# Today's Treatment

# Use of antibiotics

## Cephalosporins

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The availability of six cephalosporins, all with somewhat similar properties (not to mention names), is confusing to the clinician who is attempting to choose the best antibiotic for his patient, as well as for the bacteriologist who is trying to report the susceptibility of a particular organism to these drugs. The position is likely to become even more confusing as three or four more may be marketed in the near future. I will discuss the general properties of this group of drugs and then comment on the individual preparations. The marketed antibiotics are cephaloridine (Ceporin), cephalothin (Keflin), cephalexin (Ceporex and Keflex), cephradine (Velosef and Eskacef), cephazolin (Kefzol), and cefuroxime (Zinacef). Cefamandole (Kefadol), cefoxitin (Mefoxin), and cefaclor should appear soon.

### Antibacterial properties

With the exception of cefoxitin, the cephalosporins are semisynthetic derivatives of cephalosporin C, an antibiotic substance obtained from the *Cephalosporium* mould. Cefoxitin is more correctly a cephamycin rather than a cephalosporin as it is derived from the *Streptomyces* species. The structural difference between these two groups of compounds is that there is a methoxy group at the 7-position (fig 1) in the cephamycins.

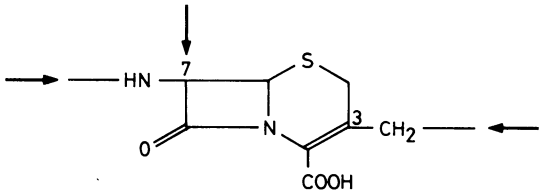


FIG 1—Structure of cephalosporin nucleus.

Generalising somewhat one can say that it is alterations at the 7-amino position that alter antibacterial activity, while changes at the 3-position affect the drug's pharmacology.

All the cephalosporins are bactericidal, act on the cell wall, and have a broad spectrum of antibacterial activity. Most are susceptible, in varying degrees, to the enzymes that bacteria can elaborate to hydrolyse these compounds, the β-lactamases. A compound that is more stable to a range of differing β-lactamases should in theory be a better antibiotic, as bacteria are less likely to be able to destroy it. Against this one has to weigh the other properties of the drug. A good example is cephradine, which appears to have good stability to several β-lactamase enzymes but suffers from the drawback that, weight for weight, it is among the least active of the cephalosporins.

The problem of the relative importance of β-lactamase stability and intrinsic activity is difficult to resolve as evidence is conflicting. The question, although interesting, is now becoming somewhat academic. Two of the newer compounds, cefuroxime and cefoxitin, do combine great stability with a wide range of β-lactamases with considerable intrinsic activity.[1 2]

Stability to β-lactamase is of clinical interest as up to 35% of the two commonest urinary tract pathogens, *Escherichia coli* and *Proteus mirabilis*, are resistant to ampicillin because they carry resistance (R) factor genes, which code for β-lactamase production. An appreciable proportion of these organisms can also elaborate enzymes that will destroy some of the older cephalosporins as well.

With the exception of cefoxitin, cephradine, cefaclor, and cephalexin, all the cephalosporins have a good degree of activity against *Staphylococcus aureus*. The strains that are penicillin sensitive are much more susceptible to benzylpenicillin than to the cephalosporins. The penicillin-resistant strains are sensitive to cephalosporins, cephaloridine being the most active. Those rare strains that are resistant to methicillin are also resistant to the cephalosporins. The β-haemolytic streptococci (Lancefield group A), which are very susceptible to benzylpenicillin, are also sensitive to the cephalosporins, but benzylpenicillin is the preferred drug as it is more active than the newer compounds. The faecal streptococci (Lancefield group D) are resistant to all the cephalosporins. Pneumococci are moderately sensitive to all the cephalosporins, with cefamandole and cefuroxime being the most active.

*Clostridium welchii* is sensitive to the cephalosporins, but some of the other *Clostridium* spp may be more resistant. Corynebacteria are also sensitive, but like the other Gram-positive organisms are all more susceptible to benzylpenicillin.

Against Gram-negative organisms these antibiotics have a broad spectrum of activity. They are active against most clinical isolates of *E coli*, klebsiellae, and *Pr mirabilis*. A few strains of each are resistant to the older cephalosporins yet will be sensitive to the β-lactamase-stable antibiotics cefoxitin and cefuroxime. These two compounds are also more active against the rarer *Proteus* and *Serratia* spp. Only cefoxitin has any useful degree of activity against the anaerobic *Bacteroides fragilis*. Most of these antibiotics have poor activity (in comparison with ampicillin) against *Haemophilus influenzae*, but of the available drugs taken by mouth cefaclor is the most active, while cefuroxime and cefamandole, both given by injection, are considerably more effective. Strains of this organism, which are

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ampicillin resistant (β-lactamase producing), are susceptible to cefaclor or cefamandole but the most dependable and active cephalosporin against *H influenzae* is cefuroxime.

There is a wide variation in degree of activity against *Neisseria gonorrhoea*, with cefuroxime being as active as benzylpenicillin and cephaloridine being at least 100 times less active. It is important to note that β-lactamase-producing strains are as susceptible as the penicillin-sensitive strains to cefuroxime.[3] Cefuroxime would appear to be the β-lactam drug of choice in treating β-lactamase-producing strains of *N gonorrhoea*.

## Pharmacology

Whereas cephalexin, cephradine, and cefaclor are absorbed from the gastrointestinal tract, the others have to be injected. The absorption of cephalexin and cephradine is more efficient than that of cefaclor. In the blood the cephalosporins are bound in variable degrees to serum protein, and only the free component can diffuse into the interstitial fluid and act on bacteria. Considerable importance has been given to the possible adverse effects of high protein binding by the proponents of certain poorly bound drugs. Protein binding can certainly affect an antibiotic's in vitro performance. It is difficult to be sure of the influence of antibiotic binding in man. Binding does not interfere with the penetration of a drug into an inflammatory exudate as cefuroxime (about 30% bound) attains comparable concentrations to cefoxitin (about 70% bound) in a skin abrasion technique (fig 2),[4] and other evidence supports this.[5] I believe that protein binding is not of any great clinical importance until it exceeds 90% (cephazolin is the most highly bound member of this group of drugs at 80–85%).

All the cephalosporins are excreted primarily through the kidneys, for the most part unchanged—although cephalothin is appreciably metabolised to the desacetyl form. It may be necessary, therefore, to reduce the frequency of the dose or the dose itself in accordance with any degree of renal failure, but as these antibiotics are less toxic than, say, the aminoglycosides, it is not essential to be so precise. For example, when using cephazolin in patients with moderate impairment of renal function, up to 500 mg 12-hourly can be given. When the creatinine clearance is less than 5 ml min up to 250 mg a day can be given.

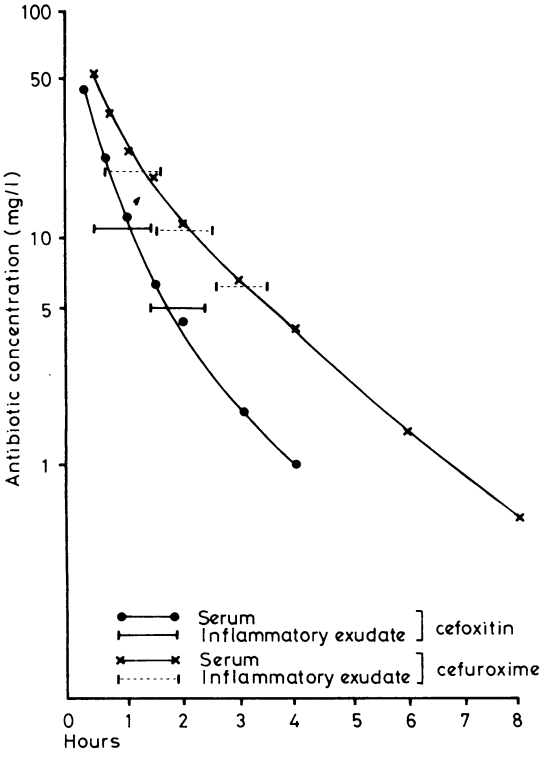


FIG 2—Serum and tissue concentrations of cefuroxime and cefoxitin.

In the patient with normal renal function the frequency of the dose can be judged from a knowledge of the serum half life. Cephalothin is rapidly excreted (the half life being about 30 minutes). As with penicillin, large doses need to be given frequently, up to 4 g intravenously every four hours in severe illness. This complicates treatment and is expensive. Cephaloridine and cephazolin have serum half lives of about one and a half hours, so that dosing intervals of eight hours are adequate.

As with the other β-lactam antibiotics, these drugs penetrate poorly into the cerebrospinal fluid, and if the meninges are not inflamed the amount of drug that can cross the blood-cerebrospinal fluid barrier is negligible. The biliary route of excretion is relatively minor, but usefully high concentrations can be attained in the non-obstructed gall bladder and bile ducts. As the main route of excretion is renal high concentrations are attained in the urine. Even in severe renal failure urinary concentrations may be well above the amount necessary to inhibit commonly infecting organisms.

## Toxicity

The cephalosporins are relatively free from serious toxicity. All the β-lactam antibiotics show some immunological side effects. There appears to be a measure of cross-allergenicity with the penicillins. About one in eight patients who are allergic to penicillin will show an effect with a cephalosporin. If a patient requires a β-lactam antibiotic yet is allergic to a penicillin then a cephalosporin should be used with caution.

Many clinicians associate cephalosporins with nephrotoxicity. Certainly cephaloridine may affect renal function, especially when used with a potent diuretic such as frusemide or ethacrynic acid or if the patient already has some degree of renal failure; tubular damage in such cases is well documented. The effect of the other cephalosporins is far less clear. When used in high doses in combination with gentamicin cephalothin has been suspected of causing renal damage, and when this cephalosporin has been used with potent diuretics there has been some evidence of renal toxicity. The other cephalosporins have rarely been implicated.

Cephalosporins taken by mouth may be accompanied by gastrointestinal upsets such as diarrhoea, nausea, or vomiting. Pruritus and moniliasis (thrush) have been seen. Some of the drugs may rarely be associated with central nervous system disturbances, which are more common in renal failure when high concentrations of the drug accumulate. A direct positive Coombs test has accompanied the use of several of these drugs, but this appears to have little significance other than to interfere with cross-matching blood.

## Properties of individual cephalosporins

The individual properties and the dosage schedules of the various cephalosporins differ as follows.

*Cephaloridine* was the first to be marketed in Britain. It is one of the more active cephalosporins but is moderately readily hydrolysed by staphylococcal penicillinase. The drug must be used parenterally at an adult dose of 500 mg 8-hourly, which may be increased in severe infections. The drug should be avoided in renal failure and when potent diuretics are being used, because of its nephrotoxicity. A good case could be made now for using another cephalosporin rather than cephaloridine.

*Cephalothin* has never been used as much in Britain as in North America. Being less active than cephaloridine, it may be used in large doses, even up to 20 g a day. It is more resistant to β-lactamase attack than cephaloridine. This compound is

painful when given intramuscularly and may cause phlebitis when given by an intravenous drip.

*Cephalexin* has the advantage that it can be given by mouth and is well absorbed. The main disadvantage is that it is far less active than the parenteral preparations. Although it is less susceptible to the β-lactamase of staphylococci, it has a relatively poor degree of activity against this organism. In the usual dosage of 500 mg four times a day peak serum concentrations of 15–25 mg/l will be attained.

*Cephradine* can be given by mouth or parenterally. This potential advantage must be weighed against the fact that cephradine is less active than other cephalosporins. When taken by mouth concentrations similar to cephalexin are achieved.

*Cephazolin*—The antimicrobial activity of cephazolin is similar to that of cephalothin; therefore it is considerably more active than cephradine or cephalexin. Cephazolin has poor stability to β-lactamases. The relatively long serum half life means that the usual adult dose of 500 mg can be given 8-hourly.

*Cefaclor* is a little more active than cephradine or cephalexin. This is most pronounced against *H influenzae*, where there is about a fourfold difference. There appears to be some stability to the β-lactamase of some of these organisms (the ampicillin-resistant strains), but this is not complete. The oral absorption of cefaclor is relatively inefficient compared with the other two oral agents. The adult dose will probably be 250–500 mg three to four times a day.

*Cefuroxime* has good "all round" properties, being resistant to many Gram-negative β-lactamases and so having a wide spectrum. It is particularly active against *H influenzae* and *N gonorrhoea*, including the β-lactamase-producing strains of both. It is not as active as many cephalosporins against *Staph aureus*. Cefuroxime must be injected and would appear to be free from serious toxicity. The usual adult dose is 750-1500 mg three times daily.

*Cefoxitin* is a cephamycin and an interesting antibiotic: it has a low degree of activity against staphylococci, but with this exception it has a broad antibacterial spectrum. This compound is extremely stable to β-lactamases including those of the resistant *Haemophilus* and *Neisseria* spp (but unlike cefuroxime it has less intrinsic activity against these organisms). A particular advantage is the activity against *B fragilis*, which considerably broadens its clinical usefulness. Cefoxitin has to be given intravenously in an adult dose of 1–2 g every six to eight hours. It is painful if given intramuscularly.

*Cefamandole* also has enhanced resistance to β-lactamase but not as pronounced as the other two new compounds. It is more active than cefuroxime against staphylococci and also against a wide range of Gram-negative organisms, but in comparison with these other two drugs it has gaps in its spectrum because of its incomplete stability to β-lactamase hydrolysis. It is the most active available cephalosporin against *H influenzae*. Cefamandole is given by injection, and the usual adult dose is 500 mg-2 g every four to eight hours.

## When should a cephalosporin be used?

This powerful group of drugs falls between two stools when indications for their use are considered. They are certainly an improvement on the broad-spectrum penicillins, such as ampicillin, but they often lack the breadth of activity of the aminoglycosides. The newer compounds such as cefuroxime and cefoxitin go some way to bridge this gap.

*Urinary tract infections*—Their use in simple infections should be discouraged, for there are many cheaper alternatives available. In difficult cases they can be used after the antibiotic sensitivities are known.

*Chest infections*—Many of the cephalosporins are parenteral agents, and one would not expect much enthusiasm for their use in common chest infections. Although cephalosporins by mouth are used against the exacerbations of chronic bronchitis, there is no evidence to show that they are superior to ampicillin or co-trimoxazole.

*Staphylococcal sepsis*—Antibiotics are often used as an adjuvant to surgical drainage. As the cephalosporins are active against both penicillin-sensitive and resistant staphylococci they may at times be useful. There are other specific antistaphylococcal drugs such as cloxacillin, flucloxacillin, and fusidic acid, which many would consider preferable.

*Severe sepsis*—It is a common clinical problem to have to treat a severe infection without knowing the infecting organism or its antibiotic sensitivity. Often an educated guess can be made. A cephalosporin is a reasonable choice in such cases. In particular cefoxitin could be used if an intra-abdominal focus is suspected and an anaerobe implicated. The lack of activity of any of these compounds against *Pseudomonas aeruginosa* might militate against its use in certain groups of patients, such as the immunologically suppressed.

*Other infections*—These drugs have been used in many conditions. If β-lactamase producing gonococci become a clinical problem then there is undoubtedly a place for an active agent such as cefuroxime. Further information as to the efficacy of cefuroxime and cefamandole in meningitis would be welcome as ampicillin-resistant strains of *H influenzae* are a clinical problem (but remember that chloramphenicol is still very active). Their broad spectrum indicates that the cephalosporins may have a part to play in surgical prophylaxis of potentially infected areas if the duration of treatment is very short and resistance does not emerge.

## The future

The new cephalosporins recently marketed are a distinct advance over the older members of the group. There are indications that in future several interesting compounds may be clinically available. Enhanced activity, stability to β-lactamase, and an increase in spectrum to include *Ps aeruginosa* and other difficult organisms are all probable. The possibilities for a "cure-all" antibiotic are there, but experience shows that the bacteria are second only to the pharmaceutical industry in their ingenuity.

## References


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WORDS Pharmacy derives from the Greek *pharmakon*, a drug or poison. Many drugs must have been poisonous in ancient times, as now. Interestingly, the Greeks had one word for both. The safest epoch pharmaceutically seems to have been the century 1840 to 1940 when, with few exceptions, drugs were neither poisonous nor effective. Special interest attaches to the derivation of the words TOXIC and TOXIN. In Greek *toxon* is a bow (the sort that flings an arrow) and *toxikon* is its adjective. Toxophily is the sport of archery. The Greeks must have known of arrow poisons, but they called them bow poisons —*toxikon pharmakon*. As so often happens, the noun was dropped and the qualifying adjective remained to become a noun in its turn; leaving *toxicon*, a bow, for poison, hence toxic and toxin. Three arrow poisons have come into use as drugs and add an extra etymological flavour to the use of the root *pharmakon*. CURARE, still used by the natives of the South American jungle, was introduced as the first muscle relaxant for anaesthesia and from which others were developed. STROPHANTHUS and OUABAÏNE are cardiac glycosides of the digitalis group, obtained from the seeds of African plants.