

Third Generation Cephalosporins: Safety Profiles After 10 Years of Clinical Use

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Compared with aminoglycosides, chloramphenicol, sulfonamides, tetracyclines, and even penicillins, the cephalosporins represent a remarkably safe class of antibiotics. Among the cephalosporins, the extended spectrum, third generation agents developed generally produce few side effects and appear to be less allergenic than the penicillins. Nephrotoxicity has not been a problem at recommended doses. Some third generation agents can cause hypoprothrombinemia if not administered with vitamin K, and disulfiram-like reactions occur with some agents because of the presence of a thiomethyl tetrazole moiety affixed to the cephem nucleus. There is a greater incidence of diarrhea associated with the agents excreted through a primarily biliary route, and this may contribute to the selection of drug resistant bacteria. Some agents are less active against staphylococci and their use may result in an increased incidence of superinfection or overgrowth of enterococci. If attention is given to the potential for adverse effects, many of these problems can be avoided and the third generation cephalosporins can be used safely in hospitals, nursing homes, and home care settings.

Since the 1940s there has been remarkable growth in the number of antimicrobial agents. Although the perfect antimicrobial drug probably will never be developed, physicians today have the luxury of choosing from among a wide array of potent and safe pharmacologic agents.

As the number of available antibacterial drugs grows, an increasing emphasis has been placed on the formulation of drugs with low potential to cause adverse reactions. With the successful development of highly effective broad-spectrum as well as narrow-spectrum drugs, physicians are able to avoid exposing patients to significant toxic risks even in the face of life threatening infections.

The cephalosporins account for a major part of the new antibiotics introduced since the mid 1970s, and today are among the most widely prescribed agents. A distinguishing feature of the cephalosporins is their safety profile. The safety profile of the first generation agents, such as cefazolin or the oral agent cephalexin, have been characterized by lack of nephrotoxic effects, ototoxic effects, and bleeding;

allergic reactions have also been rare. The early cephalosporins have not been associated with a significant incidence of diarrhea or superinfection.

Among the parenteral third generation cephalosporins, cefotaxime has been in use the longest. It is, therefore, worthwhile to examine its safety profile after 10 years of use, as well as to compare its safety profile with that of other cephalosporins and other antimicrobial agents introduced in the past decade.

After 10 years of clinical experience in hundreds of thousands of patients, it is evident that cefotaxime remains an excellent agent for a broad range of patients, from the neonate to the octogenarian, with a variety of infections. Cefotaxime, like other compounds that contain the amino-thiazolyl imino-methoxy side chain, has excellent activity against hemolytic streptococci, *Streptococcus pneumoniae*, *Haemophilus* species, good activity against staphylococci, excellent activity against most of the Enterobacteriaceae, and is β -lactamase stable.¹ Third generation cephalosporins have become first line drugs for use in the hospital and for use in various outpatient settings. Neither cefotaxime, the oldest agent, nor its active metabolite, desacetyl cefotaxime, has been shown to have appreciable side effects in the elderly.² This is especially important as the U.S. population ages because the elderly are particularly prone to develop infection. In addition, the elderly have frequently received oral agents that have

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caused them to be infected with β -lactamase-producing species.

The comparable *in vitro* potency and pharmacokinetic properties afforded by many of the newer antimicrobial agents often reduce the therapy choice to an issue of safety. Safety considerations involve both direct and indirect toxicities, including neurologic, hematologic, gastrointestinal, hepatic, and renal effects. In addition, factors such as dose, duration of therapy, concomitant therapy, age, genetic background, and physiologic status of the patient affect the safety profile of any drug. In terms of these and other standard parameters, cefotaxime as the prototype advanced cephalosporin rarely has been implicated in major toxic reactions.

COMPARATIVE TOXICITIES

As with all drugs, minor adverse reactions do occur with cephalosporins. However, compared with other classes of widely used drugs such as the penicillins, aminoglycosides, and even the carbapenems, cephalosporins infrequently produce adverse reactions when used to treat a wide variety of infections. Common adverse effects fall into several general categories—allergic reactions, gastrointestinal disturbances, clinical superinfections, hematologic effects, hepatotoxicity, cardiopulmonary responses, nephrotoxicity, neurotoxicity, ototoxicity, and drug-drug interactions (Table).

Allergic Reactions

Antimicrobial drug-induced anaphylaxis is extremely rare, but occurs most often with penicillin.³ Fortunately, cephalosporins infrequently cause anaphylaxis in spite of their structural similarity to penicillin. When first generation cephalosporins were introduced for the treatment of staphylococcal infections, it was found that they could be administered to patients who had developed a rash—but not anaphylaxis—to penicillin.⁴ Second generation cephalosporins can also be given safely to these patients, although as with first generation drugs, a rash may develop as it does to third generation cephalosporins.

Although isolated cases of IgE-mediated anaphylactic reactions of the type associated with penicillins have been reported for third generation cephalosporins, the incidence of hypersensitivity is exceedingly low. Cefotaxime has been safely administered to a large number of patients with meningitis who were said to be allergic to penicillin, and the patients did not have an anaphylactoid response.⁵ Nevertheless, there are no convincing stud-

ies to indicate that cefotaxime or other cephalosporins can be given routinely to patients with Type I anaphylaxis to penicillin.

The incidence of allergic skin reactions to the β -lactams (e.g., penicillins, cephalosporins, monobactams, and carbapenems) varies and is drug-specific. The incidence of skin rash, fever, or late-onset urticaria with a third generation cephalosporin such as cefotaxime is in the range of 2 to 3%.⁶ Aztreonam, a monobactam, does not cause these symptoms. Although rash occurs when patients with infectious mononucleosis are given ampicillin, this reaction has rarely been caused by cephalosporins.

In the era when penicillin was given at dosages of 20–40 million units per day, antigen-antibody serum sickness was observed, but this is not a problem at the dosages currently used and does not occur with the second or third generation cephalosporins. A serum-sickness-like illness does occur—albeit infrequently—in patients treated orally with cefaclor, a first generation cephalosporin widely used in pediatrics.

Gastrointestinal Disturbances

Gastrointestinal disturbances have been a problem with some classes of antimicrobial drugs. For instance, ampicillin causes diarrhea even though the drug will kill *Clostridium difficile*, the organism that produces a toxin associated with antibiotic-induced pseudomembranous colitis. Cefoxitin, a second generation cephalosporin, has been associated with *C. difficile* diarrhea more frequently than the other second or third generation cephalosporins. In general, pseudomembranous enterocolitis has been noted with use of all penicillins and cephalosporins. Most of the older oral cephalosporins have a very low incidence of diarrhea, but cefixime, a third generation cephalosporin, has produced loose stools in a proportion of patients. This incidence is similar to that found in patients receiving some parenterals.⁷ Diarrhea and significant disturbances of the intestinal flora have been infrequently associated with use of a third generation cephalosporin such as cefotaxime.

A higher incidence of diarrhea has been reported for ceftriaxone in adults because of the high biliary excretion (45%), which raises intraintestinal concentrations and alters the fecal flora.^{8–16} In contrast, for cefotaxime and ceftizoxime, only 5% is excreted in the bile. A 1.2% incidence of diarrhea in nearly 2600 patients was found for cefotaxime.¹⁷ The high biliary excretion of ceftriaxone has also been associated with biliary sludging and symptoms suggestive of acute cholecystitis in pediatric and adult pa-

TABLE

Common Adverse Effects of β -lactams

Type of Reaction	Drug	Remarks
Allergic		
Anaphylaxis/Rash	Penicillins Cephalosporins Imipenem	Rare anaphylaxis; no rash or anaphylaxis to aztreonam
Contact dermatitis	Ampicillin most common	In patients with Epstein-Barr syndromes, but occurs with all agents
Gastrointestinal (Diarrhea)	Ampicillin Oral cephalosporins Cefoperazone Ceftriaxone Ceftazidime	Disturbs normal flora Low incidence of diarrhea Excreted in gut, occasional diarrhea Diarrhea in pediatric population Occasional overgrowth with <i>Clostridium</i> , staphylococci, enterococci
Bacterial or fungal overgrowths		
Hematologic		
Hemolytic anemia	Penicillin G Oxacillin Nafcillin	At high doses Infrequent with cephalosporins
Neutropenia	Cephalexin Carbenicillin Ticarcillin Moxalactam Cephalosporins Penicillin Moxalactam Cefoperazone Cefamandole	Occurs with all β -lactam agents, albeit infrequently Infrequent At high doses Low incidence related to thiomethyl tetrazole moiety
Platelet dysfunction		
Thrombocytopenia		
Hypoprothrombinemia		
Hepatic		
Rise in transaminase levels	Nafcillin Oxacillin Ticarcillin Aztreonam Imipenem Ceftriaxone Penicillin G	Rarely to >2-3x normal High biliary excretion Excessively rapid administration of K ⁺ salt causes arrhythmia
Biliary sludging		
Cardiopulmonary		
Renal		
Hypokalemia	Carbenicillin Ticarcillin Methicillin Penicillin G Imipenem	Due to accumulation of nonreabsorbable anion product in distal tubule Can occur with all β -lactams Can occur with other penicillins also if decreased renal function occurs
Interstitial nephritis		
Neurologic (Seizures)		
Drug-drug interactions		
Disulfiram-like reactions	Moxalactam Cefoperazone Moxalactam Cefamandole Cefotetan Cefoperazone	Due to thiomethyl tetrazole group (use vitamin K to prevent)
Coagulopathies with anticoagulants		

tients. Thus it is unwise to use dosages exceeding 2 g/d.¹⁸⁻²⁰ In pediatric patients receiving ceftriaxone, diarrhea may be a problem¹⁵ although cefotaxime and ceftizoxime appear to be quite safe in this regard.

In some series the third generation cephalosporin cefoperazone has been associated with diarrhea, probably because a large amount of the drug is excreted by the biliary system into the intestine.²¹ The incidence of diarrhea with cefoperazone has been

reported to range from 10.8% to 32%, which is consistent with its 75% biliary excretion.²²⁻²⁷

Alteration of gut flora is thought to be a predisposing factor for the overgrowth of resistant organisms and superinfection, both of which have been observed clinically by a number of investigators.²⁸⁻³² Interestingly, there is no appreciable diarrhea associated with the use of metronidazole, even though the intestinal anaerobic flora of the gut are destroyed. In fact, metronidazole is used to treat the diarrhea caused by *Cl difficile*. As a class, the aminoglycoside antibacterials do not cause diarrhea because they are not excreted into the bowel.

In the neonate, one agent that does predispose to diarrhea is ceftriaxone. In addition to the potential problem of diarrhea in the neonate, ceftriaxone is highly protein bound and competes with bilirubin for binding to albumin, raising free bilirubin levels.³³⁻³⁶ Therefore, caution must be exercised before it is administered to hyperbilirubinemic neonates.

Clinical Superinfections

Jones reviewed the literature to determine the magnitude of risk of superinfection following β -lactam therapy with the anti-pseudomonas penicillins, cefoperazone, cefotaxime, ceftazidime, imipenem, and moxalactam.³⁷ Of the drugs surveyed, cefotaxime had the lowest incidence of superinfections: 1.1%. The incidence of superinfection with gram-positive organisms including enterococci was very low. The highest rates of superinfection occurred with moxalactam and the penicillins. Ceftazidime was associated with secondary gram-positive infections including *Clostridium* spp, enterococci, and *Staphylococcus aureus*. The rates of superinfection for ceftazidime and cefoperazone were higher than for cefotaxime. This may be related to a lower *in vitro* activity against some gram-positive species such as staphylococci and enterococci. As a result, some researchers recommend combining vancomycin with ceftazidime for empiric treatment of the neutropenic patient.³⁸⁻⁴⁰

Hematologic Effects

Antibiotics cause a variety of hematologic toxicities. Hemolytic anemia has occurred with use of most of the β -lactams, but occurs most frequently with sulfonamides. However, it is extremely rare with the aminoglycosides or with macrolides such as erythromycin or with clindamycin. Patients who are re-

ceiving nitrofurantoin or sulfonamides who are glucose-6-phosphate dehydrogenase deficient are particularly susceptible to hemolytic anemia.⁴³ Hemolytic anemia was caused by some of the early cephalosporins, but only with doses greater than 12 g/d. Although 12-g doses of cefotaxime were given by Smith et al in two studies, hemolytic anemia was never noted.^{42,43} At the appropriate doses of 1 to 6 g/d of cefotaxime or ceftizoxime, it would be extremely unlikely to occur.

All β -lactams have been associated with neutropenia. It is caused most commonly by some of the semisynthetic penicillins such as oxacillin and nafcillin when these drugs are administered at high doses over long periods, such as 4-6 weeks. Neutropenia is also seen with cephalixin, an oral cephalosporin, and with virtually all other antimicrobials including cefotaxime and ceftriaxone, although it has been very rare.¹³ In general, neutropenia is not associated with the use of aminoglycosides. There has been manifest bone marrow depression in patients receiving trimethoprim-sulfamethoxazole; this is particularly the case in AIDS patients being treated for *Pneumocystis carinii*.⁴⁴

Agranulocytosis has been noted in association with cephalosporins.^{45,46} A change in class labeling will soon be made to include agranulocytosis as a possible adverse effect of all cephalosporins. This change reflects the accumulated data of many years of experience with these agents.

It is well documented that chloramphenicol is associated with aplastic anemia in 1 of every 40,000 to 60,000 patients.⁴⁷ In fact, it is now rarely used to treat meningitis, although it readily crosses the blood-brain barrier and is quite effective for a number of infections. Today, most physicians prefer to use a third generation cephalosporin such as cefotaxime or ceftriaxone for meningitis of unknown etiology, or when a β -lactamase-producing *Haemophilus influenzae* is suspected.

Carbenicillin, in high doses, has caused platelet dysfunction. It binds to the adenosine diphosphate (ADP) receptor site that is critical to platelet aggregation.⁴⁸ Ticarcillin affects platelets similarly, but since it is administered at lower doses, platelet dysfunction is rarely a problem. This effect is associated to a lesser extent with the use of mezlocillin, azlocillin, and piperacillin. The one cephalosporin most frequently associated with platelet dysfunction is moxalactam, which is used infrequently in the United States; virtually all patients who receive more than 4 g/d of moxalactam, have some degree of platelet dysfunction, but this can be caused by many antimicrobials of different classes.

Thrombocytopenia has been observed with sul-

fonamides, cephalosporins, the penicillins, and rifampin. The incidence with the third generation cephalosporins is equal to or less than that of the first and second generation cephalosporins.

Another hematologic toxicity that occurs with some antibiotics is hypoprothrombinemia. Hypoprothrombinemia has been observed with a wide variety of cephalosporins, but particularly moxalactam used at dosages greater than 4 g/day. It occasionally occurs with ceftriaxone, cefoperazone, cefotetan, cefmetazole, and cefamandole.² All cephalosporins that possess an N-methyl thiotetrazole side group on the cephem nucleus have the potential to cause hypoprothrombinemia and disulfiram-like reactions.⁴⁹ Cefotaxime and ceftriaxone do not contain this group. Ceftriaxone, however, does possess an N-methyl thiotriazine ring that may produce a comparable effect.⁴⁹⁻⁵² The thiomethyl tetrazole group is metabolized and forms a dimer that interferes with glutamate synthesis, and therefore with the production of prothrombin.

Hypoprothrombinemia occurred in 18 of 28 patients treated with cefoperazone and not given vitamin K.⁵³ In another study, 14 of 32 cefoperazone-treated patients had hypoprothrombinemia, and seven of them had clinically significant hemorrhage.⁵⁰ Vitamin K usually eliminates the problem, but 12 of 64 (19%) patients developed at least one coagulation abnormality during cefoperazone therapy, even though they had received vitamin K, and 33% of patients not receiving vitamin K also developed coagulopathies.⁵⁴ The condition is treatable and rapidly reversible with administration of vitamin K.

Hepatotoxicity

Administration of high doses of β -lactams for long periods have often been associated with a minor rise in serum transaminase levels,⁶ an effect that is more often seen with the use of semisynthetic penicillins such as nafcillin and oxacillin than with oral compounds or older anti-staphylococcus drugs like methicillin. Increased serum transaminase levels have also been reported to result from use of ticarcillin, aztreonam, and imipenem. It is rare to see major hepatic toxicities when a cephalosporin is administered.

Biliary sludging has been reported primarily in children receiving high doses of ceftriaxone, but it can also occur in adults. In a recent study, biliary pseudolithiasis occurred in 25% of patients (5 of 20) treated with ceftriaxone.⁵⁵ Cefotaxime and ceftizoxime have not produced biliary sludging.

Cardiopulmonary Toxicity

None of the cephalosporins has been associated with pulmonary toxicities. Cephalosporins do not cause cardiac toxicity, and arrhythmias have never been a problem.

Nephrotoxicity

Direct renal toxicity is not encountered with the cephalosporins in use today. One of the first cephalosporins, cephaloridine, was associated with nephrotoxicity at dosages greater than 4 g/d, but neither first generation drugs such as cephalothin and cefazolin; nor second generation agents, including cefoxitin, cefuroxime, and cefamandole; nor third generation drugs have been associated with nephrotoxicity. Interstitial nephritis was caused by methicillin, the first anti-staphylococcus penicillin. Cephalosporins rarely produce interstitial nephritis, but it probably is unwise to administer a cephalosporin to a patient who has developed interstitial nephritis from use of a penicillin. Renal tubular nephrotoxicity occurs with aminoglycosides but is rare for cephalosporins.

Cefotaxime is routinely given at doses of 1-2 g every 8 hours, but it has been given in dosages up to 12 g/d without renal toxicity. Other drugs that are comparable are ceftizoxime and cefoperazone. The latter has been used in doses as high as 2 g every 6 hours (8 g/d). Cephalosporins do not affect the kidney's ion-clearance mechanism, as do carbenicillin, ticarcillin, and some of the other antipseudomonas penicillins, which when given in large doses, cause hypokalemia, a result of nonreabsorbable anion in the distal tubule, thereby distorting hydrogen ion exchange.⁵⁶ Hypokalemia has not been observed when the new cephalosporins are administered at recommended doses.

Neurotoxicity

Cephalosporins are very safe with regard to neurologic toxicities.⁵⁷ For example, cefotaxime has been used at doses up to 12 g/d to treat patients with brain abscesses and meningitis. Such patients are at greatest risk of having seizures, and yet increased neurologic toxicity has not been observed within this population when cefotaxime, ceftriaxone, or ceftizoxime have been administered.¹ Aminoglycosides and vancomycin have induced neurotoxicity in the form of deafness or damage to the vestibular apparatus.⁵⁸ Peripheral neuropathy does not occur with the new cephalosporins.

Seizures have been a problem in some patients with decreased renal function who were treated with very high doses of penicillin. Seizures are reported with imipenem and occur infrequently with ampicillin.⁵⁹ None of the cephalosporins has a propensity to cause seizures. Myoclonic or grand mal seizures have not been reported for any of the third-generation cephalosporins.

Cefotaxime is the drug of choice when treating newborns for meningitis or sepsis of unknown origin. Although ceftriaxone can be considered for such use, more than 90% of it is bound to serum albumin, and in newborns there is a risk of displacing bilirubin and causing brain damage (kernicterus).

Ototoxicity

None of the cephalosporins are known to cause ototoxicity, whereas an agent such as vancomycin can cause deafness, particularly in combination with an aminoglycoside. There is no evidence that the use of a third generation cephalosporin in conjunction with aminoglycosides, such as would be used to treat *Pseudomonas* infections or mixed infections, produces an ototoxic reaction.

Drug-Drug Interactions

Third generation cephalosporins interact infrequently with most other drugs and are generally safe when included in combination drug regimens. None of the cephalosporins affect microsomal p450 enzyme function of the liver, where many drugs are metabolized. For instance, there is no change in the half-life of drugs such as dilantin, cyclosporine, or similar drugs as are caused by some of the other antibiotics. Cephalosporins with the N-methyl thio-tetrazole side group, such as cefoperazone, moxalactam, and cefotetan, may interact with alcohol or anticoagulants.²

HOME HEALTH CARE

Home health care is the most rapidly growing segment of the health care market. In particular, the availability of home intravenous therapy represents a significant cost-effective means of treating many infectious diseases. The elderly are also an increasingly important group of users of intravenous antibiotics. In both the home health care environment, as well as for elderly patients, key factors in the choice of an intravenous antibiotic include, not only efficacy, but also safety, product stability, and ease of

administration. Considering the compromised renal and hepatic functions of many elderly patients, antibiotics with the lowest toxic profile should be considered first-line agents. Many elderly patients receive multiple medications, and it is important that drug-drug interactions of antibiotics be minimized and not compromise the activity of other drugs. Most of the newer cephalosporins interact weakly or not at all with most other drugs. Of particular importance in home care, when using a cephalosporin, would be the avoidance of disulfiram-like effect with alcohol, which can occur with cefamandole, cefoperazone, or moxalactam. When cefoperazone is used it should be administered with vitamin K.

Drugs that have only a minimal potential to cause diarrhea should be favored for home care use, as are drugs that have convenient dosing regimens. In the elderly with diminished renal function, an agent such as cefotaxime can be administered every 12 hours because of the increased half-life of the desacetyl metabolite. Recently developed programmable intravenous infusion devices such as the CADD-II system now make it possible to administer a drug three times a day as easily as once each day.

SUMMARY

The third generation cephalosporins are extremely effective antibiotics. They inhibit the gram-positive species such as pneumococci, streptococci, staphylococci; the respiratory pathogens *Haemophilus* and *Branhamella*, and the enterobacteriaceae. The pharmacokinetics of the agents allow very flexible dosing programs that can be adjusted to marked differences in renal and hepatic function. They are particularly suited to today's multicare environments. Based on the fact that the oldest third generation cephalosporin has a side effect profile and proven efficacy over the last decade, these agents are appropriate choices to treat many patients in hospitals, at home, or in nursing homes. As with all drugs, however, the final choice is determined by the specific demands of individual cases.

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