Sorting Out the Cephems:
The Role of New Cephalosporins in Pediatric Therapeutics

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The myriad of cephalosporins currently available is often a source of confusion for the pediatrician who wants to treat infections in an optimal fashion, yet avoid unnecessary expense and potential complications for the patient. This review will concentrate primarily on pediatric indications for currently available antibiotics in the cephalosporin class and will also present information relating to new developments and research in the area that will have implications for treatment of infections in infants and children in the future.

HISTORICAL ASPECTS

The cephalosporin agents (Table 1) first began to appear on the US market in 1964 with cephalexin (Keflin). There followed a steady proliferation of drugs with a bacteriological spectrum identical to that of the initial compound. Although there were some variations in the pharmacology of these analogues, including the development of an oral form, there were really no new developments regarding antibacterial spectrum until the appearance of the so-called second-generation agents cefoxitin (Mefoxin) and cefamandole (Mandol) in 1978, cefaclor (Cefclor) in 1979, and cefuroxime (Zinacef), cefonicid (Monocid) and ceforanide (Precef) which reached the US armamentarium in 1984. The third-generation agents have a spectrum that is considerably broadened beyond that of the second-generation compounds and include cefotaxime (Claforan) and moxalactam (Moxam) that appeared in 1981, cefoperazone (Cefobid) in 1982, and ceftizoxime (Cefizox) that was released in 1984. Although the third-generation cephalosporins do have a wide antibacterial spectrum, they are generally inferior to drugs in the first and second categories in treatment of infections due to gram-positive pathogens.

ORAL CEPHALOSPORINS

The indications for cephalosporins administered by this route in pediatrics are quite broad, but primarily include infections of the skin, urinary tract, pneumonia, otitis media and as part of one regimen for Staphylococcus aureus osteomyelitis. All first-generation oral cephalosporins are effective therapy for infections of skin and soft tissues caused by the group A streptococcus or S. aureus. They also offer excellent coverage for urinary tract infections caused by community-acquired Escherichia coli, Proteus mirabilis and Klebsiella species, but are ineffective for treatment of enterococcal infections. The oral first-generation agents are also reliable treatment for pneumonia due to Streptococcus pneumoniae. They may also be used in S. aureus osteomyelitis once the acute clinical picture has improved in response to a parenteral first or second-generation cephalosporin or penicillinase-resistant penicillin, but must be given in high dosage and for a prolonged continued on page 280
## TABLE 1
CURRENTLY MARKETED CEPHALOSPORINS

<table>
<thead>
<tr>
<th></th>
<th>First-Generation</th>
<th>Second-Generation</th>
<th>Third-Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefradin (Kellex)</td>
<td>2</td>
<td>Cefazolin (Kefzol, Ancef)</td>
<td>Cefazolin (Kefzol, Ancef)</td>
</tr>
<tr>
<td>Cephradine</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefradin (Duracef, Ultracef)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephaprin (Cefadyl)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephradine</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin (Kefzol, Ancef)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Not approved for pediatric use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†Technically not a cephalosporin.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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period of time. The benefits and risks of use of oral cephalosporins in pediatric orthopedic patients with bone and joint infections has been reviewed in detail by Nelson and co-workers, who state that careful laboratory monitoring of compliance and serum bactericidal activity must be carried out in patients treated by this regimen.1,2

Cefaclor is the sole oral agent in the second-generation class presently available. Its most useful application is in the treatment of otitis media, where it is more effective than the first-generation drugs against Hemophilus influenzae and quite effective against ampicillin-resistant isolates of H. influenzae and Branhamella catarrhalis. In addition, it is also preferred over ampicillin or amoxicillin for treatment of bacterial pneumonia if ampicillin-resistant H. influenzae is suspected. Our current practice is to begin treatment of otitis media with amoxicillin and switch to cefaclor or another agent if clinical improvement does not occur. With regard to possible H. influenzae pneumonia, therapy should be started with an appropriate parenteral agent and change made to cefaclor only if it appears indicated based upon laboratory studies indicating ampicillin resistance and after clinical improvement allows change to an oral agent.

In addition to the major potential applications for oral cephalosporins detailed above, these drugs generally are also utilized when a penicillin cannot be used because of a history of delayed hypersensitivity reaction, when the propensity for resistance to a penicillin is high, or as in S. aureus osteomyelitis, when the uniquely good absorption allows use of oral as opposed to parenteral treatment for completion of the course of therapy.

The only real difference between the first-generation oral agents is a pharmacokinetic one, where the drug cefadroxil or hydroxyethyl cephalaxin has a longer half-life and can be given less frequently than the parent compound. It is also notable that the absorption of cefadroxil when given with food, is considerably better in children than cephalaxin when given under the same circumstances. The half-life of cephradine is even shorter than that of cephalaxin and absorption considerably less as evidenced by the smaller "area under the curve" (AUC) noted in comparative studies of these agents in children.3

The pharmacology of cefaclor is similar to that of the first-generation oral agents but it has a shorter half-life and smaller AUC than either cephalaxin, cefadroxil or cefazolin.3 In view of these pharmacokinetic parameters, the wisdom of the recommended every 8-hour administration schedule for cefaclor has been questioned.4 The range of half-lives in pediatric patients,3 and dosage schedules listed for the oral cephalosporins are outlined in Table 2.

### PARENTERAL CEPHALOSPORINS

The first-generation agents are identical in bacteriologic spectrum. Pathogens well covered in infections outside of the central nervous system include S. aureus, group A streptococci, pneumococci, P. mirabilis, E. coli, and Klebsiella species. Cephalothin, cephradine and cephradine are also similar in pharmacology, but cefazolin gives considerably higher blood levels and has a longer half-life of 1.8 hours in normal adults as compared to cephalothin which has a half-life of 0.6 hours.5 The first-generation drugs are the most resistant to the enzymes of S. aureus and are preferred to the second and third-generation agents if a cephalosporin is to be used for treatment of an infection due to this pathogen. The indications for use of a parenteral first-generation agent in pediatrics are quite limited and generally include treatment of serious S. aureus, pneumococcal or streptococcal infections in the patient with delayed penicillin hypersensitivity, which is quite uncommon in pediatrics. In regard to the use of cephalosporins in penicillin allergic patients, it should be noted that fatal anaphylactic reactions have occurred in patients following the use of these agents when there was a history of an immediate reaction following penicillin. First-generation parenteral cephalosporins have also been used in certain other infec-

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TABLE 2

PEDiatric DOSAGES OF ORAL CEPHALosporINS IN CURRENT USE

<table>
<thead>
<tr>
<th>Agent</th>
<th>T½ (Min)</th>
<th>Total Daily Dosage*</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalxin</td>
<td>57</td>
<td>25 to 100 mg/kg for infant and child</td>
<td>q6—q12 hrs</td>
</tr>
<tr>
<td>Cephradine</td>
<td>46</td>
<td>25 to 100 mg/kg for infant (≥9 mos.) and child on up to 1 g qid</td>
<td>q6—q12 hrs</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>78</td>
<td>30 mg/kg for infant and child</td>
<td>q12 hrs</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>36</td>
<td>20 to 40 mg/kg for infant and child on up to 1 g daily if needed</td>
<td>q8 hrs</td>
</tr>
</tbody>
</table>

* Total dose and frequency depends on type and severity of infection. Please see text for discussion. See package insert for details.

continued from page 280

ations of a critical nature, such as proved Klebsella pneumoniae pneumonia, where it is at times given in combination with an aminoglycoside. This combination is potentially nephrotoxic and, if used, renal function should be monitored carefully. An additional use of first-generation cephalosporins has been as part of a combined regimen for suspected sepsis in the neutropenic compromised host, where it has been given with a broad spectrum penicillin such as ticarcillin.

The second-generation cephalosporins are antibiotics with a number of applications in pediatrics because of considerable improvements over the first-generation drugs in their antibacterial spectrum and, with regard to one agent approved for children, excellent penetration into the cerebrospinal fluid (CSF). Cefoxitin and cefamandole have special indications in the pediatric patient. The former is the most effective of the cephalosporins against Bacteroides fragilis, a common anaerobic pathogen, and has found good indications in surgery as a prophylactic agent following intra-abdominal or pelvic surgery in children and adults. This is because cefoxitin in addition to the spectrum of the first-generation agents provides anaerobic coverage as well. Additional pathogens that may be covered by cefoxitin include indole-positive Proteus, Providencia and H. influenzae infections outside of the central nervous system. Cefoxitin, in our experience, may not always be effective in an established intra-abdominal anaerobic infection and other agents such as clindamycin or chloramphenicol may at times be indicated. Metronidazole (Flagyl) given by the intravenous route is also highly effective in serious anaerobic infections, but is not approved for use in pediatrics because its safety and effectiveness have not been established in children. The enterococcus is not included in the spectrum of cefoxitin, or any other cephalosporin, and effective treatment of a serious surgical infection with this pathogen generally requires a penicillin-aminoglycoside or ampicillin-aminoglycoside combination.

Cefamandole has found extensive use in pediatrics because of its efficacy as a single agent in serious community-acquired pneumonia due to S. aureus, H. influenzae or S. pneumoniae. We have had considerable experience with the use of cefamandole for initial therapy in this indication, but have generally changed to specific therapy, such as penicillin for the pneumococcus or nafcillin for the staphylococcus, once the diagnosis is confirmed. Cefamandole is continued if ampicillin-resistant H. influenzae is isolated or therapy could be changed to chloramphenicol, cefotaxime or moxalactam if clinical progress is not satisfactory. The major drawback of cefamandole, and a serious one for pediatrics, is its lack of penetration into the CSF. Several cases of H. influenzae meningitis have been reported as developing during cefamandole therapy for soft tissue infections. Cefuroxime, although new in the US, has been used for several years in Europe with a good safety record and is the most commonly employed cephalosporin in the United Kingdom. It may replace cefamandole in all of its pediatric indications, including pneumonia and soft tissue infections, because of its spectrum, which includes H. influenzae (ampicillin-sensitive or resistant), S. pneumoniae, and S. aureus as well as other organisms covered by the first-generation cephalosporins and because of its good penetration into CSF. Cefuroxime was recently found to be equivalent to cefamandole in vitro in quantitative susceptibility studies on 100 blood culture isolates of S. aureus carried out in our laboratory. Cefuroxime is approved for use in meningitis due to H. influenzae, S. pneumoniae, S. aureus and Neisseria meningitidis. Several studies document its equivalence to the ampicillin-chloramphenicol regimen in pediatric meningitis due to H. influenzae, S. pneumoniae and N. meningitidis and it may well become a candidate as the
### TABLE 3
PEDiatric DOSAGES OF PARENTErAL CEPHALOSPORINS IN CURRENT USE

<table>
<thead>
<tr>
<th>Agent</th>
<th>$T_{1/2}$ [Min]</th>
<th>Total Daily Dosage*</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalothin</td>
<td>30</td>
<td>80 to 160 mg/kg for infant and child</td>
<td>q4—q6 hrs</td>
</tr>
<tr>
<td>Cephradin</td>
<td>42</td>
<td>40 to 80 mg/kg for infant (≥ 3 mos) and child</td>
<td>q 6 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 to 100 mg/kg for infant (≥ 1 mo) and child</td>
<td>q 6 hrs</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>90</td>
<td>25 to 100 mg/kg for infant (≥ 1 mo) and child</td>
<td>q6—q8 hrs</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>47</td>
<td>50 to 150 mg/kg for infant (≥ 6 mos) and child</td>
<td>q4—q8 hrs</td>
</tr>
<tr>
<td>Cefotixin</td>
<td>48</td>
<td>80 to 160 mg/kg for infant (≥ 3 mos) and child</td>
<td>q4—q6 hrs</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>90</td>
<td>50 to 100 mg/kg for infant (≥ 3 mos) and child</td>
<td>q6—q8 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For Meningitis: 200 to 240 mg/kg IV</td>
<td>q6—q8 hrs</td>
</tr>
<tr>
<td>Cefotaxime†</td>
<td>246</td>
<td>0 to 1 wk, 100 mg/kg</td>
<td>q12 hrs</td>
</tr>
<tr>
<td></td>
<td>162</td>
<td>1 to 4 wks, 150 mg/kg</td>
<td>q8 hrs</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>1 mo to 12 yrs, (wt &lt; 50 kg) give: 50 to 180 mg/kg Child (≥ 50 kg) give: 3 to 4 g</td>
<td>q4—q6 hrs</td>
</tr>
<tr>
<td>Moxalactam†</td>
<td>324</td>
<td>Neonate (0 to 1 wk) 100-200 mg/kg</td>
<td>q12 hrs</td>
</tr>
<tr>
<td></td>
<td>264</td>
<td>Neonate (1 to 4 wks) 150-200 mg/kg</td>
<td>q8 hrs</td>
</tr>
<tr>
<td></td>
<td>216</td>
<td>Infant 200 mg/kg</td>
<td>q6 hrs</td>
</tr>
<tr>
<td></td>
<td>102</td>
<td>Child 150 to 200 mg/kg</td>
<td>q6—q8 hrs</td>
</tr>
<tr>
<td>Cefizoxime†</td>
<td>96</td>
<td>Child (≥ 6 mos) 150 to 200 mg/kg</td>
<td>q6—q8 hrs</td>
</tr>
<tr>
<td>Ceforanide</td>
<td>116</td>
<td>Child (≥ 1 year) 20 to 40 mg/kg</td>
<td>q12 hrs</td>
</tr>
</tbody>
</table>

* Not to exceed recommended adult dose.
† Higher dosage range must be used for meningitis. See package insert for specific recommendations of the manufacturers regarding meningitis therapy.

A single drug choice for treating childhood meningitis because of its spectrum and lower cost.8

Ceforanide is a newly released parenteral second-generation agent that is similar in spectrum to cefamandole. The recommended schedule of administration advised by the manufacturer is every 12 hours based upon a 2-hour half-life in pediatric patients. Very limited studies have indicated efficacy in selected bone, joint and soft tissue infections in children.9 It appears to have limited indications in pediatrics except perhaps as a prophylactic antibiotic in surgery.

The other currently marketed second-generation cephalosporin is cefonicid, which has a spectrum that is similar to the other agents in this group. However, it is not indicated for treatment of meningitis. Its major advantage appears to be its long half-life of 4.5 hours as compared to 0.5 hours for cefamandole when studied in normal adults, which allows once daily administration with the potential for economic advantages. Cefonicid is not approved for use in pediatric patients,
as safety and effectiveness in children have not been established.

Third-generation cephalosporins that are currently on the market include cefotaxime, cefoperazone and ceftriaxone. Moxalactam, because of laboratory and pharmacologic similarities, is included in discussions of the third-generation cephalosporins, but is totally synthetic and technically not a cephalosporin. It is an oxa-β-lactam because of replacement of the sulfur atom of the cephalosporin nucleus with oxygen. The antibacterial spectrum of these third-generation drugs is quite broad and may include a variety of organisms, although in some instances the coverage may be rather spotty. For example, these antibiotics are clearly less effective against S. aureus than either the first or second-generation cephalosporins. In addition, Listeria monocytogenes, a well-known pediatric pathogen in the neonate and compromised host, is not covered by these antibiotics and the importance of this observation will be reviewed in the discussion on meningitis.

*Pseudomonas aeruginosa*, although often listed in the antibacterial spectrum of the third-generation agents, may require high concentrations of these drugs for a bactericidal effect, and we generally treat serious infections with this organism with combinations of ticarcillin or mezlocillin and an aminoglycoside such as gentamicin. With these many reservations about the third-generation agents, one might well ask if they have any indications at all in pediatrics. The answer is yes, in that they have certain applications in which they are quite effective and specific, particularly related to meningitis.

Cefoperazone is a third-generation agent that has a half-life of 2.0 hours in adults and therefore an every 12-hour schedule of administration has been recommended. It has not been approved as yet for use in pediatric patients. Cefoperazone has been found by many investigators to be more active in vitro than the other agents against *P. aeruginosa*, including our own findings on community hospital blood culture isolates. However, we continue to use combinations of a broad spectrum penicillin plus an aminoglycoside as described previously for serious *Pseudomonas* infections rather than a third-generation agent until more clinical experience is available with these drugs in that indication.

Ceftriaxone is a newly released third-generation drug with a spectrum that is similar to that of the other agents yet more active in vitro against gram-positive organisms. It is approved for use in pediatric patients beyond 6 months of age but data regarding its effectiveness in infections in children are limited. Ceftriaxone, like all third-generation cephalosporins, has in vitro activity against anaerobes including *B. fragilis* but our clinical use of any of these agents for anaerobic infection awaits more extensive data for clinical confirmation of their effectiveness and superiority over established regimens.

**CEPHALOSPORINS AND DIMINISHED RENAL FUNCTION**

The majority of the currently available cephalosporins (Table 1) are excreted by the kidney and require reduction of dosage with diminished renal function. Cefaclor is primarily excreted by renal mechanisms but it has been demonstrated that there is no accumulation when given to adults who are functionally anephric. Therefore, a reduction of the dose is usually not necessary if the creatine clearance (CrC) is >40 ml/minute. Similar recommendations have been made in adults for cefadroxil where modification of the dosage is not necessary for patients with CrC >50 ml/minute.

Few specific recommendations regarding reduction of cephalosporin dosages in renal failure are available for children. One exception is in regard to cefazolin where the manufacturer recommends a normal loading dose followed by 60% of the normal daily dose divided every 12 hours with a CrC of 40 to 70 ml/minute, 25% divided every 12 hours with a CrC of 20 to 40 ml/minute, and 10% of the normal daily dose given every 24 hours if the CrC is 5 to 20 ml/minute.

Cefotaxime recommendations for adults with renal impairment indicate that modifications of the dose are not necessary in patients with a CrC of >20 ml/minute and advise administration of half the usual dose at the usual time interval with a CrC of <20 ml/minute. One plan for moxalactam administration in adults is the usual dose every 12 to 24 hours for CrC of 30 to 60 ml/minute, every 24 to 36 hours for CrC of 40 to 30 ml/minute and one-half the usual dose every 18 to 24 hours for CrC of <10 ml/minute.

Cefoperazone is the only currently marketed cephalosporin that does not have renal excretion as the main route of elimination. Therefore reduction of the dose is not necessary with diminished renal function. However, there is a two to four fold increase in the half-life with hepatic disease and/or biliary obstruction and this must be taken into account in administration of this drug to patients with disorders of hepatic function.

**CEPHALOSPORINS IN MENINGITIS**

The physician treating meningitis with a cephalosporin must be aware of the rather specific indications for use of these drugs in this application. Cefuroxime is approved for treatment of meningitis in patients over 3 months of age due to *H. influenzae*, *N. meningitidis*, *S. pneumoniae* and *S. aureus*. Pharmacologic studies have shown that CSF levels of cefuroxime are many times higher than needed to inhibit the growth of *H. influenzae*, *N. meningitidis* and *S. pneumoniae* and that penetration into CSF is 5% to 30% of the serum level. The drug has also been found to be well-tolerated in these investigations. Schaad and co-workers presented data on the efficacy and pharmacology continued on page 286.
the use of cephalosporins in treatment of meningitis has rather specific indications.

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of cefuroxime in 78 pediatric patients and in addition reviewed 117 patients from the literature including an evaluation by a Swedish group which demonstrated the equivalence of cefuroxime to the ampicillin-chloramphenicol regimen.15

S. aureus meningitis is listed as an approved indication for use of cefuroxime, but the author has been unable to find much published documentation for this. In one Egyptian study, 12 patients received the drug for treatment of S. aureus meningitis.16 Three children with cefuroxime-resistant S. aureus died on the fifth or sixth day after admission, and in addition, one infant with a ventricular shunt infected with cefuroxime-sensitive S. aureus died on the second day of treatment. The recommendation of the Swedish study group that further studies should be undertaken regarding the use of the drug in S. aureus meningitis is a valuable one.15 Cefuroxime is not advised for E. coli, group B streptococcal or L. monocytogenes meningitis but is effective for the common bacterial agents of childhood meningitis including ampicillin-resistant H. influenzae.

The manufacturer of cefuroxime formerly advised a reduction of the daily dose once clinical improvement had occurred. This was an unusual recommendation since most antibiotics penetrate less well into CSF as inflammation improves. This recommendation was changed as clinical experience was gained with the use of cefuroxime in meningitis and the initial dosage is now continued throughout treatment.

Moxalactam was the first drug in the cephalosporin group to be approved in the US for use in certain specific types of pediatric meningitis. Several studies have demonstrated its good CSF penetration and equivalence without toxicity to the ampicillin-chloramphenicol regimen for H. influenzae meningitis including ampicillin-resistant isolates.17 It is not recommended as an initial single agent for childhood meningitis because of poor activity against S. pneumoniae, the group B streptococci, L. monocytogenes and lack of data regarding efficacy for N. meningitidis. In addition to Hemophilus meningitis it is also indicated for neonatal meningitis due to gram-negative enteric bacilli. In a cooperative study it was found to be equivalent to a combination of ampicillin and amikacin against coliforms.18 A prospective study in gram-negative bacillary meningitis in children and adults demonstrated the efficacy of moxalactam in sterilization of the CSF but the mortality remained high (35%) due to the underlying disease.19

Cefotaxime is approved for use in meningitis due to E. coli, Klebsiella pneumoniae, H. influenzae, S. pneumoniae and N. meningitidis and its efficacy and good CSF pharmacology were recently reviewed.20 Cefoperazone has had limited evaluation in pediatric patients and several reasons for avoiding its use in severe neonatal infections, including meningitis, were presented by Schaad.21 Ceftriaxone has recently received approval for use in treatment of H. influenzae meningitis and it has been used successfully in a limited number of cases of S. pneumoniae meningitis. Advice regarding use of this agent for treatment of pediatric meningitis or other infections in children must await further clinical experience with this new antibiotic.

In summary, the use of cephalosporins in treatment of meningitis has rather specific indications as described above. Moxalactam or cefotaxime should not be used alone in neonatal meningitis because of incomplete or poor coverage of group B streptococci and L. monocytogenes. Indeed, moxalactam was combined with ampicillin as initial therapy in the third neonatal meningitis cooperative research study and the latter drug discontinued after the pathogen was identified as gram-negative enteric bacillus.

NEW CEPHALOSPORINS AND PEDIATRICS

Several new cephalosporin antibiotics are currently in various stages of development. Two of these, ceftriaxone and ceftazidime appear to have excellent potential for pediatric use and will soon be available. Ceftriaxone offers several advantages over moxalactam but differs in the longer half-life of 4 to 7.5 hours in children, excellent resistance to beta-lactamases, increased rate of bactericidal killing, and excellent activity against the group B streptococci and S. pneumoniae.22-24 It has very good penetration into the CSF in meningitis which is enhanced by high serum concentrations. Ceftriaxone was found to be equivalent to the ampicillin-chloramphenicol regimen in three studies of pediatric meningitis as reviewed by Steele and Bradsher23 and Chadwick and associates24 who point out its potential for pediatric meningitis except that due to L. monocytogenes. The long half-life of ceftriaxone will probably allow dosing on a 12 to 24 hourly schedule. Studies in adults have indicated that the route of elimination of ceftriaxone is about two-thirds renal and one-third predominantly biliary. Administration to adults with poor renal function yielded only minor increases in half-life and suggest that there is little need to reduce the dosage with diminished renal function unless there is also hepatic insufficiency.15

The other new agent of promise for pediatrics is ceftazidime which has good penetration into the CSF and has been shown to be similar in efficacy to the ampicillin-chloramphenicol regimen in pediatric meningitis.26 It is the most effective of the third-generation agents against P. aeruginosa in vitro27 and has recently been found to be an effective and less toxic alternative to combined ticarcillin-tobramycin therapy in gram-negative bone and joint infections in
adults. 27 Ceftazidime is excreted via the kidney and reduced doses are necessary with renal failure.

CEPHALOSPORIN TOXICITY

The first-generation cephalosporins have generally been considered to be among the least toxic of the antimicrobials. The second-generation agents have also been relatively safe drugs, but a serum-sickness like reaction has been described on occasion in children who have received multiple courses of cefaclor, usually for recurrent otitis media. 28 Rather than toxicity, one problem has been the development of resistant organisms, particularly resistant enterobacter species, in hospitals where cefamandole was used extensively. We have not observed this to be a significant problem in our community hospital setting where cefamandole has been used frequently.

The third-generation agents carry much more of a risk of serious toxic reactions including disulfiram-like effects when given to adults who drink alcohol. This is theoretically also possible in children who are given alcohol-containing medications. 29 Problems that have been demonstrated with moxalactam administration include platelet dysfunction and disturbance in vitamin K metabolism with resultant deaths. 30 Because of the potential for serious bleeding problems the concomitant administration of vitamin K is now advised during moxalactam therapy.

The extremely broad antibacterial spectrum of these agents can lead to almost total sterilization of the gut and the potential for problems secondary to this is unknown. Certainly these patients may be predisposed to fungal infections and Closstridium difficile-related colitis. The intestinal side effects of cepoforazone were so prominent that one research study in adults that the authors concluded that cepoforazone use should be limited to selected purposes. 31

One additional major concern at the present is that extensive use of these agents will lead to the development of inducible beta-lactamase enzymes in the gram-negative rod population and the development of an antibiotic resistance problem of major proportions.

CONCLUSION

The cephalosporin antibiotics have limited uses in pediatric medicine and for the most part the second and third-generation agents find more application in infants and children. Cefaclor is useful in otitis media that is unresponsive to standard treatment with amoxicillin. Cefuroxime is effective in serious community-acquired pneumonia and in addition appears safe and effective for meningitis of childhood. Moxalactam and cefotaxime are effective for H. influenzae infections including pneumonia and meningitis due to ampicillin and chloramphenicol-resistant organisms. These two agents are also effective for coliform meningitis but are not reliable for Listeria infections. Two investigational agents of promise for pediatric use which warrant further investigation for treatment of a variety of infections in children are ceftriaxone and ceftazidime.

REFERENCES