothin (Keflin)</td>
<td>Causes pain on IM admin. Short half-life (0.5 h). 1st generation cephalosporin with least susceptibility to staphylococcal β-lactamase</td>
</tr>
<tr>
<td>Cefazolin (Kefzol, Ancef)</td>
<td>Longer half-life (1.8h). Highly protein bound. Well tolerated.</td>
</tr>
<tr>
<td>Cephapirin (Cefadyl)</td>
<td>Very similar activity to cephalothin. Short half-life.</td>
</tr>
<tr>
<td>Cephalexin (Keflex)</td>
<td>Oral agent. Less active against Staphylococci. 90% excreted in urine.</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Serum and urine concentrations more sustained than with cephalexin, with similar activity. May use qd or bid for UTIs.</td>
</tr>
<tr>
<td>Cephradine (Velosef)</td>
<td>Identical activity to cephalexin. Available PO and IV/IM. Nearly complete bioavailability.</td>
</tr>
</tbody>
</table>
C. Second Generation Cephalosporins – Spectrum

Prototype drug is CEFUROXIME (IV) and CEFUROXIME AXETIL (oral). CEFOXITIN has good activity vs. anaerobes.

1. Expanded activity against gram negative bacilli. Still have excellent activity against gram positive (Staph. and Strep.) bacteria.

Activity for Gram negative bacteria

- *Neisseria sp.* (some gonococci resistant)
- *H. influenzae* (including some ampicillin-resistant strains)
- *Moraxella catarrhalis* (some resistance esp. to cefaclor)
- *E. coli*
- *Proteus mirabilis*
- *Indole + Proteus* (some strains resistant)
- *Morganella morganii* (some strains resistant)
- *Klebsiella pneumoniae*
- *Serratia sp.* (many strains resistant)

2. Anaerobic infections - CEFOXITIN & CEFOTETAN only

- Moderate activity against *Bacteroides fragilis* group.
- Good activity for other *Bacteroides sp.*, *Peptostreptococcus*, *Fusobacterium*, *Clostridium sp.*

D. Second Generation Cephalosporins – Uses

1. Community-acquired pneumonia - Cefuroxime is widely used for empiric therapy. Has activity vs. many ampicillin-resistant *H. influenzae* strains.

2. Skin and soft tissue infection

3. Urinary tract infections

4. Upper respiratory tract infections (otitis media, sinusitis). Some resistance to *H. influenzae* to cefaclor (20-30%).

5. Mixed aerobic & anaerobic infections - Cefoxitin & Cefotetan. Resistance to *B. fragilis* is increasing.

6. Surgical prophylaxis - Cefoxitin or cefotetan are widely used in cases where mixed aerobic & anaerobic infections may occur, esp. intra-abdominal, colorectal, and gynecologic operations. For cardiovascular and orthopedic procedures, cefuroxime and others may be used, but cefazolin is cheaper and appears to work well.
### TABLE 21A. COMMENTS ON INDIVIDUAL 2ND GENERATION CEPHALOSPORINS FOR PARENTERAL USE

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime (Zinacef)</td>
<td>Prototype drug. Short half-life,</td>
</tr>
<tr>
<td>Cefoxitin (Mefoxin)</td>
<td>Activity vs. anaerobes because of -OCH3 group on A ring. Resistant to Bacteroides (-)-lactamases. Short half-life</td>
</tr>
<tr>
<td>Cefotetan (Cefotan)</td>
<td>Has anaerobic activity like cefoxitin. Long half-life. Give b.i.d.</td>
</tr>
<tr>
<td>Cefonicid (Monocid)</td>
<td>Long half-life (4-5 h). Similar spectrum to cefuroxime</td>
</tr>
<tr>
<td>Cefmetazole (Zefazone)</td>
<td>Me-too. Has anaerobic activity.</td>
</tr>
</tbody>
</table>

### TABLE 21B. COMMENTS ON INDIVIDUAL 2ND GENERATION CEPHALOSPORINS FOR ORAL USE

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime axetil (Ceftin)</td>
<td>Reasonably well absorbed (F = 35-45%). Better antimicrobial activity than cefaclor. Taste is fair. Recently became available as a liquid. BID dosing.</td>
</tr>
<tr>
<td>Cefaclor (Ceclor)</td>
<td>Long experience. Widely used. Resistance to both <em>H. influenzae</em> &amp; <em>Moraxella catarrhalis</em> for otitis media. Shorter half-life but still can use either t.i.d. or even b.i.d. Good taste. Generally well tolerated (some rash, serum-sickness). Moderate cost, available as generic.</td>
</tr>
<tr>
<td>Loracarbef (Lorabid)</td>
<td>Carbacephem (C instead of S). BID dosing. High bioavailability (&gt;90%). Basically a me-too. Expensive.</td>
</tr>
</tbody>
</table>

### E. Third Generation Cephalosporins - Spectrum

Prototype drugs are CEFOTAXIME (IV) and CEFIXIME (oral). CEFTAZIDIME (for *Pseudomonas aeruginosa*).

Further expansion of Gm negative spectrum to include hard to treat organisms such as *Enterobacter, Serratia, and Pseudomonas*. In addition to better Gm negative spectrum, this group has improved pharmacokinetic properties (longer half-lives) that allow once daily dosing with some agents. In general, activity toward Gm + bacteria is reduced. These are specialty antibiotics that should be reserved for specific uses.

Enterobacteriaceae that are almost always sensitive (>95% sensitive)

- *E. coli*
- *Proteus mirabilis* (indole –)
- *Proteus vulgaris* (indole +)
- *Klebsiella pneumoniae*
Gram negative bacilli that are generally sensitive (>75% sensitive)

*Morganella morganii*
*Providencia retgerri*
*Citrobacter freundii*
*Serratia marcescens*
*Pseudomonas aeruginosa* (Ceftazidime only)

Gram negative bacilli that are sometimes sensitive (<75% sensitive)

*Enterobacter*
*Stenotrophomonas (Xanthomonas) maltophilia* (Cefoperazone & Ceftazidime only)
*Acinetobacter*

Note: investigational agents cefepime & cefpirome are promising for these bacteria

Bacteria that are resistant

*Listeria monocytogenes*
*Pseudomonas cepacia*
*Enterococcus sp.* (investigational agents cefpiramide & cefpirome are active)

**F. Third Generation Cephalosporins - Uses**

1. Gram negative septicemia & other serious Gm – infections
2. *Pseudomonas aeruginosa* infections (Ceftazidime - 90% effective)
3. Gram negative meningitis - Cefotaxime, Ceftriaxone, Cefepime. For empiric therapy add vancomycin ± rifampin to cover resistant *Strep. pneumoniae*
4. Gonorrhea - Single shot of Ceftriaxone is drug of choice. Oral cefixime and cefditubten are also OK.
5. Complicated urinary tract infections, pyelonephritis
6. Osteomyelitis - Ceftriaxone in home health care situations
7. Lyme disease - ceftriaxone in home health care situations

**Inappropriate Uses** (yet widely prescribed)

1. Surgical prophylaxis (use 1st or 2nd generation agents)
2. Otitis media, URIs - Cefixime (Suprax), cefditubten have poor Gm + activity
3. Uncomplicated UTIs
<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (Rocephin)</td>
<td>Most potent against <em>Neisseria</em>. Long half-life of 8 h allows bid or daily dosing. Good for home health care problems. CNS penetration is adequate. Best-selling of all IV cephalosporins.</td>
</tr>
<tr>
<td>Cefotaxime (Clasforan)</td>
<td>Long experience. Excellent spectrum except for <em>Pseudomonas</em>. Reliable CNS penetration. Active desacetyl metabolite may increase activity towards anaerobes and extend duration of action.</td>
</tr>
<tr>
<td>Ceftizoxime (Cefizox)</td>
<td>Activity similar to cefotaxime. Less reliable CNS penetration.</td>
</tr>
<tr>
<td>Cefixime (Suprax)</td>
<td>First oral 3rd gen. agent. Activity similar to cefotaxime, but poorer Gm + activity than 1st and 2nd generation agents. Long half-life (4 h). Can give once a day. Good taste. Expensive.</td>
</tr>
<tr>
<td>Ceftibuten (Cedax)</td>
<td>High bioavailability (~90%). Half-life of 2.6 h, but may give once a day. Poor activity vs. <em>Staph.</em> and Group B <em>Strep.</em> Me-too of cefixime. Expensive.</td>
</tr>
<tr>
<td>Cefoperazone (Cefobid)</td>
<td>Some <em>Pseudomonas</em> activity (60%). Less active vs aerobic Gm negative bacteria than others. Low CNS penetration. High biliary excretion. Bleeding problems - Give with Vit K.</td>
</tr>
<tr>
<td>Ceftazidime (Fortaz)</td>
<td>Most active against <em>Pseudomonas</em>. Virtually no Gm + activity. CNS penetration is adequate to treat meningitis.</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>Investigational. Better activity vs. <em>Enterococcus, Enterobacter, Citrobacter, Acinetobacter, &amp; Serratia</em></td>
</tr>
</tbody>
</table>
### IV. ABSORPTION, DISPOSITION, AND METABOLISM

#### TABLE 23. PHARMACOKINETIC PROPERTIES OF THE CEPHALOSPORINS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (min)</th>
<th>Half-life in ESRD (hrs)</th>
<th>% Protein Bound</th>
<th>% Unchanged in Urine</th>
<th>Mean Peak Serum Level (µg/ml) 1g IV dose or 1g PO dose</th>
<th>CSF Penetration (inflamed meninges) (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>50-80</td>
<td>19-22</td>
<td>10</td>
<td>&gt;90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>78-96</td>
<td>20-25</td>
<td>20</td>
<td>&gt;90</td>
<td>24-35 (p.o.)</td>
<td></td>
</tr>
<tr>
<td>Cephradine</td>
<td>48-80</td>
<td>8-15</td>
<td>8-17</td>
<td>&gt;90</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>30-50</td>
<td>3-15</td>
<td>70</td>
<td>68-70</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Cepharpin</td>
<td>24-36</td>
<td>1.8-4</td>
<td>54</td>
<td>68-70</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>90-120</td>
<td>3-7</td>
<td>80-86</td>
<td>80-96</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td><strong>2nd Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>80</td>
<td>16-22</td>
<td>33-50</td>
<td>66-100</td>
<td>100</td>
<td>0.1-17</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>30-60</td>
<td>8-11</td>
<td>70</td>
<td>65-85</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>40-60</td>
<td>20</td>
<td>73</td>
<td>85-99</td>
<td>64-110</td>
<td></td>
</tr>
<tr>
<td>Cefonicid</td>
<td>270</td>
<td>11</td>
<td>98</td>
<td>95-99</td>
<td>221</td>
<td>low</td>
</tr>
<tr>
<td>Cefmetazole</td>
<td>72</td>
<td>65</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotetan</td>
<td>180-276</td>
<td>13-35</td>
<td>88-90</td>
<td>51-81</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td><strong>Oral agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>35-54</td>
<td>2-3</td>
<td>25</td>
<td>60-85</td>
<td>23-25</td>
<td></td>
</tr>
<tr>
<td>Cefdinir</td>
<td>100-120</td>
<td>17</td>
<td>60-70</td>
<td>15-30</td>
<td>2.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cefprozil</td>
<td>78</td>
<td>5.2-5.9</td>
<td>36</td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Loracarbef</td>
<td>60</td>
<td>32</td>
<td>25</td>
<td>&gt;90</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3rd Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime</td>
<td>180-240</td>
<td>11.5</td>
<td>65</td>
<td>50</td>
<td>3.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>120</td>
<td>9.8</td>
<td>60-64</td>
<td>80-90</td>
<td>8.6-13.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>102-156</td>
<td>1.3-2.9</td>
<td>82-93</td>
<td>20-30</td>
<td>75-153</td>
<td>0-11.5</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>60</td>
<td>3-11</td>
<td>30-40</td>
<td>20-36</td>
<td>42-102</td>
<td>5.6-44.3</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>84-114</td>
<td>25-30</td>
<td>30</td>
<td>80</td>
<td>60-87</td>
<td>4.6 (.5-29)</td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>348-522</td>
<td>15.7</td>
<td>85-95</td>
<td>33-67</td>
<td>151</td>
<td>1.2-39</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>114-120</td>
<td>14-30</td>
<td>&lt;10-17</td>
<td>80-90</td>
<td>69-90</td>
<td>9.8</td>
</tr>
<tr>
<td>Cefepime</td>
<td>114-144</td>
<td>16-19</td>
<td>&gt;85%</td>
<td></td>
<td>29.6</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> = after 400 mg p.o. dose  
<sup>b</sup> = after 200 mg p.o. dose  
<sup>c</sup> = after 300 mg p.o. dose

#### A. Individual Pharmacokinetic Observations

1. **First Generation Cephalosporins**
   
   i. Cephalothin & Cepharpin have short half-lives. Cefazolin has longest half-life but also has the highest protein binding (lower free levels).
   
   ii. Must reduce dose or give less often or both in renal failure.
2. Second Generation Cephalosporins

i. Pharmacokinetic properties relatively similar. Cefonicid & Cefotetan have longer half-lives such that dosing may be on a once a day basis (Cefonicid) or b.i.d. (Cefotetan). This should result in some cost savings. However, both drugs are highly protein bound - lower free levels, lower CSF levels.

ii. Oral agents similar, but urinary excretion of cefpodoxime is lower.

iii. Must reduce dose or give less often or both in renal failure, except for cefpodoxime.

3. Third Generation Cephalosporins

i. Ceftriaxone has long half-life (7-9 hrs). Used once daily. Single dose treatment for gonorrhea. Good for home health care situations. Chronic dosing may result in formation of biliary sludge.

ii. Cefoperazone is mainly excreted in the bile. Advantage in renal failure. Useful for treatment of infections of biliary tract.

iii. Must reduce dose or give less often or both in renal failure, especially for cefotaxime, ceftizoxime, cefepime, and ceftazidime.

iii. Cefoperazone & ceftriaxone highly protein bound. Cefoperazone should not be used for meningitis. Ceftriaxone CSF levels appear to be adequate, but lower than with cefotaxime.
V. ADVERSE REACTIONS

In general, Cephalosporins are very well tolerated and can be used freely. Some problems with individual agents are noted below.

A. HYPERSENSITIVITY REACTIONS (1-7%)

1. anaphylaxis (rare)
2. rash (maculopapular, urticarial) (1-3%)
3. serum sickness-like reaction, eosinophilia, + Coombs test - esp. with cefaclor
4. Some cross-sensitivity with penicillins (5-10%), perhaps as low as 1%.

B. Phlebitis, Pain on IM injection

1. Most common with cephalothin and cephapirin. Cefotaxime also.

C. Hypoprothombinemia - associated with methylthiotetrazole ring

- Common with cefoperazone, cefamandole, cefotetan, & moxolactam (discontinued).
- Occurs in 20-60% of patients.
- Give Vitamin K (menadione) as preventative. Less bleeding problems with cefotetan.
- Other ceph's. may also cause bleeding due to reduction of gut flora.

D. GI complaints (5-10%)

- Diarrhea more common with cefixime, cefdinir, and cefoperazone.

E. Elevation of liver enzymes (5-10%)

F. Disulfiram-like reaction.

- Flushing, sweating, headache, tachycardia associated with alcohol ingestion.
- Associated with methylthiotetrazole-containing cephalosporins only.
  (cefoperazone, cefamandole, cefotetan)

G. Cholecystitis-like syndrome with Ceftriaxone (~20% with chronic dosing).

- Precipitation of ceftriaxone in bile leads to biliary sludge.
- May require surgery.
- Rarely with cefoperazone.

H. Displacement of bilirubin from albumin binding sites - theoretical problem in neonates.

- Occurs with ceftriaxone & cefoperazone.
VI. DRUG INTERACTIONS

TABLE 24. DRUG INTERACTIONS OF THE CEPHALOSPORINS

<table>
<thead>
<tr>
<th>Precipitant Drug</th>
<th>Object Drug</th>
<th>Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins with methylthiotetrazol group</td>
<td>Ethanol</td>
<td>↑</td>
<td>Alcoholic beverages taken with or up to 72 h after cefametazole, cefoperazone cefazolin, or cefotetan may produce a disulfiram-like rxn. Flushing, sweating, tachycardia</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Aminoglycosides</td>
<td>↑</td>
<td>Nephrotoxicity of AGs may be potentiated with some cephs., especially cephalothin</td>
</tr>
<tr>
<td>Cephalosporins with methylthiotetrazol group</td>
<td>Anticoagulants</td>
<td>↑</td>
<td>Hypoprothrombinemic effects of anticoagulants are increased. Bleeding complications may occur. An additional problem is depletion of the gut flora resulting in decreased Vitamin K synthesis (problem with 2nd &amp; 3rd gen. cephs)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Urine glucose testing</td>
<td>↑</td>
<td>May lead to false positives in diabetics taking cephalosporins</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Cephalosporins</td>
<td>↑</td>
<td>Probenecid inhibits renal tubular secretion of cephalosporins that are primarily renally excreted.</td>
</tr>
<tr>
<td>Antacids</td>
<td>Cephalosporins</td>
<td>□</td>
<td>Reduced absorption of cefaclor CD, cefditivir, and cefpodoxime</td>
</tr>
<tr>
<td>H₂ antagonists</td>
<td>Cefpodoxime, Cefuroxine</td>
<td>□</td>
<td>Reduced absorption of cefpodoxime and celuoxime</td>
</tr>
</tbody>
</table>

VII. PRODUCTS AND DOSING

Cefazolin sodium
Powder for Injection: 250 mg, 500 mg, 1g in vials and piggyback vials. 5g, 10g, 20 g in bulk vials. (Kefzol® - Lilly, Ancef® - Glaxo SK, + generics).
Injection: 500 mg & 1g in 5% Dextrose in water (premixed, frozen) (Ancef® - Glaxo SK)

Moderate to severe infections: 500 mg to 1 g every 6-8 hours
Pneumococcal pneumonia: 500 mg every 12 hours
Acute UTIs: 1g every 12 hours
Surgical prophylaxis: 1g IV or IM, 30-60 min prior to surgery, then 0.5-1 g IV or IM q 6-8 hours up to 24 h after surgery. For long surgical procedures (>2h) - give 0.5-1g IV as needed.

Cephalexin monohydrate
Capsules: 250 mg, 500 mg (Keflex® - Dist, + generics)
Tablets: 250 mg, 500 mg, 1 g (Keftab® - Dist)
Oral Suspension: 125 mg/5ml and 250 mg/5ml (Keflex® - Dist)
Pediatric Oral Suspension: 100mg per ml (5 mg/drop) (Keflex® - Dist)

Cephalexin HCl monohydrate
Tablets: 250 mg & 500 mg (Keftab® - Dist) Note: this formulation has a more rapid dissolution.

Adults: Usual dose is 250 mg q 6 h. May give up to 4 g/day for serious infections
Streptococcal pharyngitis, skin & skin structure infections, &cystitis: 500 mg q 12 h
Children: 25-50 mg/kg/day in divided doses.
Strep. pharyngitis and skin infections: give every 12 hours.
Otitis media: 75-100 mg/kg/day in 4 divided doses.
Cefadroxil
Capsules: 500 mg (Duricef® - Bristol-Myers Squibb, + generics)
Tablets: 1 g (Duricef® - Mead Johnson, Ultracef® - Bristol, + generics)
Oral suspension: 125 mg, 250 mg, & 500 mg per 5 ml - orange-pineapple flavor (Duricef® - Bristol-Myers Squibb)

Adults: 1g/day in single or 2 divided doses. For complicated UTIs - 2 g/d in 2 divided doses.
Children: 30 mg/kg/day in divided doses q 12 h.

Cephradine
Capsules: 250 mg, 500 mg (Velosef® - Bristol-Myers Squibb)
Tablets: 250 mg, 500 mg, 1 g (Velosef® - Bristol-Myers Squibb)
Oral Suspension: 125 mg/5ml and 250 mg/5ml reconstituted. Fruit flavor. (Velosef® - Bristol-Myers Squibb)
Powder for Injection: 250 mg, 500 mg, & 1g in vials. 2g in 100 ml infusion bottles.

Adults: Mild infections: 250 - 500 mg q 6 h or 500 mg q 12 h.
Lobar pneumonia: 500 mg q 6 h or 1 g q 12h. UTIs: 500 mg -1 g q 12 h.
Children: 50-100 mg/kg/day in equally divided doses q 6 h or q 12h.

Cephalothin
Injection: 1g or 2g in 5% Dextrose (premixed, frozen) in 50 ml single dose Viaflex Plus® containers (Baxter)
Powder for Injection: 1 g or 2 g in vials (1g/10 ml) or piggyback vials (1g/100 ml) (Keflin® Neutral - Lilly, + generics). 20 g in 200 ml vials (Keflin® Neutral - Lilly).

Adults: 500 mg - 1 g q 4-6 h
Infants & children: 100 mg/kg in divided doses q 4-6 h

Cephapirin
Powder for Injection: 1 g in vials and piggyback vials (Cefadyl® - Apothecon)

Adults: 500 mg - 1 g q 4-6 h
Children: 40-80 mg/kg/day administered in 4 equally divided doses.

SECOND GENERATION CEPHALOSPORINS

Cefuroxime sodium and Cefuroxime axetil
Tablets (as axetil): 125 mg, 250 mg, and 500 mg (Ceftin® - Glaxo SK)
Powder for Injection (as sodium): 750 mg and 1.5 g in vials, Faspak and ADD-Vantage vials.
7.5 g in bulk packages (Kefurox® - Lilly, Zinacef® - Glaxo SK, + generics). 2.4 mEq Na/g.
Injection: 750 mg and 1.5 g in 50 ml (premixed, frozen).

Oral Suspension: 125 and 250 mg per 5ml Tutti-frutti flavor (Ceftin®-Glaxo SK)

Adults: 250-500 mg twice daily. UTIs: 125 mg twice daily Gonorrhea: 1 g in single dose
Infants and Children: 125 mg twice daily.
Otitis media: <2 yrs - 125 mg b.i.d., >2 yrs - 250 mg b.i.d. Note: crushed tablet has strong bitter taste.

Absorption is enhanced when given with food.
**Cefaclor**  
Capsules (Pulvules): 250 mg and 500 mg (Ceclor® - Lilly)  
Extended Release Tablets: 375 mg and 500 mg (Ceclor CD® - Lilly) –  
Administer with food. Do not crush or chew  
Powder for Oral Suspension: 125 mg, 187 mg, 250 mg, and 375 mg per 5 ml. Strawberry flavor.  
Suspension should be refrigerated after reconstitution. Discard after 14 days. (Ceclor® - Lilly)  

Adults: 250 mg q 8 h. May go up to 500 mg q 8 h for severe infections. Ceclor CD - 375-500 mg BID  
Children: 20 mg/kg/day in divided doses q 8 hours.  
**Otitis media & severe infections:** 40 mg/kg/day in 2 or 3 divided doses. Maximum dose = 1 g/day

**Cefoxitin**  
Powder for Injection: 1g and 2 g in vials, infusion bottles, and ADD-Vantage vials. 10 g in bulk bottles  
(Mefoxin® - Merck) Contains 2.3 mL Na/g.  
Injection: 1 g and 2 g in 5% Dextrose in Water (premixed, frozen in 50 ml plastic containers)  

Adults: 1-2 g q 6-8 h. Gonorrhea: 2 g IM + 1 g oral probenecid.  
**Surgery prophylaxis:** 2 g IV or IM 30-60 min prior to surgery followed by 2 g q 6 h after 1st dose for  
no more than 24 hours (72 hrs for prosthetic arthroplasty).  
Infants & Children: 80-160 mg/kg/day divided q 4-6 hrs. Do not exceed 12 g/day.  
**Prophylactic use:** 30-40 mg/kg/day q 6 h.

**Cefamandole naftate**  
Powder for Injection: 500 mg, 1 g, and 2 g in vials ADD-Vantage vials & Faspacks. 10g in 100 ml  
vials. (Mandol® - Lilly)  

Adults: 500 mg to 1 g q 4-8 h. 500 mg q 6 h is adequate for pneumonia, skin & skin structure  
infections. Serious UTIs: 1 g q 8 h.  
Infants & children (>3 mos. old): 50-100 mg/kg/day in equally divided doses

**Cefmetazole**  
Powder for Injection: 1g and 2 g in vials (Zefazone® - Pharmacia/Pfizer)  
Injection: 1g/50mL and 2g/50mL -store frozen. Do not refreeze if thawed.  

Adults: 2 g IV q 6-12 h  
**Surgical prophylaxis:** 1-2 g IV 30-60 min before surgery. Repeat 1 g dose at 8 and 16 h post-surgery.

**Cefonicid**  
Powder for Injection: 500 mg in vials; 1 g in vials and piggyback vials; 10g in bulk vials (Monocid® -  
Glaxo-SK). Contains 3.7 mEq sodium/gm  

Adults: 1 g q 24 hrs IV or by deep IM injection. May give up to 2 g per day if necessary (rare).  
**Surgical prophylaxis:** 1g one hour prior to surgery. May give for 2 additional days to patients  
undergoing prosthetic arthroplasty or open heart surgery.

**Cefotetan disodium**  
Powder for Injection: 1g in 10 & 100 ml vials, 2 g in 20 & 100 ml vials. 10 g in 100 ml vials.  
(Cefotan® - Zeneca). Contains 3.5 mEq sodium/gm  
Injection: 1g and 2g in 50mL (premixed)  

Adults: 1 or 2 g IV or IM q 12 h. **Propylaxis:** 1 or 2 g IV dose 30-60 min prior to surgery
**Cefpodoxime axetil**
Tablets: 100 mg and 200 mg (Vantin® - Pharmacia/Pfizer)
Granules for suspension: 50 and 100 mg per 5 ml. Lemon creme flavor (Vantin® - Pharmacia/Pfizer)
Adults: 100-400 mg q 12 h for 7-14 days
Children (6 mos.-12 yrs). 10 mg/kg/day divided q 12 hr (maximum 400 mg/day).

**Cefprozil**
Tablets: 250 mg and 500 mg (as anhydrous) (Cefzil® - Bristol-Myers Squibb)
Powder for suspension: 125 mg and 250 mg per 5 ml. Bubble gum flavor. (Cefzil® - BMS)
Note: Refrigerate after reconstitution.

Adults: **URIs**: 500 mg q 24 h. **Lower respiratory tract infections**: 500 mg q 12 h.
Children (6 mos -12 yrs): 15 mg/kg q 12 h for otitis media, 7.5 mg/kg for pharyngitis/tonsillitis.

**Loracarbef**
Capsules (Pulvules): 200 mg (Lorabid® - Lilly)
Powder for suspension: 200 mg per 5 ml. Strawberry bubble gum flavor. (Lorabid® - Lilly)

Adults: 200-400 mg q 12 h.
Infants and children (6 mos-12 yrs): 30 mg/kg/day q 12 h for otitis media. 15 mg/kg for pharyngitis/tonsillitis and impetigo.

**THIRD GENERATION CEPHALOSPORINS**

**Cefotaxime**
Powder for Injection: 1g and 2 g in vials, infusion bottles, & and ADD-Vantage vials. 10 g in bulk vials. (Claforan® - Aventis). Contains 2.2 mEq sodium/gm.
Injection: 1 g and 2 g in 50 ml (premixed, frozen) (Claforan® - Hoechst Marion Roussel)

Adults: 1-2 g q 8 h for moderate to severe infections. For life-threatening infections 2 g q 4 h
**Gonorrhea**: 1 g IM as single dose.
Children (1 mo. - 12 yrs): 50-180 mg/kg/day in 4-6 divided doses
Children (1-4 weeks): 50 mg/kg q 8 hrs.
Children (<1 week): 50 mg/kg q 12 h.

**Ceftiraxone**
Powder for injection: 250 mg and 500 mg in vials, 1g and 2 g in vials, piggyback vials, and ADD-Vantage vials. 10 g in bulk containers. (Rocephin® - Roche). Contains 3.6 mEq sodium/gm.
Injection: 1 g and 2 g in 50 ml plastic containers (premixed, frozen). (Rocephin® - Roche)

Adults: 1-2 g once a day.
**Gonorrhea (uncomplicated)**: 250 mg single IM dose plus doxycycline or erythromycin (if pregnant).
For children (<45kg) 125 mg IM once.
**Surgical prophylaxis**: Single 1 g dose 0.5-2 hours before surgery.
Children: 50-75 mg/kg/day (not to exceed 2 g) in divided doses q 12 h for serious infections.
**Meningitis**: 100 mg/kg/day (not to exceed 4 g) every 12 hour, with or without a loading dose of 75 mg/kg.

**Ceftizoxime sodium**
Powder for injection: 500 mg, 1 g, 2 g in 10ml or 20ml single dose flitop vials and 100 ml piggyback vials. 10 g as pharmacy bulk package. (Cefizox® - Fujisawa).
Injection: 1 or 2 g in 50 ml of 5% Dextrose in water (premixed, frozen). Contains 2.6 mEq Na/g.

Adults: 1-2 g q 8-12 h IM or IV. For life-threatening infections 3-4 g q 8 h.
**Uncomplicated UTIs**: 500 mg q 12 h.
Children (≥6 mos): 50 mg/kg q 6-8 h.
Cefoperazone sodium
Powder for injection: 1 g and 2 g in vials and piggyback units. (Cefobid® - Pfizer).
Injection: 1 or 2 g in 50 ml (premixed, frozen). Contains 1.5 mEq sodium/gm.

Adults: 2-4 g/day in equally divided doses q 12 h. For severe infections 6-12 g/day.

Ceftazidime
Powder for Injection: 500 mg, 1 g, 2 g in vials, piggyback vials, Faspak and ADD-Vantage vials (1 and 2 g only). 6 g in bulk package or 100 ml vial. (Fortaz® - Glaxo SK, Tazicef® - Glaxo SK, Bristol-Myers Squibb, Tazidime® - Lilly). Contains 2.3 mEq sodium/gm.
Powder for Injection, L-arginine formulation: 1g, 2g vials - (Ceptaz®-Glaxo SK)
Injection: 1g or 2 g in 50 ml (premixed, frozen) - (Fortaz® - Glaxo SK), Tazicef (SKB/BMS)

Adults: 1g 8-12 h. For life-threatening infections 2 g IV q 8 h.
Uncomplicated UTIs: 250 mg q 12 h. Complicated UTIs: 500 mg q 8-12 h.
Pseudomonal lung infections in cystic fibrosis patients: 30-50 mg/kg IV to a maximum of 6 g/day
Infants and children (1mo.-12 yrs): 30-50 mg/kg IV q 8 h to a maximum of 6 g/day.
Neonates ≤ 4 weeks: 30 mg/kg IV q 12 h.

Cefixime
Tablets: 200 mg and 400 mg (Suprax® - Lederle)
Powder for oral suspension: 100 mg per 5 ml. Strawberry flavor. (Suprax® - Lederle).
Note: suspension gives higher blood levels than tablets, so for otitis media use suspension.

Adults: 400 mg/day as single 400 mg tablet (for gonococcal infections) or 200 mg b.i.d.
Children: 8 mg/kg/day as single dose or 4 mg/kg q 12 h.

Ceftibuten
Capsules: 400 mg (Cedax® - Schering)
Powder for Oral Suspension: 90 mg and 180 mg per 5 ml. Cherry Flavor.
Note: Refrigerate suspension after reconstitution.

Adults: 400 mg/day
Children: 9 mg/kg per day for pharyngitis, tonsillitis or otitis media due to Strep. pyogenes and for otitis media due to H. influenzae and M. catarrhalis (note: not for Strep. pneumoniae).

Cefdinir
Capsules: 300 mg (Omnicef® - Pfizer)
Powder for Oral Suspension 125mg per 5mL: Strawberry flavor

Adults: 600 mg once daily or 300 mg BID – use BID dosing for pneumonia and skin infections.
Indications: Community-acquired pneumonia, acute exacerbation of chronic bronchitis, acute bacterial sinusitis, pharyngitis and tonsillitis due to Strep. pyogenes, uncomplicated skin and skin structure infections.
Children: 14 mg/kg once daily or 7 mg/kg BID for otitis media, sinusitis, or pharyngitis due to Strep. pyogenes.

Cefepime HCl
Powder for Injection: 1 g and 2 g (Maxipime® - Dura)

Adults: 1 to 2 g q 12 h
Approved for febrile neutropenia and complicated intra-abdominal infections.
Uncomplicated and complicated urinary tract infections, moderate-to-severe pneumonia