All cephalosporins are based on cephalosporin C, which was discovered by Edward Abraham and his colleagues in Oxford as a minor component of the antibiotic complex produced by *Cephalosporium acremonium*, a mold cultivated from a Sardinian sewage outfall by Giuseppe Brotzu in 1948. Interest in cephalosporin C was fuelled by its stability to staphylococcal β-lactamase (shared by all subsequent cephalosporins), which was causing concern at the time, and they probably owe their continued development to this property. Over 100 semisynthetic cephalosporins have since been marketed, although not all have survived into present-day use.

In all cephalosporins the β-lactam ring is fused to a six-membered dihydrothiazine ring in place of the five-membered thiazolidine ring of penicillins (see pp. 226–227). The basic 7-aminocephalosporanic acid skeleton can be modified at a number of positions.

- Alterations at the C-3 position tend to affect the pharmacokinetic and metabolic properties.
- Introduction of a methoxy group at C-7 yields a cephamycin with enhanced stability to β-lactamases, including the cephalosporinases of certain *Bacteroides* spp.
- Changes at the 7-amino position alter, in general, the antibacterial activity or β-lactamase stability or both.

Other compounds conveniently considered alongside the cephalosporins, since their properties are very similar, include:

- the oxacephems, in which the sulfur of the dihydrothiazine ring is replaced by oxygen
- the carbacephems, in which the sulfur is replaced by carbon.

### CLASSIFICATION

As new cephalosporins have become available they have been loosely classified into ‘generations’, but these descriptions are too simplistic, and are to be discouraged. The following grouping is adopted here:

- **Group 1**: Parenteral compounds of moderate antimicrobial activity and susceptible to hydrolysis by a wide variety of enterobacterial β-lactamases.
- **Group 2**: Oral compounds of moderate antimicrobial activity and moderately resistant to some enterobacterial β-lactamases.
- **Group 3**: Parenteral compounds of moderate antimicrobial activity resistant to a wide range of β-lactamases. Some are available as esters for oral administration.
- **Group 4**: Parenteral compounds with potent antimicrobial activity and resistance to a wide range of β-lactamases.
- **Group 5**: Oral compounds (often achieved by esterification) resistant to a wide range of β-lactamases. Most exhibit potent activity against enterobacteria; activity against Gram-positive cocci is variable.
- **Group 6**: Parenteral compounds with activity against *Pseudomonas aeruginosa*. They vary widely in their spectrum of activity against other bacterial species.
- **Group 7**: Compounds characterized by activity against methicillin-resistant staphylococci.

Although the ‘generation’ categories often used are imprecise, ‘first-generation’ compounds roughly correspond to Groups 1 and 2; ‘second-generation’ to group 3; ‘third-generation’ to groups 4–6. Certain group 6 and 7 compounds are sometimes allocated to so-called ‘fourth and fifth generations’.

Some cephalosporins, including cefalonic and cefalorin (group 1) and cequinone and ceftiofur (group 4) are used only in veterinary medicine and are not discussed further here.
**ANTIMICROBIAL ACTIVITY**

Most cephalosporins are active against staphylococci other than methicillin-resistant strains, including those producing β-lactamase. The degree of activity varies among different members of the group. Streptococci, including pneumococci, are susceptible but *Enterococcus faecalis, Ent. faecium* and *L. monocytogenes* are virtually completely resistant. *Streptococcus pneumoniae* strains with reduced susceptibility to penicillins are also less susceptible to the cephalosporins. Many Gram-negative species including neisseriae, *Haemophilus influenzae*, salmonellae, some klebsiellae and *Proteus mirabilis* are sensitive to varying degrees. Inoculum-related effects are common, particularly when compounds of groups 1 and 2 are tested against Gram-negative bacilli. *Ps. aeruginosa* is sensitive only to group 6 compounds. Except for cephaplexins, activity against many anaerobes is unreliable. Mycobacteria, mycoplasmas, chlamydiae and fungi are resistant.

Cephalosporins are usually bactericidal at concentrations above the minimum inhibitory concentration (MIC) and bactericidal synergy is commonly demonstrable with aminoglycosides and a number of other agents.

**ACQUIRED RESISTANCE**

The most important form of resistance is that due to the elaboration of β-lactamas (pp. 228–231). All cephalosporins are relatively stable to staphylococcal β-lactamase, but resistance among Gram-negative genera is a good deal more complicated. The chromosomal β-lactamase of *Esch. coli*, which has virtually no hydrolytic activity against ampicillin, slowly degrades some group 1 cephalosporins and is responsible for the inoculum effect observed with *Esch. coli*. Chromosomal β-lactamases of *Bacteroides fragilis* are also more active against cephalosporins than against penicillins, but cephaplexins and oxacephems are unusual in their stability to these enzymes. Cephalosporins exhibit considerable variation in stability to the enzymes of genera with an inducible, or derepressible, chromosomal β-lactamase and to plasmid-mediated enzymes of Gram-negative bacilli (pp. 230–231).

The resistance of Gram-negative bacilli does not depend solely on β-lactamase formation. It varies also with the extent to which the antibiotic can penetrate the outer cell membrane and reach the site of enzyme formation. This property, known as crypticity, can be measured by comparing the enzyme activity of intact and disrupted cells. Resistance may also result from a change in the biochemical target of the antibiotic (i.e. the penicillin-binding proteins).

**PHARMACOKINETICS**

Group 2 agents are well absorbed, with bioavailability often exceeding 85%. The bioavailability of some of the agents in other groups is enhanced by prodrug formulation. These agents tend to have improved absorption following food, whereas food has little or a deleterious effect on the absorption of group 2 compounds.

Cephalosporins are usually well distributed, achieving high concentrations in the interstitial fluid of tissues and in serous cavities. Penetration into the eye and the cerebrospinal fluid (CSF) is poor, though some cephalosporins achieve adequate levels in the CSF in the presence of meningeal inflammation. They cross the placenta.

Compounds that carry an acetoxymethyl group at C-3, such as cefalotin and cefotaxime, are susceptible to mammalian esterases that remove the acetyl group to form the corresponding hydroxymethyl derivative with reduced antibacterial activity. The relevance (if any) of deacetylation to therapy has not been established.

Cephalosporins are generally excreted into urine by glomerular filtration and tubular secretion; elimination is depressed by

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*7-Methoxycephalosporin (cephamycin).
†7-Methoxyoxacephem.
‡1-Carbacephem.*
which are extensively excreted in the bile and because of their non-absorption achieve substantial fecal concentrations.

Rare disturbances of renal function appear to have the direct toxic or allergic origins described for penicillins. Claims that the nephrotoxicity of cephalosporins is potentiated by aminoglycosides have been disputed.

As with other β-lactam antibiotics, central nervous system (CNS) disturbances may occur if they are given in excessive doses, particularly to patients with renal failure. Transient abnormalities of liver function tests without other evidence of hepatotoxicity and gastrointestinal disturbances also occur.

In addition to hypoprothrombinemia (see above) cephalosporins with a methylthiotetrazole side chain may cause a disulfiram-like reaction, evidently due to inhibition of aldehyde dehydrogenase. Patients should be advised to avoid alcohol during and 3 days after treatment with these agents.

**OTHER ADVERSE REACTIONS**

Pain at the site of intramuscular injection and phlebitis at the site of intravenous administration is fairly common. *Candida* overgrowth with vaginitis has been a feature of some studies.

Diarrhea occurs in about 5% of patients and pseudomembranous colitis has been described. Changes in bowel flora, accompanied by emergence of resistant organisms, including *Clostridium difficile*, are particularly likely with those agents.
**L. monocytogenes, Enterobacter, Ps. aeruginosa or Serratia spp.**

Despite their in-vitro potency, they do not appear to offer any advantage over established therapy in the treatment of meningitis due to *Neisseria meningitidis*. Their activity and resistance to β-lactamases has led to their successful use for the treatment of infection due to β-lactamase-producing gonococci.

### GROUP 5

Those oral compounds may replace the group 2 agents if resistance to the earlier compounds becomes significant. The relatively lower activity of cefixime and ceftibuten against Gram-positive cocci suggests they should be used with caution in infections with these organisms.

### GROUPS 6 AND 7

Ceftazidime has been widely used in serious infection due to *Ps. aeruginosa*. Cefusolidin and cefoperazone are indicated only in proven or highly suspected pseudomonas infection and in combination with an appropriate aminoglycoside. Other group 6 compounds are appropriate for use in patients with severe infections caused by bacteria with plasmid and chromosomally mediated β-lactamases. Their main use is in hospital-acquired infections or in serious problems in the neutropenic patient.

The newer group 7 compounds have been specifically developed for their action against methicillin-resistant staphylococci.

### Further information


### GROUP 1 CEPHALOSPORINS

#### CEPHALOTIN

Cephalothin. Molecular weight (sodium salt): 418.4.

A semisynthetic cephalosporin supplied as the sodium salt.

### ANTIMICROBIAL ACTIVITY

Its activity against common pathogenic bacteria is shown in Table 13.1. Cefalotin is active against staphylococci, including β-lactamase-producing strains. Streptococci, including penicillin-sensitive pneumococci, but not enterococci, are highly susceptible. It is active against a range of enterobacteria, but is hydrolyzed by many enterobacterial β-lactamases. *Pasteurella* and *Vibrio* spp., *H. influenzae*, *Bordetella* and *Brucella* spp. are moderately resistant. *Campylobacter*, *Citrobacter*, *Enterobacter*, *Pseudomonas* and *Listeria* spp. are resistant. Most anaerobes, with the exception of *B. fragilis*, are susceptible: *Treponema pallidum* and *Leptospira* spp. are susceptible, but mycobacteria and mycoplasma are resistant.

### PHARMACOKINETICS

- $C_{max}$: 1 g intravenous = 30 mg/L after 15 min
- 1 g intramuscular = 15–20 mg/L after 0.5–1 h
- Plasma half-life: c. 0.8 h
- Volume of distribution: 0.26 L
- Plasma protein binding: 60–70%

Distribution

Intramuscular administration is commonly painful and it is normally given intravenously. Continuous infusion of 12 g per day produces steady-state plasma levels of 10–30 mg/L. Penetration into the CSF is very poor, rising in the presence of inflammation to less than 2 mg/L after a 2 g intravenous dose.

#### Table 13.1 Activity of group 1 cephalosporins against common pathogenic bacteria: MIC (mg/L)

<table>
<thead>
<tr>
<th></th>
<th>Cefamandole</th>
<th>Cefalotin</th>
<th>Cefazolin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>0.5–1</td>
<td>0.25–0.5</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>0.06–1</td>
<td>0.1</td>
<td>0.1–0.25</td>
</tr>
<tr>
<td>Str. pneumoniae</td>
<td>0.06–16</td>
<td>0.06–0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>32–R</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>0.06</td>
<td>0.25–2</td>
<td>0.1–0.5</td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>0.1–0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>0.25–2</td>
<td>4–8</td>
<td>2–8</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0.5–4</td>
<td>4–8</td>
<td>0.5–4</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>0.5–2</td>
<td>4</td>
<td>1–4</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>R</td>
<td>32–64</td>
<td>16–32</td>
</tr>
</tbody>
</table>

R, resistant (MIC >64 mg/L).
Concentrations in sputum are 10–25% of the corresponding serum levels. An intravenous dose of 1 g produces a concentration in bone around 4 mg/kg.

**Metabolism and excretion**

It is deacetylated by hepatic esterases. The metabolite has about 20% of the activity of the parent compound and accounts for 20–30% of concentrations in serum and urine.

Urinary concentrations of 500–2000 mg/L are achieved during the first 6 h after a 1 g dose. Excretion is depressed by probenecid, indicating significant tubular secretion, and by renal failure although, because of metabolism, the plasma half-life of the drug is only moderately prolonged to about 3 h, while that of the principal metabolite rises to 12 h or more. Impaired tubular secretion is responsible for the elevated levels of the drug found in newborn and premature infants. Biliary excretion is trivial and liver disease has little effect on its half-life or plasma protein binding.

**TOXICITY AND SIDE EFFECTS**

In volunteers receiving very large doses (8 g per day for 2–4 weeks) a serum-sickness-like illness developed. Positive Coombs’ reactions associated with red cell agglutination, but very seldom with hemolysis, are common. Thrombocytopenia and leukopenia have been described. Coagulopathy with prolonged prothrombin time has been encountered in patients with renal failure or very high plasma levels resulting from excessive dosage. Evidence has been cited of exaggeration of pre-existing renal disease or renal damage, perhaps enhanced by simultaneous administration of aminoglycosides or furosemide (frusemide), in which direct tubular injury or allergic nephritis may have been involved.

**CLINICAL USE**

It has been used in staphylococcal and streptococcal infections in penicillin-allergic patients, but is no longer recommended.

**Preparations and dosage**

**Proprietary name:** Keflin.

**Preparation:** Injection.

**Dosage:** Adults, i.m., i.v., 0.5–1 g every 4–6 h; up to 12 g per day in severe infections. Children, 50–150 mg/kg per day in divided doses.

No longer widely available.

**Further information**


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**CEFAZOLIN**

Cephazolin. Molecular weight (sodium salt): 476.5.

A semisynthetic cephalosporin supplied as the sodium salt.

**ANTIMICROBIAL ACTIVITY**

Activity against common pathogenic bacteria is shown in Table 13.1. *Enterobacter, Klebsiella, Providencia, Serratia* spp. and *Pr. vulgaris* are all resistant. *B. fragilis* is resistant, but other anaerobes are susceptible.

**PHARMACOKINETICS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max intramuscular</td>
<td>65–70 mg/L at 1 h</td>
</tr>
<tr>
<td>1 g intravenous bolus</td>
<td>180–200 mg/L end infusion</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>1.5–2.0 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>c. 10 L</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>75–85%</td>
</tr>
</tbody>
</table>

**Distribution**

The volume of distribution is the smallest of the cephalosporins in group 1, perhaps an indication of relative confinement to the plasma space. It crosses inflamed synovial membranes, but the levels achieved are well below those of the simultaneous serum levels and entry to the CSF is poor. In patients receiving 10 mg/kg by intravenous bolus, mean concentrations in cancellous bone were 3.0 mg/kg when the mean serum concentration was 33 mg/L, giving a bone:serum ratio of 0.09. Some crosses the placenta, but the concentrations found in the fetus and membranes are low.

**Metabolism and excretion**

It is not metabolized. Around 60% of the dose is excreted in the urine within the first 6 h, producing concentrations in excess of 1 g/L. Excretion is depressed by probenecid. The renal clearance is around 65 mL/min and declines in renal failure, when the half-life may rise to 40 h, although levels in the urine sufficient to inhibit most urinary pathogens are still found. It is moderately well removed by hemodialysis and less well by peritoneal dialysis.
Levels sufficient to inhibit a number of enteric organisms likely to infect the biliary tract are found in T-tube bile (17–31 mg/L after a 1 g intravenous dose), but this is principally due to the high serum levels of the drug and the total amounts excreted via the bile are small.

**TOXICITY AND SIDE EFFECTS**

Side effects are those common to other cephalosporins (p. 172), including rare bleeding disorders and encephalopathy in patients in whom impaired excretion or direct instillation leads to very high CSF levels. Neutropenia has been described and hypoprothrombinemic bleeding has been attributed to the side chain.

**CLINICAL USE**

Cefazolin has been widely used in surgical prophylaxis, especially in biliary tract (because of the moderately high concentrations achieved in bile), orthopedic, cardiac and gynecological surgery.

### Preparations and dosage

**Proprietary name:** Kefzol.

**Preparation:** Injection.

**Dosage:** Adults, i.m., i.v., i.v. infusion 0.5–2 g every 6–12 h, up to 12 g per day in severe infections. Children, 25 mg/kg per day in divided doses, increasing to 100 mg/kg per day in severe infection.

Widely available.

### Further information


### OTHER GROUP 1 CEPHALOSPORINS

#### CEFACETRILE

Its spectrum resembles that of cefalotin. Following an intramuscular dose of 1 g, a peak plasma concentration around 15 mg/L is achieved at 1 h. About 25% is bound to plasma protein. Penetration into the CSF is limited. About 80% of the drug is excreted in the urine, producing concentrations in excess of 1 g/L, 25% of which is in the desacetylated form. Clearance is depressed by probenecid and in renal failure. Little is excreted in the bile.

Manifestations of hypersensitivity in patients not known to be allergic to β-lactam antibiotics are common. It is no longer used.

#### CEFALORIDINE (CEPHALORIDINE)

Its activity and spectrum are similar to those of cefalotin. A 1 g intramuscular dose produces peak plasma levels of 20–40 mg/L at 1 h. The plasma half-life is 1.5 h. It is about 20% bound to plasma protein. In the presence of inflammation, CSF concentrations are around 25% of simultaneous plasma levels.

It is excreted unchanged in the urine, mainly in the glomerular filtrate. Moderate doses produce many hyaline casts in the urine and large doses sometimes cause proximal tubular necrosis, occasionally leading to oliguria and renal failure. Renal toxicity is enhanced by furosemide and ethacrynic acid. It is no longer used.

#### CEFAMANDOLE

A semisynthetic cephalosporin supplied as the nafate, an antibacterially inactive ester hydrolyzed in the body to cefamandole. It is active against common pathogenic bacteria (Table 13.1), but there is considerable strain variation in susceptibility. It is somewhat more stable than other group 1 agents to enterobacterial β-lactamases. Acinetobacter, Serratia and Pseudomonas spp. are often resistant. Some anaerobic Gram-negative rods are susceptible but B. fragilis is resistant.

A 1 g intramuscular dose achieves a plasma concentration of 20–35 mg/L after 1 h. It is widely distributed in body tissues. CSF levels are poor in the absence of meningeal inflammation. Therapeutically effective concentrations (c. 9 mg/kg) are found in bone after an intravenous dose of 2 g. Protein binding is 65–80%.

Renal excretion with a plasma half-life of around 50 min is mainly by both glomerular and tubular routes. A small amount is excreted in the bile and concentrations around 150–250 mg/L are found in T-tube bile following a 1 g intravenous dose. Only about 5% is removed by hemodialysis.

Cefamandole is one of the analogs containing the methylthiotetrazole side chain associated with bleeding (p. 172). Rare renal damage or enhancement of existing renal damage has been described. Thrombophlebitis on intravenous administration is relatively common.
Experience in the treatment of a variety of infections and for surgical prophylaxis has been mixed and it is no longer recommended.

**Further information**


**CEFAPIRIN**

Its antibacterial spectrum is almost identical to that of cephalotin, but it is more labile to staphylococcal \( \beta \)-lactamase. Intramuscular injections can be painful. A peak plasma concentration of 15–25 mg/L is obtained 0.5 h after intramuscular injection of 1 g. The plasma half-life is 0.4–0.8 h. It is c. 50% plasma protein bound and metabolized to the desacetyl form. The metabolite accounts for almost half the drug in the urine. Less than 1% of the dose appears in the bile.

A serum-sickness-like illness analogous to that seen with cephalotin has been observed. It is no longer used.

**CEFONICID**

Activity against Gram-positive and Gram-negative organisms in vitro is depressed by the presence of 50% serum. It is highly bound to plasma protein (98%) and has an extended plasma half-life of 4.5–5 h. A 1 g intramuscular dose achieves a mean peak plasma concentration of around 83 mg/L. Following a 1 g intravenous bolus dose, mean peak plasma concentrations of 130–300 mg/L have been reported. In patients treated for community-acquired pneumonia, concentrations of 2–4 mg/L have been found in sputum.

It is predominantly excreted by renal secretion, 83–89% being recovered unchanged in the urine over 24 h. Plasma half-life is linearly related to creatinine clearance. As a result of its high protein binding it is not removed by hemodialysis.

It is generally well tolerated; phlebitis and pain at the site of injection are reported in some patients with occasional transient neutropenia and increased transaminase levels. It has been used principally for the treatment of infections due to Gram-positive cocci, including staphylococcal and streptococcal soft-tissue infections, but is no longer widely available.

**Further information**


**GROUP 2 CEPHALOSPORINS**

**CEFACLOR**

Molecular weight (monohydrate): 385.8.

A semisynthetic oral cephalosporin available as the monohydrate. Aqueous solutions are stable at room temperature and 4°C for 72 h at pH 2.5 but rapidly lose activity at pH 7. A delayed-release formulation is available.

**ANTIMICROBIAL ACTIVITY**

Its activity against common pathogenic bacteria is shown in Table 13.2. It is less resistant than other group 2 cephalosporins to staphylococcal \( \beta \)-lactamase. It is active against *N. gonorrhoeae* and *H. influenzae* and against most enterobacteria, but it is susceptible to common enterobacterial \( \beta \)-lactamases. *P. vulgaris* and *Providencia, Acinetobacter* and *Serratia* spp. are resistant. *B. fragilis* and clostridia are resistant but other anaerobes are commonly susceptible.
**PHARMACOKINETICS**

**Absorption**

Food intake increases the time taken to reach peak plasma levels and reduces the peak by 25–50%. The actual amount absorbed is unaffected. In children receiving 15 mg/kg per day (maximum daily dose 1 g) the mean peak serum level was 16.8 mg/L at 0.5–1 h. There is no accumulation of the drug during repeated administration.

**Distribution**

In patients receiving 500 mg every 8 h for 10 days, concentrations were 0–1.7 (mean 0.5) mg/L in mucoid sputum and 0–2.8 (mean 1.0) mg/L in purulent sputum. In children with chronic serous otitis media receiving 15 mg/kg per day, the mean peak concentration in middle ear secretion was 3.8 mg/L within 30 min of the dose when the mean simultaneous serum concentration was 12.8 mg/L.

**Metabolism and excretion**

No metabolites have been identified, but the drug probably chemically degrades in serum. About half of the dose is recovered from the urine in the first 6 h and 70% in 24 h. Probencid prolongs the plasma levels but in renal insufficiency the plasma half-life is only moderately increased. In patients with creatinine clearance values of 5–15 mL/min the mean plasma elimination half-life rose to 2.3 h and the 24 h urinary excretion fell to less than 10%. In patients requiring intermittent hemodialysis and receiving 500 mg every 8 h for 10 days, the half-life rose to 2.9 h. Dialysis removed 34% of the dose.

**TOXICITY AND SIDE EFFECTS**

Apart from mild gastrointestinal disturbance, the drug is well tolerated. Transiently increased transaminase levels and symptomatic vaginal candidosis have been noted. Clusters of a serum sickness-like illness have been described in children.

**CLINICAL USE**

Uses are similar to those of other group 2 cephalosporins. It is among the few suitable for use in respiratory infections because of its activity against *H. influenzae*.

**Preparations and dosage**

**Proprietary name:** Distaclor.

**Preparations:** Tablets, suspension, capsules.

**Dosage:** Adults, oral, 250–500 mg every 8 h, depending on severity of infection (maximum dose, 4 g per day). Children >1 month, 20 mg/kg per day in divided doses every 8 h. In more severe infections, 40 mg/kg per day in divided doses (maximum dose, 1 g per day). Widely available.

**Further information**


**Table 13.2 Activity of group 2 cephalosporins against common pathogenic bacteria: MIC (mg/L)**

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Cefaclor</th>
<th>Cefadroxil</th>
<th>Cefatrizine</th>
<th>Cefalexin</th>
<th>Cefprozil</th>
<th>Loracarbef</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2–4</td>
<td>2–4</td>
<td>0.5–1</td>
<td>2–4</td>
<td>0.25–4</td>
<td>1–8</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>0.25</td>
<td>0.1–0.5</td>
<td>0.03–0.1</td>
<td>0.5–2</td>
<td>0.06–0.25</td>
<td>0.12–1</td>
</tr>
<tr>
<td><em>Str. pneumoniae</em></td>
<td>0.5–1</td>
<td>1</td>
<td>0.25–0.5</td>
<td>2</td>
<td>0.06–0.25</td>
<td>0.5–2</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>0.1–0.5</td>
<td>4</td>
<td>0.25–0.5</td>
<td>0.5–4</td>
<td>0.12–0.25</td>
<td>0.004–1</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>1–2</td>
<td>16–32</td>
<td>2–8</td>
<td>8–32</td>
<td>0.006–8</td>
<td>0.5–2</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>2–8</td>
<td>8–16</td>
<td>2–8</td>
<td>8</td>
<td>1–4</td>
<td>1–2</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>4–8</td>
<td>8–16</td>
<td>8</td>
<td>8</td>
<td>1–64</td>
<td>1–8</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

*Cefradine and cefroxadine have almost identical activity. R, resistant (MIC >64 mg/L).*
### Cefadroxil

Molecular weight (monohydrate): 381.4.

\[ \text{HO} \quad \text{CHCONH} \quad \text{S} \quad \text{COOH} \]

\[ \text{NH}_2 \quad \text{CH}_3 \]

\( \beta \)-Hydroxycephalexin, available as the mono- and trihydrate.

### Antimicrobial Activity

Resembles closely that of cefalexin (Table 13.2).

### Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; 250 mg oral</td>
<td>9 mg/L after 1.2 h</td>
</tr>
<tr>
<td></td>
<td>500 mg oral</td>
</tr>
<tr>
<td></td>
<td>18 mg/L after 1.2 h</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>1–1.5 h</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>20%</td>
</tr>
</tbody>
</table>

Absorption is little affected by administration with food. Distribution is similar to that of cefalexin. It is eliminated unchanged by glomerular filtration and tubular secretion; 90% of the dose appears in the urine over 24 h, most in the first 6 h, producing concentrations exceeding 500 mg/L.

### Toxicity and Side Effects

Side effects described are those common to oral cephalosporins.

### Clinical Use

It has been used for various community-acquired infections for which oral cephalosporins are appropriate.

### Preparations and Dosage

**Proprietary name:** Baxan.

**Preparations:** Capsules, suspension, tablets.

**Dosage:**
- Adults, oral, ≥40 kg, 0.5–1 g every 12 h. Children <1 year, 25 mg/kg per day in divided doses; children 1–6 years, 250 mg every 12 h; children >6 years, 500 mg every 12 h.
- Widely available.

### Further Information


### Cefalexin


\[ \text{CHCONH} \quad \text{S} \quad \text{COOH} \]

\[ \text{NH}_2 \quad \text{CH}_3 \]

### Antimicrobial Activity

Activity against common pathogens is shown in Table 13.2. It is resistant to staphylococcal \( \beta \)-lactamase. Gram-positive rods and fastidious Gram-negative bacilli, such as *Bordetella* spp. and *H. influenzae*, are relatively resistant. It is active against a range of enterobacteria, but it is degraded by many enterobacterial \( \beta \)-lactamases. *Citrobacter, Edwardsiella, Enterobacter, Hafnia, Providencia* and *Serratia* spp. are all resistant. Gram-negative anaerobes other than *B. fragilis* are susceptible. Because of its mode of action (p. 13) it is only slowly bactericidal to Gram-negative bacilli.

### Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; 500 mg oral</td>
<td>10–20 mg/L after 1 h</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>0.5–1 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>15 L</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>10–15%</td>
</tr>
</tbody>
</table>

Absorption and distribution

It is almost completely absorbed when given by mouth, the peak concentration being delayed by food. Intramuscular preparations are not available: injection is painful and produces delayed peak plasma concentrations considerably lower than those obtained by oral administration.

In synovial fluid, levels of 6–38 mg/L have been described after a 4 g oral dose, but penetration into the CSF is poor. Useful levels are achieved in bone (9–44 mg/kg after 1 g orally) and in purulent sputum. Concentrations of 10–20 mg/L have been found in breast milk. Concentrations in cord blood following a maternal oral dose of 0.25 g were minimal.
Metabolism and excretion

It is not metabolized. Almost all the dose is recoverable from the urine within the first 6 h, producing urinary concentrations exceeding 1 g/L. The involvement of tubular secretion is indicated by the increased plasma peak concentration and reduced urinary excretion produced by probenecid. Renal clearance is around 200 mL/min and is depressed in renal failure, although a therapeutic concentration is still obtained in the urine. It is removed by peritoneal and hemodialysis. Some is excreted in the bile, in which therapeutic concentrations may be achieved.

TOXICITY AND SIDE EFFECTS

Nausea, vomiting and abdominal discomfort are relatively common. Pseudomembranous colitis has been described and overgrowth of Candida with vaginitis may be troublesome. Otherwise, mild hypersensitivity reactions and biochemical changes common to cephalosporins occur. Very rare neurological disturbances have been described, particularly in patients in whom very high plasma levels have been achieved. There are rare reports of Stevens–Johnson syndrome and toxic epidermal necrolysis.

CLINICAL USE

As for group 2 cephalosporins (p. 172). It should not be used in infections in which H. influenzae is, or is likely to be, implicated. It should not be used as an alternative to penicillin in syphilis.

Preparations and dosage

Proprietary names: Keflex, Ceporex.
Preparations: Capsules, tablets, suspension.
Dosage: Adults, oral, 1–2 g per day in divided doses; for severe infections, increase dose to 1 g every 8 h or 3 g every 12 h. Children, 25–50 mg/kg per day in 2–3 divided doses, for severe infection increase dose to 100 mg/kg per day in 4 divided doses (maximum dose, 4 g per day).
Widely available.

Further information


CEFPROZIL

Molecular weight (monohydrate): 407.5.

A semisynthetic oral cephalosporin formulated as the monohydrate.

ANTIMICROBIAL ACTIVITY

Activity against Gram-positive cocci and Gram-negative bacilli is better than that of cefadroxil (which it structurally resembles) but is not as good as that of group 5 agents (Tables 13.2 and 13.5). It is moderately stable to hydrolysis by the common plasmid-mediated β-lactamases, but is hydrolyzed by the chromosomal enzymes of Gram-negative bacilli (p. 230).

PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Cmax</td>
<td>250 mg oral</td>
</tr>
<tr>
<td></td>
<td>500 mg oral</td>
</tr>
<tr>
<td></td>
<td>5–7 mg/L after 1 h</td>
</tr>
<tr>
<td></td>
<td>10 mg/L after 1 h</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>1–1.4 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>15–20 l</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>35–45%</td>
</tr>
</tbody>
</table>

Absorption and distribution

It is almost completely absorbed and well distributed, penetrating well into tonsillar and other tissues and inflammatory exudate. Absorption is unaffected by food or antacids and there is no accumulation on multiple dosing regimens.

Metabolism and excretion

Most of the dose is excreted unchanged in urine, though about 20% is found in feces. Urinary concentrations after a 500 mg oral dose usually exceed 1 g/L. The elimination half-life is prolonged in patients with renal impairment, reaching 6 h in anuric patients. About half the drug is removed in 3 h by hemodialysis.

TOXICITY AND SIDE EFFECTS

It is well tolerated. Diarrhea and gastrointestinal discomfort may occur. There have been a few reports of pseudomembranous colitis and serum sickness-like reactions.
CLINICAL USE

It has been used for various infections for which oral cephalosporins are appropriate.

Preparations and dosage

Proprietary name: Cefzil.
Preparations: Tablets, suspension.
Dosage: Adults, oral, 250–500 mg every 12–24 h depending on infection being treated. Children, 7.5–15 mg/kg every 12 h.
Available in the UK, USA and continental Europe.

Further information


OTHER GROUP 2 CEPHALOSPORINS

CEFRADINE

Cefradine. A semisynthetic cephalosporin available in both oral and injectable forms. The antibacterial spectrum and susceptibility to β-lactamases are almost identical to those of cefalexin (Table 13.2).

It is almost completely absorbed when given by mouth. A 500 mg oral dose achieves a concentration of about 18–20 mg/L after 1 h. The peak is delayed and reduced by food, but the half-life is not altered. Intramuscular administration of 1 g results a plasma concentration of 10–12 mg/L within 2 h. The plasma half-life is around 1 h and protein binding low.

Concentrations of up to 40% of those simultaneously found in the serum have been demonstrated in lung tissue. Penetration into the CSF is poor. Levels in sputum were about 20% of those simultaneously present in the plasma following a 1 g oral dose and similar levels have been found in bone. Breast milk concentrations approaching 1 mg/L have been found after 500 mg orally every 6 h and similar concentrations have been found in amniotic fluid. Cord blood concentration is said to be similar to that in the maternal blood.

It is excreted unchanged in the urine mostly in the first 6 h, achieving concentrations exceeding 1 g/L. Probenecid markedly increases the plasma concentration and delays the peak. There is some biliary excretion.

The parenteral forms may give rise to local pain or thrombophlebitis. Other side effects common to cephalosporins have been described. In some patients Candida vaginitis has been troublesome.

Clinical use is similar to that of cefalexin, but it has been largely superseded by later cephalosporins.

Preparations and dosage

Proprietary name: Velosef.
Preparations: Capsules, syrup, injection.
Dosage: Adults, oral, 250–500 mg every 6 h, or 0.5–1 g every 12 h (maximum dose, 4 g per day). Children, 25–100 mg/kg per day in 2–4 divided doses. Adults, i.m., i.v., 2–8 g per day in divided doses depending on severity of infection. Children, 50–100 mg/kg per day in four divided doses; more serious illnesses may require 200–300 mg/kg per day. Widely available.

Further information

at the C-3 position. The antimicrobial spectrum is identical to that of cefradine and cefalexin (Table 13.2). A dose of 1 g as film-coated tablets produced mean peak plasma levels of 25 mg/L at 1 h. Absorption is depressed and delayed by administration with food. The plasma elimination half-life is 0.8 h, rising to 40 h in end-stage renal failure and falling to 3.4 h during hemodialysis. Around 85% of an oral dose is excreted unchanged in the urine. It is available in Japan.

**Further information**


**LORACARBEF**

An oral carbacephem, with carbon replacing sulfur in the fused ring structure. Its structure and properties are otherwise closely related to those of cefaclor, but it has improved chemical stability. Activity and stability to β-lactamases correspond closely to those of cefaclor (Table 13.2).

It is almost completely absorbed by the oral route, but food delays absorption. A 500 mg oral dose achieves a serum concentration of around 16 mg/L after 1.3 h. Adequate concentrations are achieved for the treatment of upper respiratory tract infection. Sputum concentrations have been found to be around 2% of the corresponding plasma level. The plasma half-life is about 1 h and protein binding is 25%.

Most of the dose is excreted unchanged in the urine, 60% within 12 h. The elimination half-life is increased in patients with impaired renal function. Probenecid delays excretion.

Diarrhea is the most prominent side effect, occurring in about 4% of patients. Other gastrointestinal upsets are also reported. It has been used for the oral treatment of upper respiratory tract infection, skin and soft-tissue infections, and uncomplicated urinary tract infection caused by sensitive organisms, but is not widely available.

**Further information**


**GROUP 3 CEPHALOSPORINS**

**CEFOXITIN**

Molecular weight (sodium salt): 449.4.

A semisynthetic cephamycin available as the sodium salt for intramuscular or intravenous injection.

**ANTIMICROBIAL ACTIVITY**

Its activity against common pathogenic bacteria is shown in Table 13.3. Most Gram-positive bacilli are susceptible, but

<table>
<thead>
<tr>
<th>Table 13.3 Activity of group 3 cephalosporins against common pathogenic bacteria: MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td><strong>Streptococcus pyogenes</strong></td>
</tr>
<tr>
<td><strong>Str. pneumoniae</strong></td>
</tr>
<tr>
<td><strong>Enterococcus faecalis</strong></td>
</tr>
<tr>
<td><strong>Neisseria gonorrhoeae</strong></td>
</tr>
<tr>
<td><strong>N. meningitidis</strong></td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
</tr>
<tr>
<td><strong>Bacteroides fragilis</strong></td>
</tr>
</tbody>
</table>

R, resistant (MIC >64 mg/L).
\( L.\ monocytogenes \) is resistant. It is resistant to many Gram-negative \( \beta \)-lactamases and is active against organisms elaborating them, including some \( \text{Citrobacter, Providencia, Serratia} \) and \( \text{Acinetobacter} \) spp. \( \text{Enterobacter} \) spp. are resistant. It is moderately active against \( \text{Bacteroides} \) spp., but considerable strain variation in susceptibility occurs.

### ACQUIRED RESISTANCE

Resistant strains of \( \text{Bacteroides} \), some of which produce \( \beta \)-lactamases that hydrolyze cefoxitin, have been described. Resistance may be transferable to other \( \text{Bacteroides} \) spp. It is a potent inducer of chromosomal cephalosporinases of certain Gram-negative bacilli (p. 230) and can antagonize the effect of cefotaxime and other \( \beta \)-lactam agents.

### PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (500 mg i.m.)</td>
<td>11 mg/L after 20 min</td>
</tr>
<tr>
<td>1 g i.v.</td>
<td>c. 150 mg/L end injection</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>0.7–1 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>c. 10 L</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>65–80%</td>
</tr>
</tbody>
</table>

#### Absorption

It is not absorbed when given orally, but is very rapidly absorbed from intramuscular sites. Doubling the dose approximately doubles the plasma level. It is absorbed from suppositories to varying degrees depending on the adjuvants: peak serum levels around 9.8 mg/L have been obtained after a dose of 1 g, giving a bioavailability of around 20%. In infants and children treated with 150 mg/kg per day, mean serum concentrations 15 min after intravenous and intramuscular administration were 81.9 and 68.5 mg/L, with elimination half-lives of 0.70 and 0.67 h, respectively.

#### Distribution

About 20% of the corresponding serum levels are found in sputum. In patients given 1 g by intravenous bolus preoperatively, concentrations in lung tissue at 1 h were around 13 mg/g. Penetration into normal CSF is very poor; even in patients with purulent meningitis CSF concentrations seldom exceed 6 mg/L. In children with meningitis receiving 75 mg/kg every 6 h, peak concentrations of 5–6 mg/L were found around 1 h after the dose. In patients receiving 2 g intravenously before surgery, the mean penetration into peritoneal fluid was 86%. In patients receiving 2 g intramuscularly before hysterectomy, mean concentrations in pelvic tissue were 7.8 mg/g. Breast milk contained 5–6 mg/L after a 1 g intravenous dose. Concentrations up to 230 mg/L have been found in bile after 2 g intravenously.

#### Metabolism and excretion

Less than 5% of the drug is desacetylated and in a few subjects deacetylation of 1 or 2% of the dose to the antibacterially inactive descarbamyl form also occurs.

It is almost entirely excreted in the urine by both glomerular filtration and tubular secretion, 80–90% being found in the first 12 h after a parenteral dose, producing concentrations in excess of 1 g/L. Furosemide, in doses of 40–160 mg, had no effect on the elimination half-life of doses of 1 or 2 g. Probenecid delays the plasma peak and decreases the renal clearance and urine concentration. The renal clearance has been calculated variously to lie between 225 and 330 mL/min. The plasma half-life increases inversely with creatinine clearance to reach 24 h in oliguric patients, with corresponding reduction in total body clearance. In patients on peritoneal dialysis, peritoneal clearance accounted for only 7.5% of mean plasma clearance and the mean plasma half-life during 6 h dialysis was 7.8 h.

#### TOXICITY AND SIDE EFFECTS

Reactions are those common to cephalosporins. Pain on intramuscular, and thrombophlebitis on intravenous, injection occur. Substantial changes can occur in the fecal flora, with virtual eradication of susceptible enterobacteria and \( \text{non-fragilis Bacteroides} \), and appearance of, or increase in, yeasts, enterococci and other resistant bacteria including \( \text{C. difficile} \). Development of meningitis due to \( \text{H. influenzae} \) and \( \text{Str. pneumoniae} \) in patients treated for other infections has been observed.

#### CLINICAL USE

As for other group 3 cephalosporins, with particular emphasis on mixed infections including anaerobes, notably abdominal and pelvic sepsis. In considering its use, its low activity against aerobic Gram-positive cocci should be noted.

### Preparations and dosage

- **Proprietary name:** Mefoxin.
- **Preparation:** Injection.
- **Dosage:** Adults, i.m., i.v., 1–2 g every 6–8 h (maximum dose, 12 g per day in 4–6 divided doses). Children <1 week, 20–40 mg/kg every 12 h; children 1–4 weeks, 20–40 mg/kg every 8 h; children >1 month, 20–40 mg/kg every 6–8 h (maximum dose, 200 mg/kg per day).

Widely available.

### Further information

Group 3 Cephalosporins


CEFUROXIME

Molecular weight (sodium salt): 446.4.

A semisynthetic cephalosporin supplied as the sodium salt, or as the acetoxyethyl ester (cefuroxime axetil).

ANTIMICROBIAL ACTIVITY

Activity against common pathogenic bacteria is shown in Table 13.3. The methoximino side chain provides stability to most Gram-negative β-lactamases and it is active against most enterobacteria, including many multiresistant strains. Actinobacter spp., S. marcescens and Ps. aeruginosa are resistant, although some Burkholderia cepacia strains are susceptible. Some anaerobic Gram-negative rods are susceptible, but B. fragilis is resistant. The minimum immobilizing concentration for the Nichol’s strain of T. pallidum is 0.01 mg/L.

PHARMACOKINETICS

Oral absorption (axetil) 40–50%
Cmax 500 mg intramuscular c. 18–25 mg/L after 0.5–1 h
0.75 g intravenous infusion c. 50 mg/L end infusion
500 mg oral (axetil) 6–9 mg/L after 1.8–2.5 h
Plasma half-life 1.1–1.4 h
Volume of distribution 11–15 L
Plasma protein binding 30%

Absorption

The acetoxyethyl ester (cefuroxime axetil) is rapidly hydrolyzed on passage through the intestinal mucosa and in the portal circulation to liberate cefuroxime, acetaldehyde and acetic acid. No unchanged ester is detectable in the systemic circulation. Absorption is independent of dose in the range 0.25–1 g, and there is no accumulation on repeated dosing.

Bioavailability is improved after food to around 50%. In elderly subjects receiving doses of 500 mg every 8–12 h, peak plasma levels were 5.5 mg/L after 1.5–2 h in the fasting state, rising to 7.6 mg/L after 20 min when the dose was administered with food.

Distribution

In patients with severe meningeal inflammation, the mean CSF concentration after a 1.5 g intravenous dose was in the range 1.5–3.7 mg/L. In about one-third of patients with normal CSF, no drug could be detected and in the remainder concentrations were 0.2–1 mg/L. In children treated for meningitis with 50 or 75 mg/kg, the CSF:serum ratios were 0.07 and 0.10, respectively. Concentrations in pleural drain fluid after thoracic surgery approximated to serum levels at 2 h after doses of 1 or 1.5 g and exceeded serum levels at 4 h, when they were still around 10 mg/L. Levels in pericardial fluid were similar, with fluid:serum ratios of 0.44 between 0.5 and 2 h. In patients receiving 1.5 g by intravenous bolus preoperatively, concentrations around 22 mg/L were found in subcutaneous tissue at about 5 h with an elimination half-life of about 1.5 h.

Mean bone:serum ratios in the femoral head after 750 mg intramuscular and 1.5 g intravenous bolus injections were 0.14 and 0.23, respectively. In patients with chronic otitis media treated with 0.75 g every 8 h for 6–8 days, peak concentrations in the middle ear of 0.7–1.7 mg/L were reached about 2 h after the dose. In patients given 750 mg intramuscularly on five consecutive days the mean sputum concentration rose from 0.57 mg/L on the first day to 1.15 mg/L on the third.

Excretion

The drug is excreted unchanged in the urine mostly within 6 h of administration, producing concentrations exceeding 1 g/L. About 45–55% of the drug is excreted by tubular secretion, so that the administration of probenecid increases the serum peak and prolongs the plasma half-life. Renal clearance is slightly affected by the route of administration but lies between 95 and 180 L/min. The plasma half-life is prolonged in the elderly up to 2.4 h.

TOXICITY AND SIDE EFFECTS

It is well tolerated with little pain or phlebitis on injection. Minor hypersensitivity reactions and biochemical changes common to cephalosporins are described.

The axetil ester may cause diarrhea and, in some cases, vomiting. Changes in the bowel flora, sometimes with the appearance of C. difficile, have been reported in about 15% of patients. Vaginitis is reported in about 2% of female patients.

CLINICAL USE

It has been used successfully to treat urinary, soft-tissue and pulmonary infections, as well as septicemia, and as a single-dose treatment (with probenecid) of gonorrhea due to β-lactamase-producing strains. It has been widely used for surgical prophylaxis.
### Preparations and dosage

**Cefuroxime**
- **Proprietary name:** Zinacef.
- **Preparation:** Injection.
- **Dosage:** Adults, i.m., i.v., 750 mg every 6–8 h; 1.5 g every 6–8 h in severe infections. Children, 30–100 mg/kg per day in 3–4 divided doses; 50–60 mg/kg every 8 h for severe infections. Neonates, 30–100 mg/kg per day in 2–3 divided doses.
- Widely available.
- **Cefuroxime axetil**
  - **Proprietary name:** Zinnat.
  - **Preparations:** Tablets, suspension, sachets.
  - **Dosage:** Adults, oral, 250–500 mg every 12 h depending on severity of infection. Children 3 months to 2 years, 10 mg/kg (maximum 125 mg) twice daily; >2 years 15 mg/kg (maximum 250 mg) twice daily.
  - Widely available.

### Further information


### OTHER GROUP 3 CEPHALOSPORINS

#### CEFBUPERAZONE

A semisynthetic cephemycin antibiotic with properties similar to those of cefoxitin, but somewhat more active against *B. fragilis* and enterobacteria. It is not hydrolyzed by common β-lactamases and as a result its activity is not affected by inoculum size. Its activity against common pathogenic bacteria is shown in Table 13.3. It is not active against cefoxitin-resistant strains. It is available in Japan.

### Further information


### CEFMETAZOLE

A semisynthetic cephemycin antibiotic. Activity against common pathogenic bacteria is shown in Table 13.3. It is active against *Pr. mirabilis*, *Pr. vulgaris*, *Morganella morganii*, *Yersinia* spp. and most anaerobes. *S. marcescens* is moderately susceptible, but *Ps. aeruginosa* and *E. faecalis* are resistant. It is active against *Mycobacterium fortuitum* and some strains of *M. chelonae*. It is resistant to a wide range of β-lactamases.

The serum concentration at the end of a 1 g intravenous infusion is around 77 mg/L. Plasma protein binding is 68%. It is principally excreted in the urine with a plasma half-life of 1.3 h; 70% is recovered over the first 6 h. In patients whose creatinine clearance is less than 10 mL/min, plasma levels are elevated and the plasma half-life is increased to around 15 h.

Side effects associated with the methylthiotetrazole group at position C-3 have been reported. Uses are similar to those of cefoxitin, but it is not widely available.

### Further information


### CEFMINOX

A semisynthetic cephemycin. Activity is similar to that of cefoxitin and cefotetan, but the activity against enterobacteria and *B. fragilis* is somewhat better (Table 13.3). *C. difficile* is inhibited by 4–16 mg/L. It is stable to the common β-lactamases of enterobacteria and *Bacteroides* spp.

A 15-min intravenous infusion of 1 g achieves a serum concentration of 30 mg/L after 1 h. The plasma half-life is c. 2 h and around 68% is protein bound.

Its safety profile and uses are similar to those of other cephemycins. It is available in Japan.

### Further information


### CEFOTETAN

A semisynthetic cephemycin formulated as the disodium salt for intravenous administration. The activity is similar to that of cefoxitin, but cefotetan exhibits more potent activity against enterobacteria and more modest activity against *Staph. aureus* (Table 13.3).

A 1 g intravenous dose achieves a serum concentration of 140–180 mg/L. There is no evidence of accumulation on a dosage of 1 g every 12 h. Tissue fluid concentrations are about 30% of the simultaneous serum level. The plasma half-life is about 3 h and protein binding is around 88%.

### Further information

About 85% of the drug is eliminated in the urine over 24 h. Accumulation in renal failure is inversely related to the creatinine clearance, the plasma half-life rising to 20 h in patients requiring hemodialysis. During hemodialysis the half-life falls to around 7.5 h and on peritoneal dialysis it falls to 15.5 h, 5–10% of the dose being recovered in the dialysate over 24 h.

Side effects are those typical of the group. Anaphylaxis has been described. Because of the methylthiotetrazole side chain there is some risk of hypoprothrombinemia, and disulfiram-like reactions can occur. Marked changes in the bowel flora, with appearance of C. difficile, have been reported. Uses are similar to those of other cephemycins, but it is not widely available.

Further information

CEFOTIAM

A semisynthetic cephalosporin formulated as the dihydrochloride for injection and as a prodrug ester, cefotiam hexetil, for oral administration. Activity is similar to that of cefuroxime, but it is somewhat more active against a range of enterobacteria (Table 13.3).

A 30-min intravenous infusion of the dihydrochloride produces a peak serum concentration of 35 mg/L, the corresponding concentration after a 1 g intramuscular dose is 17 mg/L. Oral absorption of the hexetil ester is around 65%. Food delays absorption of the ester. The plasma half-life is 0.6–1.1 h. Around 40% is bound to plasma protein.

Urinary excretion is almost complete 4 h after the end of intravenous infusion, but only 50–67% is recovered unchanged; there is substantial non-renal elimination and some evidence of saturation of renal tubular excretion at doses above 2 g. In anuria the plasma elimination half-life rises to 13 h and plasma and renal clearances parallel creatinine clearance. A small amount is excreted in bile. In patients with cholelithiasis given 0.5 or 1 g intravenously, mean concentrations in gallbladder bile and gallbladder wall 30 min after the dose were around 17 and 32 mg/L, respectively. In patients with normal liver function, hepatic bile concentrations can exceed 1 g/L.

It is generally well tolerated and has been used successfully to treat lower respiratory infections, skin and soft-tissue infection. It is not widely used, but is available in Japan and some other countries.

Further information

ANTIMICROBIAL ACTIVITY

The aminothiazoyl and methoximino groups at the 7-amino position confer, respectively, potent activity against many Gram-negative rods and cocci (Table 13.4) and stability to most β-lactamases. P. aeruginosa, Sten. maltophilia and other pseudomonads are often resistant. Brucella melitensis and some strains of Nocardia asteroides are susceptible. Activity against L. monocytogenes and B. fragilis is poor.

ACQUIRED RESISTANCE

Many enterobacteria resistant to other β-lactam agents are susceptible, but selection of resistant strains with derepressed chromosomal molecular class C cephalosporinases (see p. 230) may occur. Gram-negative bacilli producing variants of the TEM enzymes (pp. 230–231) are resistant.

PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, 500 mg intramuscular</td>
<td>10–15 mg/L after 0.5–1 h</td>
</tr>
<tr>
<td>1 g intravenous (15-min infusion)</td>
<td>90 mg/L end infusion</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>c. 1 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>32–37 L</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>c. 40%</td>
</tr>
</tbody>
</table>

Distribution

It is widely distributed, achieving therapeutic concentrations in sputum, lung tissue, pleural fluid, peritoneal fluid, prostatic tissue and cortical bone. In patients receiving 2 g every 8 h, mean CSF concentrations in aseptic meningitis were
0.8 mg/L. Levels of 2–15 mg/L can be found in the CSF in the presence of inflammation after doses of 50 mg/kg by intravenous infusion over 30 min. A single intraventricular dose of 40 mg/kg produced levels at 2, 4 and 6 h of 6.4, 5.7 and 4.5 mg/L, respectively.

**Metabolism**

About 15–25% of a dose is metabolized by hepatic esterases to the desacetyl form, which may have some clinical importance because of its concentration in bile and accumulation in renal failure. Desacetylcefotaxime has about 10% of the activity of the parent against enterobacteria, less against *Staph. aureus*. Its half-life in normal subjects is around 1.5 h.

**Excretion**

Elimination is predominantly by the renal route, more than half the dose being recovered in the urine over the first 24 h, about 25% as the desacetyl derivative. Excretion is depressed by probenecid and declines in renal failure with accumulation of the metabolite. In patients with creatinine clearances in the range 3–10 mL/min, the plasma half-life rose to 2.6 h while that of the metabolite rose to 10 h.

### Clinical Uses

Cefotaxime is widely used in neutropenic patients, respiratory infection, meningitis, intra-abdominal sepsis, osteomyelitis, typhoid fever, urinary tract infection, neonatal sepsis and gonorrhea.

### Table 13.4 Activity of group 4 cephalosporins against common pathogenic bacteria: MIC (mg/L)

<table>
<thead>
<tr>
<th></th>
<th>Cefmenoxime</th>
<th>Cefodizime</th>
<th>Cefotaxime</th>
<th>Ceftizoxime</th>
<th>Ceftriaxone</th>
<th>Latamoxef</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2–4</td>
<td>2–8</td>
<td>2–4</td>
<td>2–4</td>
<td>4</td>
<td>8–16</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>0.03</td>
<td>0.06–0.1</td>
<td>0.03–0.06</td>
<td>0.03</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td><em>Str. pneumoniae</em></td>
<td>0.06</td>
<td>0.03–0.25</td>
<td>0.1</td>
<td>0.1</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>R</td>
<td>8–R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>&lt;0.01–0.03</td>
<td>0.008</td>
<td>&lt;0.01–0.03</td>
<td>&lt;0.01–0.03</td>
<td>&lt;0.01–0.06</td>
<td>0.03–0.1</td>
</tr>
<tr>
<td><em>N. meningitidis</em></td>
<td>&lt;0.01</td>
<td>0.008</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>0.03</td>
<td>0.008</td>
<td>&lt;0.01–0.03</td>
<td>0.03</td>
<td>&lt;0.01–0.03</td>
<td>0.1</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>0.06–0.1</td>
<td>0.1–1</td>
<td>0.03–0.1</td>
<td>0.03</td>
<td>0.06–0.1</td>
<td>0.1–0.25</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>0.03</td>
<td>0.1–2</td>
<td>0.03–0.1</td>
<td>0.01</td>
<td>0.03–0.06</td>
<td>0.1–0.25</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>16–32</td>
<td>R</td>
<td>8–32</td>
<td>32–64</td>
<td>16–32</td>
<td>4–16</td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em></td>
<td>8–64</td>
<td>8–R</td>
<td>2–32</td>
<td>8–64</td>
<td>16–64</td>
<td>0.5–4</td>
</tr>
</tbody>
</table>

*a* Penicillin-resistant strains are often less susceptible. R, resistant (MIC >64 mg/L).

### Toxicity and Side Effects

Minor hematological and dermatological side effects common to group 4 cephalosporins have been described. Superinfection with *Ps. aeruginosa* in the course of treatment has occurred. Occasional cases of pseudomembranous colitis have been reported.

### Preparations and dosage

**Proprietary name:** Claforan.  
**Preparation:** Injection.  
**Dosage:** Adults, i.m., i.v., 1–2 g every 8–12 h depending on severity of infection (maximum dose, 12 g per day). Neonates, <7 days, 25 mg/kg every 12 h; 7–21 days, 25 mg/kg every 8 h; 21–28 days, 25 mg/kg every 6–8 h; children >1 month, 50 mg/kg every 8–12 h (every 6 h in severe infections and meningitis; maximum 12 g daily). Widely available.

### Further information

CEFTRIAXONE

Molecular weight (disodium salt) 600.6.

A semisynthetic cephalosporin supplied as the disodium salt.

ANTIMICROBIAL ACTIVITY

Activity is almost identical to that of cefotaxime (Table 13.4). Most β-lactamase-producing enterobacteria are highly susceptible, as are streptococci (but not enterococci) and fastidious Gram-negative bacilli, although brucellae are less sensitive (MIC 0.25–2 mg/L). Treatment failure has been reported in tularemia. Ps. aeruginosa, mycoplasmas, mycobacteria and L. monocytogenes are resistant.

ACQUIRED RESISTANCE

It is hydrolyzed by some chromosomal enzymes, including those of Enterobacter spp. and B. fragilis. Derepression of chromosomal β-lactamase production can cause resistance in some species of Gram-negative bacilli in vitro and has been observed in patients.

PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax 500 mg/L intramuscular</td>
<td>c. 40 mg/L after 2 h</td>
</tr>
<tr>
<td>1 g intravenous (15–30 min infusion)</td>
<td>c. 120–150 mg/L end infusion</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>6–9 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.15 L/kg</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>95%</td>
</tr>
</tbody>
</table>

Distribution

It penetrates well into normal body fluids and natural and experimental exudates. In children treated for meningitis with 50 or 75 mg/kg intravenously over 10–15 min, mean peak CSF concentrations ranged from 3.2 to 10.4 mg/L, with lower values later in the disease. In patients receiving 2 g before surgery, concentrations in cerebral tissue reached 0.3–12 mg/L. In patients with pleural effusions of variable etiology given a 1 g intravenous bolus, concentrations of 7–8.7 mg/L were found at 4–6 h. In patients with exacerbations of rheumatoid arthritis receiving the same dose, joint fluid contained concentrations close to those in the serum, but with wide individual variation. Tissue fluid:serum ratios have varied from around 0.05 in bone and muscle to 0.39 in cantharides blister fluid. The apparent volume of distribution is increased in patients with cirrhosis where the drug rapidly enters the ascitic fluid, but its elimination kinetics are unaffected.

It rapidly crosses the placenta, maternal doses of 2 g intravenously over 2–5 min producing mean concentrations in cord blood of 19.5 mg/L, a mean cord:maternal serum ratio of 0.18; and in amniotic fluid 3.8 mg/L, a fluid:maternal serum ratio of 0.04. The plasma elimination half-life appears to be somewhat shortened in pregnancy (5–6 h). Some appear in the breast milk, the milk:serum ratio being about 0.03–0.04, secretion persisting over a long period with a half-life of 12–17 h.

Metabolism and excretion

It is not metabolized. Biliary excretion is unusually high, 10–20% of the drug appearing in the bile in unchanged form, with concentrations up to 130 mg/g in biopsied liver tissue from patients receiving 1 g intravenously over 30 min. The insoluble calcium salt may precipitate in the bile leading to pseudolithiasis. About half the dose appears in the urine over the first 48 h, somewhat more (c. 70%) in neonates. Excretion is almost entirely by glomerular filtration, since there is only a small effect of probenecid on the excretion of the drug. The half-life is not linearly correlated with creatinine clearance in renal failure and, in keeping with the low free plasma fraction, it is not significantly removed by hemodialysis. The volume of distribution is not affected by renal failure.

TOXICITY AND SIDE EFFECTS

Reactions are those common to other cephalosporins. Mention has been made of thrombocytopenia, thrombocytosis, leukopenia, eosinophilia abdominal pain, phlebitis, rash, fever and increased values in liver function tests. Diarrhea is common and suppression of the aerobic and anaerobic fecal flora has been associated with the appearance of resistant bacteria and yeasts.

Biliary pseudolithiasis due to concretions of insoluble calcium salt has been described in adults but principally in children. The precipitates can be detected in a high proportion of patients by ultrasonography and can occasionally cause pain, but resolve on cessation of treatment. The drug is better avoided in patients with pre-existing biliary disease, but the principal hazard appears to be misdiagnosis of gallbladder disease and unnecessary surgery.

CLINICAL USES

Uses are similar to those of cefotaxime, the long half-life offering the advantage of once-daily administration. It is used in the treatment of acute bacterial meningitis and as an alternative to rifampicin (rifampin) in the prophylaxis of meningococcal disease.
Preparations and dosage

Proprietary name: Rocephin.
Preparation: Injection.
Dosage: Adults, i.m., i.v., 1 g per day as a single dose, 2–4 g once or twice each day in severe infections. Neonates, i.v. infusion, 20–50 mg/kg once daily; children >1 month, 50 mg/kg once daily, increased up to 80 mg/kg in severe infections and meningitis; older children weighing >50 kg, 1 g daily, increased to 2–4 g daily in severe infections and meningitis.

Further information


OTHER GROUP 4 CEPHALOSPORINS

CEFODIZIME

Activity is typical of the group (Table 13.4) but its overall activity is somewhat less than that of cefotaxime against enterobacteria. There has been some interest in its immunomodulating properties, which affect a number of functions.

A 1 g intramuscular dose achieves a plasma concentration of 55–60 mg/L after about 1.5 h. The plasma half-life is around 3.5 h. Protein binding is c. 88%. It penetrates into lung, sputum, serous fluids and prostate. Excretion is mainly renal with about 60% of the dose appearing in the urine over 12 h in adults and 80–90% in children. Elimination is inversely correlated with creatinine clearance.

It is well tolerated apart from some pain at the site of injection, mild gastrointestinal upset and rash in a few patients. It has been used mainly to treat respiratory and urinary tract infection.

Further information


CEFIZOXMIME

A semisynthetic cephalosporin supplied as the sodium salt. The properties are very similar to those of cefotaxime, but it lacks the acetoxymethyl group at position C-4 and is therefore not subject to deacetylation. Activity against common pathogenic bacteria (Table 13.4) is very similar to that of cefotaxime.

A 500 mg intramuscular injection achieves a plasma concentration of around 14 mg/L. A concentration of 85–90 mg/L is produced 30 min at the end of a 30-min intravenous infusion. The plasma half-life is 1.3–1.9 h. Protein binding is 30%. It is well distributed. In children with meningitis receiving 200–250 mg/kg per day in four equally divided doses for 14–21 days, mean CSF concentrations 2 h after a dose were 6.4 mg/L on day 2 and 3.6 mg/L on day 14.

About 70–90% of the dose is recovered in the urine in the first 24 h, principally by glomerular filtration. Probenecid increases the plasma half-life by about 50%. In patients receiving 1 g intravenously over 30 min, the plasma elimination half-life rose to 35 h when the corrected creatinine clearance was <10 mL/min. It is partly removed by peritoneal and hemodialysis.

Adverse reactions and clinical use are similar to those of cefotaxime.

Further information


CEFMENOXIME

A semisynthetic cephalosporin supplied as the hydrochloride. Its activity is very similar to that of cefotaxime (Table 13.4). A 500 mg intramuscular injection achieves a plasma concentration of 15 mg/L after 40 min. Around 77% is protein bound. Probenecid increases peak plasma levels and extends the plasma half-life to 1.8 h. Therapeutic concentrations are achieved in CSF. There is a degradation product with a long half-life (around 40 h), but 80–92% of the drug is recovered unchanged from the urine. In patients with renal insufficiency, no significant relation was found between creatinine clearance and peak serum concentrations but there was a linear relationship with plasma half-life and total body clearance. About 10% of the dose appears in the feces, mostly extensively degraded, possibly by the fecal flora.

Toxicity, side effects and clinical use are those common to group 4 cephalosporins.

Further information

**FLOMOXEF**

An oxa-cephem which differs from latamoxef in the side chains carried at the 7-amino and C-3 positions, but which retains the 7-methoxy group that confers β-lactamase stability. The methyl group of the methylthiotetrazole side chain of latamoxef has been modified to hydroxymethyl in an attempt to avoid the undesirable side effects, while the side chain at the 7-amino position is F₂-CH-S-CH₂-. Activity is similar to that of latamoxef, but activity against *Staph. aureus* is improved and it is claimed to be a poor inducer of penicillin-binding protein 2′, which is associated with resistance in methicillin-resistant strains.

Intravenous injection of 2 g achieves a peak plasma concentration of around 50 mg/L, falling to 2.6 mg/L after 6 h. The plasma half-life is about 50 min. It appears to be well distributed and penetrates moderately well into lung, mucosal tissue of the middle ear and bone.

Flomoxef does not seem to be prone to the effects on platelet function of latamoxef and it has a less marked effect on vitamin K metabolism. It does not cause a disulfiram-like reaction with alcohol.

It is available in Japan, where it appears safe and effective in a wide range of infections.

**Further information**


**LATAMOXEF**

Moxalactam. A semisynthetic 7-methoxyoxacephem, supplied as the disodium salt. Activity against common pathogenic bacteria is shown in Table 13.4. It is generally slightly less active than cefotaxime, especially against *Staph. aureus*, but unlike other group 4 cephalosporins it exhibits fairly good activity against *B. fragilis*. Other Bacteroides spp. are generally less susceptible. The 7-methoxy substitution, also found in cephamycins such as cefoxitin, confers resistance to hydrolysis by a wide range of β-lactamases including those of *Staph. aureus*, various enterobacteria and *B. fragilis*. Resistance, predominantly in Enterobacter spp., *Ps. aeruginosa* and *Serratia marcescens* due to induction of chromosomal enzymes (p. 230), has been found in vitro and in some patients.

A 500 mg intramuscular injection achieves a serum concentration of 12–22 mg/L after 1.2 h. Infusion of 1 g over 30 min results in a concentration of 60 mg/L. The plasma half-life is c. 2 h and plasma protein binding 40–50%. There is reasonably good penetration into serous fluids, the concentration in ascitic fluid reaching 75% and in pleural fluid 50% of the concentration simultaneously present in the serum. Levels of 5–35 mg/L have been obtained in inflamed meninges. Sputum levels are of the order of 2 mg/L following 1 g of the drug intravenously.

Renal elimination accounts for 90% of the clearance, but significant concentrations are found in the feces. Excretion is depressed in renal failure. Hemodialysis removes 48–51% of the drug in 4 h; peritoneal dialysis has little or no effect.

Increased bleeding and decreases in platelet function associated with the methylthiotetrazole side chain are sufficiently common to have been cited as reasons for restricting use of the agent. Use is contraindicated in patients on anticoagulant therapy. Uses are similar to those of group 4 cephalosporins. It is generally less successful in the treatment of infections due to Gram-positive organisms.

**Further information**


**GROUP 5 CEPHALOSPORINS**

**CEFDITOREN**

Molecular weight (pivoxil ester): 620.73

![Chemical structure of cefditoren](image)

A semisynthetic cephalosporin formulated for oral use as the pivaloyloxymethyl ester, cefditoren pivoxil.

**ANTIMICROBIAL ACTIVITY**

Activity against common pathogens is shown in Table 13.5. It exhibits good activity against staphylococci, streptococci (but not enterococci), *H. influenzae* and *M. catarrhalis*, including β-lactamase-producing strains. Isolates of *Str. pneumoniae* exhibiting reduced susceptibility to penicillin are less susceptible (MIC 0.125–2 mg/L). Most enterobacteria, including many Enterobacter, Citrobacter, Serratia and *Proteus* spp., are susceptible. It is not active against *Ps. aeruginosa*, *Sten. maltophilina* or atypical respiratory pathogens such as *Chlamydia pneumoniae* and *M. pneumoniae*. It is stable to staphylococcal and common enterobacterial β-lactamases.
CHAPTER 13  β-LACTAM ANTIBIOTICS: CEPHALOSPORINS

**Pharmacokinetics**

Oral absorption   c. 70%
C<sub>max</sub> 200 mg oral  c. 1.8 mg/L after 1.5–3 h
Plasma half-life  0.8–1.3 h
Volume of distribution  9.3 L
Plasma protein binding  88%

After oral administration the pivaloyl ester is rapidly cleaved by esterases in the gut wall. Ingestion with food improves the bioavailability. Plasma concentrations are raised in elderly patients. There is no accumulation on repeated dosing.

It is excreted unchanged in the urine with a half-life of around 1.5 h, achieving a concentration of 150–200 mg/L within 4 h. Dosage adjustment is recommended in patients with deteriorating renal function.

**Toxicity and Side Effects**

In common with other pivoxil esters it may cause carnitine deficiency. Other side effects are those common to cephalosporins, mainly gastrointestinal disturbance.

**Clinical Use**

It has been advocated for community-acquired upper and lower respiratory tract infections and skin infections.

**Preparations and Dosage**

**Proprietary name:** Spectracef.

**Preparation:** 200 mg tablets.

**Dosage:** 400 mg every 12 h for 10 days.
Available in USA and Japan; not available in the UK.

**Further Information**


**Cefixime**

Molecular weight (anhydrous): 453.4; (trihydrate): 507.5.

An oral cephalosporin formulated as the anhydrous compound or the trihydrate.
ANTIMICROBIAL ACTIVITY

Activity against common pathogenic bacteria is shown in Table 13.5. It is active against *N. gonorrhoeae, M. catarrhalis, H. influenzae* and a wide range of enterobacteria, including most strains of *Citrobacter, Enterobacter* and *Serratia* spp. Its antistaphylococcal activity is poor. It is not active against *Acinetobacter* spp., *Ps. aeruginosa* or *B. fragilis*. It is resistant to hydrolysis by common β-lactamases.

PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Oral absorption</th>
<th>c. 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; 400 mg oral</td>
<td>4–5.5 mg/L after 4 h</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>3–4 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.1 L/kg</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>60–70%</td>
</tr>
</tbody>
</table>

Absorption and distribution

Oral absorption is slow and incomplete, but is unaffected by aluminum magnesium hydroxide. Penetration into cantharides blister fluid was very slow but exceeded the plasma level. CSF concentrations are poor even in the presence of meningeal inflammation, reaching an average of around 0.22 mg/L in children with meningitis.

Metabolism and excretion

It is not metabolized and is excreted unchanged in urine (mainly by glomerular filtration) and in bile, in which concentrations exceeding 100 mg/L have been found. Less than 20% of an oral dose is recovered from the urine over 24 h, falling to less than 5% in patients with severe renal impairment, with a corresponding increase in plasma concentration. It is not removed by peritoneal or hemodialysis.

TOXICITY AND SIDE EFFECTS

It is well tolerated, but diarrhea is fairly common and pseudomembranous colitis has been reported. Other side effects common to cephalosporins are occasionally seen.

CLINICAL USE

Cefixime has been used successfully in uncomplicated cystitis, upper and lower respiratory tract infections and various other infections. Its failure to provide adequate cover for staphylococci should be noted.

CEFPODOXIME

Molecular weight (proxetil ester): 557.6.

A semisynthetic cephalosporin supplied as the prodrug ester, cefpodoxime proxetil.

ANTIMICROBIAL ACTIVITY

The hydrolysis product is very similar to cefotaxime and it shares its potent, broad-spectrum activity (Table 13.5). It is stable to a wide range of plasmid-mediated β-lactamases. It induces the chromosomal β-lactamases of *Ps. aeruginosa, Enterobacter* spp., *S. marcescens* and *Citrobacter* spp., but is a less potent inducer than cefoxitin.
**PHARMACOKINETICS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption</td>
<td>c. 50%</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; 200 mg oral</td>
<td>2.1 mg/L after 3 h</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>c. 2.2 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>c. 35 L</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>20–30%</td>
</tr>
</tbody>
</table>

**Absorption and distribution**

The ester is rapidly hydrolyzed to the parent compound in the small intestine. Bioavailability increases to 65% if taken with food, but antacids and H<sub>2</sub>-receptor antagonists reduce absorption. Unabsorbed drug is hydrolyzed and excreted in the feces.

It is well distributed and penetrates well into tissues (including lung tissue) and inflammatory exudate to achieve concentrations inhibitory to common pathogens.

**Metabolism and excretion**

The hydrolyzed prodrug is not subject to further metabolism. About 80% of the absorbed compound (30–40% of the original dose) appears in the urine over 24 h. Excretion is by glomerular filtration and tubular secretion; probenecid delays secretion and increases the peak plasma concentration.

**TOXICITY AND SIDE EFFECTS**

The drug is well tolerated, but gastrointestinal disturbance with diarrhea is common. Pseudomembranous colitis has been reported occasionally. Other side effects are those common to cephalosporins.

**CLINICAL USE**

Cefpodoxime has been used principally for the treatment of upper and lower respiratory tract infections in children and adults.

**Further information**


**OTHER GROUP 5 CEPHALOSPORINS**

**CEFCAPENE**

A semisynthetic cephalosporin formulated for oral administration as the prodrug ester, cefcapene pivoxil. Activity and uses are similar to those of cefditoren.

Available in Japan.

**CEFIDINIR**

An oral cephalosporin similar in structure to cefixime, but with a slightly modified side chain at the 7-amino position. Activity is similar to that of cefixime, but it is more active, especially against staphylococci (Table 13.5). It is not hydrolyzed by staphylococcal or the common plasmid-mediated enterobacterial β-lactamases. An enhancing effect on phagocytosis has been demonstrated in vitro.

Oral absorption is about 35%. A 200 mg oral dose achieves a plasma concentration of 1 mg/L after c. 3 h. Absorption is reduced after a fatty meal. Concentrations equal to or higher than corresponding plasma levels were present in blister fluid 6–12 h after administration of an oral dose. The plasma half-life is 1.5 h. Protein binding is 60–70%. A total of 12–20% of the dose was excreted in the urine within 12 h, the renal elimination declining with increasing dose. The elimination half-life and peak plasma concentration are increased in renal failure. About 60% of the drug is removed by hemodialysis.

Side effects and uses are those common to oral cephalosporins.

**Further information**


**CEFETAMET**

A semisynthetic cephalosporin formulated for oral use as the prodrug ester, cefetamet pivoxyl. It is less active than cefaclor and cefadroxil against *Staph. aureus*, but as active against streptococci and more active against enterobacteria, *H. influenzae* and *N. gonorrhoeae*, including β-lactamase-producing strains. *L. monocytogenes*, *C. difficile*, *Sten. maltophilia* and *Burk. cepacia* are all resistant. It is resistant to hydrolysis by common plasmid-mediated enzymes.

The absolute bioavailability is about 50%. The plasma peak is delayed by food. Binding to plasma protein is about 20%. The volume of distribution approximates to the extracellular water. It is excreted into urine with a half-life of 2–2.5 h, principally in the glomerular filtrate. Elimination is linearly related to creatinine clearance. Side effects and uses are similar to those of other group 5 cephalosporins.

**CEFTERAM**

A semisynthetic cephalosporin formulated for oral administration as the prodrug ester, cefteram pivoxil. Activity is similar to that of cefixime, but with slightly better activity against staphylococci and some Gram-negative rods.

Available in Japan.

**CEFTIBUTEN**

A semisynthetic cephalosporin formulated as the dihydrate for oral administration.

Activity against common pathogens is shown in Table 13.5. It exhibits good activity against many Gram-negative bacilli, but its activity against Gram-positive cocci is very poor. It is stable to hydrolysis by the common plasmid-mediated β-lactamases, but not derepressed chromosomal enzymes (see p. 230).

It is rapidly and almost completely absorbed by mouth and is excreted in the urine with a half-life of 1.5–3 h. An oral dose of 400 mg achieves a peak plasma concentration of around 15 mg/L. Binding to plasma proteins is 65–77%.

Side effects mostly consist of mild gastrointestinal symptoms and mild liver function test changes. Clinical trials have mainly been conducted in urinary tract and respiratory tract infections which, despite the poor in-vitro activity against *Str. pneumoniae*, have shown ceftibuten to be as efficacious as comparator agents.

**Preparations and dosage**

**Proprietary name:** Cedax.

**Preparations:** Capsules, suspension.

**Dosage:** Adults and children >10 years (>45 kg), oral, 400 mg per day as a single dose. Children >6 months, 9 mg/kg per day as a single dose.

Available in USA and Japan; not available in the UK.

**Further information**


**GROUP 6 CEPHALOSPORINS**

**CEFEPIME**

Molecular weight (dihydrochloride monohydrate): 571.5.

![Chemical structure of cefepime](image)

A semisynthetic parenteral cephalosporin formulated as the hydrochloride with arginine as a pH stabilizer.

**ANTIMICROBIAL ACTIVITY**

Its activity against common pathogens (Table 13.6) is comparable to that of group 4 cephalosporins, but it is somewhat more active against *Ps. aeruginosa*. Like cefpirome it has low affinity for the molecular class C cephalosporinases of many Gram-negative rods (p. 230) and is consequently active against most strains of *Citrobacter* spp., *Enterobacter* spp., *Serratia* spp. and *Ps. aeruginosa* that are resistant to cefotaxime and ceftriaxime. It has poor activity against *L. monocytogenes* and against anaerobic organisms.

**PHARMACOKINETICS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, 2 g intravenous (30-min infusion)</td>
<td>c. 160 mg/L end infusion</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>c. 2 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>14–20 L</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>10–19%</td>
</tr>
</tbody>
</table>
It is well distributed. Penetration into tissues, including lung, appears to be similar to that of other aminothiazoyl cephalosporins. Very low concentrations are achieved in CSF in the absence of meningeal inflammation. It is secreted in breast milk.

It is partially metabolized, but 85% of the dose is excreted unchanged in the urine, achieving a concentration approaching 1 g/L within 4 h of a 1 g intravenous dose. Dosage adjustment is required in patients with impaired renal function, but hepatic impairment does not affect the pharmacokinetic properties.

**TOXICITY AND SIDE EFFECTS**

It is generally well tolerated, adverse events being those typical of the group.

**CLINICAL USE**

It is used in the treatment of serious infections, particularly those in which resistant Gram-negative pathogens are known or suspected to be involved.

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### Further information


### CEFTAZIDIME

Molecular weight (anhydrous): 546.6; (pentahydrate): 636.7.

A semisynthetic parenteral cephalosporin formulated as the pentahydrate.

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### Preparations and dosage

**Proprietary name:** Maxipime.

**Preparation:** Injection.

**Dosage:** Adult, i.m., i.v., 1–6 g per day in 2–3 divided doses.

Available in USA, most of Europe and Japan; not available in the UK.

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### Antimicrobial activity

Its activity against common pathogenic bacteria is shown in Table 13.6. Its activity is comparable to that of cefotaxime and ceftizoxime, but it is more active against *Ps. aeruginosa*, including almost all gentamicin-resistant strains, and *Burk. cepacia*. It is, however, less active against *Staph. aureus*. It is
stable to a wide range of β-lactamases, but is hydrolyzed by some TEM variants (see pp. 230–231).

PHARMACOKINETICS

<table>
<thead>
<tr>
<th></th>
<th>500 mg intramuscular</th>
<th>2 g intravenous (20-min infusion)</th>
<th>Plasma half-life</th>
<th>Volume of distribution</th>
<th>Plasma protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>18–20 mg/L</td>
<td>185 mg/L end infusion</td>
<td>1.5–2 h</td>
<td>16 L</td>
<td>c. 10%</td>
</tr>
</tbody>
</table>

No accumulation was seen in subjects receiving 2 g every 12 h over 8 days. In premature infants given 25 mg/kg every 12 h, mean peak plasma concentrations were 77 mg/L after intravenous and 56 mg/L after intramuscular administration, with plasma elimination half-lives of 7.3 and 14.2 h, respectively. Postnatal age was the most important determinant of elimination rate, which was halved after 5 days. In newborn infants given 50 mg/kg intravenously over 20 min, mean peak plasma concentrations varied inversely with gestational age from 102 to 124 mg/L, with half-lives of 2.9–6.7 h.

Distribution

The concentration into serous fluids reaches 50% or more of the simultaneous serum level. In patients given 1 g intravenously during abdominal surgery, detectable concentrations appeared within a few minutes in the peritoneal fluid, reaching a peak around 67 mg/L with a half-life of 0.9 h. Following a similar intravenous dose, a mean peak of 9.4 mg/L was reached at 2 h in ascitic fluid. Concentrations in middle ear fluid after 1 g intravenously were broadly comparable to those of the plasma.

In patients with meningitis, CSF concentrations of 2–30 mg/L have been found 2–3 h after doses of 2 g intravenously over 30 min given every 8 h for four doses. Concentrations are substantially less in the absence of meningitis. Concentrations of 3–27 mg/g were found in patients with intracranial abscesses treated with 0.5–2 g every 8 h. Concentrations around 0.4 mg/g in skin, 0.6 mg/g in muscle and 0.2 mg/g in fatty tissue have been found in patients given 2 g intravenously over 5 min preoperatively. A similar dose has produced mean prostate tissue:serum ratios of around 0.14. Effective concentrations are achieved in bone: in patients given 1 g intravenously mean bone concentrations were 14.4 mg/kg 35–40 min after the dose. There is secretion in breast milk, peak concentrations being around 5 mg/L at about 1 h in patients receiving 2 g intravenously every 8 h.

Metabolism and excretion

No metabolites have been detected. Elimination is almost exclusively renal, predominantly via the glomerular filtrate, with 80–90% of the dose appearing in the urine in the first 24 h. Elimination half-life is inversely correlated with creatinine clearance: as the values fall to 2–12 mL/min, the mean plasma half-life rises to 16 h. In patients maintained on hemodialysis the half-life fell to 2.8 h on dialysis. No accumulation occurred over 10 days in severe renal impairment on a daily dose of 0.5–1 g.

Concentrations of 6.6–58 mg/L have been found in bile 25–160 min after the dose at times when the mean serum concentration was 77.4 mg/L. In T-tube bile there was considerable interpatient variation, with mean concentrations of 34 mg/L at 1–2 h after the dose. No accumulation occurs in patients with impaired hepatic function, but the presence of ascites, low plasma albumin and accumulation of protein-binding inhibitors may increase the volume of distribution.

TOXICITY AND SIDE EFFECTS

It is generally well tolerated. Preparations containing arginine have replaced those with sodium carbonate, which causes pain on intramuscular injection. Reactions common to cephalosporins have been observed in some patients, including positive antiglobulin tests without hemolysis, raised liver function test values, eosinophilia, rashes, leukopenia, thrombocytopenia and diarrhea, occasionally associated with toxigenic C. difficile.

Failure of therapy has been associated with superinfection with resistant organisms, including Staph. aureus, enterococci and Candida. Resistance caused by induction of chromosomal β-lactamases may emerge in Ps. aeruginosa, Ser. marcescens or Enterobacter spp.

CLINICAL USE

It is used, often combined with an aminoglycoside, to treat a wide range of severe urinary, respiratory and wound infections, mostly due to enterobacteria or Ps. aeruginosa. Reference is made to its use in pneumonia, sepsis, meningitis (especially if caused by Ps. aeruginosa), peritonitis, osteomyelitis, neonatal sepsis, burns and melioidosis. Concern has been expressed at the relative frequency with which failure is associated with superinfection or the emergence of resistance.

Preparations and dosage

**Proprietary names:** Fortum, Kefadim, Ceptaz, Fortaz.
**Preparation:** Injection.
**Dosage:** Adults, i.m., i.v., 1–6 g per day in divided doses, depending on severity of infection. Neonates and children 25 mg/kg (neonates <7 days every 24 h; 7–21 days, every 12 h, older infants and children, every 8 h). The dose may be doubled in severe infection to a maximum of 6 g/day in children >1 month (9 g in cystic fibrosis).

Widely available.
**Further information**


**OTHER GROUP 6 CEPHALOSPORINS**

**CEFOPERAZONE**

A semisynthetic parenteral cephalosporin. It is unstable, losing activity on storage even at −20°C. A formulation with sulbactam is available in some countries (see p. 241). Activity against common pathogenic bacteria is shown in Table 13.6. It exhibits moderate activity against carbenicillin-sensitive strains of *P. aeruginosa*. Activity against *Burk. cepacia* and *Sten. maltophilia* is unreliable. It is much less stable to enterobacterial β-lactamases than most other cephalosporins of groups 4–6 and consequently has unreliable activity against many species, including β-lactamase-producing strains of *H. influenzae* and *N. gonorrhoeae*. It is active against *Achromobacter*, *Flavobacterium*, *Aeromonas* and associated non-fermenters. *Past. multocida* is extremely susceptible (MIC <0.01–0.02 mg/L). It exhibits modest activity against most Gram-negative anaerobes, but not *B. fragilis*. Sulbactam increases activity against many, but not all, enterobacteria and non-fermenters, and almost all *B. fragilis*.

A 2 g intravenous infusion achieves a peak plasma concentration of 250 mg/L. The plasma half-life is 1.5–2 h. Over 85% is bound to plasma proteins. It achieves therapeutic concentrations in tissue and inflammatory exudates. Variable low levels are found in the sputum up to 1.5% of simultaneous serum levels. Penetration into CSF is unreliable even in the presence of meningeal inflammation.

The bile is a major route of excretion, accounting for almost 20% of the dose. About 20–30% is eliminated in urine, almost entirely by glomerular filtration. Clearance is effectively unchanged by renal failure or dialysis.

Side effects associated with the methylthiotetrazole side chain have been reported. Diarrhea has been notable in some studies. Marked suppression of fecal flora, with the appearance of *C. difficile*, has occasionally been found. There is a 5–10% incidence of mild transient increases in liver function tests.

Its potential toxicity and the availability of compounds with better β-lactamase stability and more reliable antipseudomonal activity have undermined its popularity.

**Further information**


**CEFPOZOPRAN**

An aminothiazole cephalosporin formulated as the hydrochloride. Activity is similar to that of ceftazidime, but it is more active against methicillin-susceptible staphylococci (MIC 1 mg/L). Representative MICs against Gram-negative species are: *Eshc coli* 0.25 mg/L; *K. pneumoniae* 1 mg/L; *Ps. aeruginosa* 1–8 mg/L. Activity against *Acinetobacter* spp., *Sten. maltophilia* and *B. fragilis* group is poor.

A 20-min infusion of 1.5 g achieved a plasma concentration of around 125 mg/L at the end of infusion. Almost 90% of the dose was excreted in the urine over 24 h. The mean terminal half-life was around 2 h. Adverse reactions appear to be typical of those of other group 6 cephalosporins.

It is available in Japan.

**Further information**


**CEFPIMIZOLE**

A semisynthetic parenteral cephalosporin. It exhibits modest activity compared to other antipseudomonal cephalosporins. Like cefoperazone, it is susceptible to many enterobacterial β-lactamases. In volunteers receiving 0.1–1 g intramuscularly, mean peak plasma concentrations reached 15–20 and 35–40 mg/L, respectively. There was no accumulation when the dose was repeated every 8 h for 7 days. No metabolites have been detected. The plasma elimination half-life is 1.8–2.1 h. The principal route of elimination is renal, 70–80% being recovered unchanged in the urine.

Significant pain at the site of infection has been a prominent adverse event. It is no longer widely available.

**CEFPIRAMIDE**

A semisynthetic parenteral cephalosporin. It exhibits a broad range of activity, which includes *Ps. aeruginosa*, though the
overall activity is rather modest (Table 13.6). It is moderately stable to most β-lactamases but less so than ceftazidime or cefpirome.

In volunteers given 0.5 or 1 g by intravenous bolus, the mean plasma concentration shortly after injection was around 150 or 300 mg/L, respectively. There was no accumulation when the same doses were repeated every 12 h for 11 doses. It is highly bound to plasma protein (c. 95%). The mean plasma half-life is around 5 h. Less than one-quarter of the dose appears in the urine over 24 h; the rest is excreted in bile and high concentrations are found in feces. Renal impairment has little effect on elimination in patients with normal liver function.

Diarrhea may be associated with marked suppression of gut flora resulting from biliary excretion of the drug. The molecule includes a C-3 methylthiotetrazole side chain and side effects associated with that substituent are to be expected.

It is available in Japan.

Further information


CEFPIROME

A semisynthetic aminothiazoyl cephalosporin formulated as the sulfate for parenteral administration. Activity against common pathogens (Table 13.6) is similar to that of cefotaxime and ceftriaxone, but it is more active against Ps. aeruginosa. Unlike other cephalosporins it exhibits activity against some strains of enterococci (MIC 4–16 mg/L), but this is of doubtful clinical benefit. It is generally very stable to β-lactamases. It is active against strains of Enterobacter spp., Citrobacter spp., Haemophilus spp., Providencia spp., Ser. marcescens and Pr. vulgaris producing molecular class C cephalosporinases (see p. 230). Sten. maltophilia is resistant.

A 1 g intramuscular injection produces a plasma concentration of 25 mg/L after 1.6–2.3 h. A similar intravenous dose achieves a peak concentration of 97 mg/L. The plasma half-life is 1.4–2.3 h and protein binding is around 10%. It is well distributed, achieving therapeutic concentrations in tissues and exudates. It penetrates poorly into CSF in the absence of meningeal inflammation, but concentrations around 2–4 mg/L have been found in patients with purulent meningitis.

Little, if any, of the drug is metabolized and most is excreted unchanged in the urine within 12 h, mainly by glomerular filtration. Clearance declines in proportion to renal function. Around 60% of the drug is removed in 3 h by hemodialysis. Low concentrations are found in breast milk.

Side effects are those common to other cephalosporins. Diarrhea is common and occasional cases of pseudomembranous colitis have been reported.

It is mainly used in the treatment of serious sepsis, particularly nosocomial infections in which resistant Gram-negative pathogens are known or suspected to be involved. It is not widely available, but is marketed in Japan.

Further information


CEFSULODIN

A semisynthetic parenteral cephalosporin supplied as the sodium salt. Activity against Ps. aeruginosa contrasts strikingly with poor activity against many other organisms (Table 13.6). Anaerobic Gram-negative rods, Gram-positive rods and cocci are all resistant. It is stable to many β-lactamases, including the Ps. aeruginosa chromosomal enzyme, and is a poor substrate for the enzymes of Enterobacter spp. and Mor. morganii. It is slowly hydrolyzed by TEM β-lactamases and more rapidly by the enzymes of some carbenicillin-resistant strains of Ps. aeruginosa, with which distinct inoculum effects may be seen.

A 500 mg intravenous bolus dose achieves a plasma concentration of c. 70 mg/L at the end of the injection; the corresponding intramuscular dose achieves a peak concentration of around 15 mg/L. The plasma half-life is 1.5 h. About 15–30% is protein bound.

There is some metabolism of the drug, but the main route of excretion is via the kidneys, most appearing in the urine in the first 6 h. The plasma half-life is linearly related to creatinine clearance, rising to a mean of 10–13 h in patients where clearance was <10 mL/min, falling to around 2 h on hemodialysis.

It is well tolerated, apart from nausea and vomiting in some subjects. It has been used in severe pseudomonas infections, usually in combination with an aminoglycoside, but treatment has been complicated on a number of occasions by the emergence of resistance or superinfection.

It is available in Japan.

Further information

A semisynthetic cephalosporin formulated as the watersoluble medocaril prodrug for intravenous administration.

**ANTIMICROBIAL ACTIVITY**

The most important property distinguishing it from older cephalosporins is activity against methicillin-resistant staphylococci, a property conferred by a high affinity for penicillin-binding protein 2’ (2a). MICs for methicillin-resistant strains are nevertheless somewhat higher than those seen with fully susceptible strains. A similar situation exists with coagulase-negative staphylococci and with Str. pneumoniae, for which strains with reduced susceptibility to penicillin are less susceptible than fully resistant strains, while remaining within therapeutically achievable levels.

Otherwise activity approximates to that of cephalosporins of group 4 (Table 13.7). Activity against Ps. aeruginosa is modest and much reduced against ceftazidime-resistant strains.

**ACQUIRED RESISTANCE**

It is hydrolyzed by extended spectrum β-lactamases of enterobacteria (see p. 230), which are therefore resistant. The prospects for the emergence of resistance during extensive clinical use are presently unclear, though increased resistance in Staph. aureus appears to be difficult to induce under laboratory conditions.

**PHARMACOKINETICS**

The prodrug is rapidly hydrolyzed in plasma to release the active form together with diacetyl (2,3-butanediol) and CO₂. Distribution approximates to the extracellular fluid volume in adults. There is no accumulation on repeat dosing in subjects with normal renal function.

**Table 13.7** Activity of group 7 cephalosporins against common pathogenic bacteria: MIC (mg/L)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Ceftobiprole</th>
<th>Ceftaroline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus (methicillin-sensitive)</td>
<td>0.25–0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Staph. aureus (methicillin-resistant)</td>
<td>1–2</td>
<td>0.5–1</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>0.06</td>
<td>0.008–0.03</td>
</tr>
<tr>
<td>Str. pneumoniae</td>
<td>0.015–0.25</td>
<td>0.008–0.12</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>4</td>
<td>2–4</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>0.06</td>
<td>No data</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>0.06</td>
<td>0.015–0.03</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0.03–0.06</td>
<td>0.06–0.5</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>0.03–0.12</td>
<td>0.06–0.25</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2–8</td>
<td>0.5–R</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>R</td>
<td>No data</td>
</tr>
</tbody>
</table>

R, resistant (MIC >64 mg/L).

It is chiefly excreted in urine by glomerular filtration. A urinary concentration exceeding 1 g/L is achieved within the first 2 h of a 500 mg (active drug equivalent) dose and 80–90% of active drug can be recovered within 24 h.

**TOXICITY AND SIDE EFFECTS**

Limited studies have so far revealed no unexpected side effects. Nausea, vomiting and altered taste sensation appear to be the most common.

**CLINICAL USE**

In countries in which approval has been granted, use is presently limited to complicated infections of skin and skin structures.

**Preparations and dosage**

- **Proprietary names**: Zeftera, Zevtera.
- **Preparation**: Infusion.
- **Dosage**: i.v. infusion (1–2 h), 500 mg (667 mg medocaril prodrug) every 12 h. Limited availability. Available in Canada.

**Further information**


**OTHER GROUP 7 CEPHALOSPORINS**

### CEFTAROLINE

A semisynthetic cephalosporin formulated as the water-soluble fosamil acetate prodrug for intravenous administration.

Its properties are similar to those of ceftobiprole, with which it shares an enhanced affinity for penicillin-binding protein 2′ (2a) of methicillin-resistant *Staph. aureus*. Activity against common bacterial pathogens is shown in Table 13.7. It is hydrolyzed by extended-spectrum β-lactamases and is not active against Amp-C derepressed strains of Gram-negative bacilli (see p. 230).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; 600 mg intravenous (1-h infusion)</td>
<td>19 mg/L end infusion</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>2.6 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.37 L/kg</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>&lt;20%</td>
</tr>
</tbody>
</table>

Like ceftobiprole, ceftaroline fosamil is rapidly hydrolyzed in plasma after intravenous infusion and excreted principally in urine. In preliminary clinical studies it appears to be well tolerated.

**Further information**