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Author Disclosure
Drs Parker, Mitchell, and Child have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Editor's Note

In the spirit of last month's issue emphasizing "Doing Less" and using evidenced-based guidelines for treating pneumonia and sinusitis, we present the following feature on the judicious use of cephalosporins.

Joseph A. Zenel, MD
Editor-in-Chief

Practice Gap

Although cephem antibiotics are important in a pediatrician's armamentarium, they are overused to the detriment of patients, hospitals, and communities, despite the availability of sound alternatives. Going back to the basics on mechanisms of action, resistance, and pharmacokinetic and pharmacodynamic principles facilitates smarter use and preserves cures for tomorrow.

Objectives

After reading this article, readers should be able to:

1. Describe in a general manner the mechanism of action, resistance, and pharmacokinetic and pharmacodynamic principles of cephem antibiotics.
2. Describe the advantages and disadvantages of oral cephem antibiotics compared with amoxicillin and amoxicillin–clavulanic acid.
3. Describe appropriate clinical situations in which to use cephem antibiotics.
4. Describe appropriate clinical situations where cephems are commonly used but could reasonably be replaced with an alternative, non-cephem antimicrobial.

Abbreviations

CAP:	community-acquired pneumonia
CLSI:	Clinical Laboratory Standards Institute
CSF:	cerebrospinal fluid
FDA:	Food and Drug Administration
GAS:	group A streptococcus
IM:	intramuscular
IV:	intravenous
MIC:	mean inhibitory concentration
MRSA:	methicillin-resistant *Staphylococcus aureus*
MSSA:	methicillin-susceptible *Staphylococcus aureus*
PBP:	penicillin-binding protein
PD:	pharmacodynamic
PK:	pharmacokinetic
PRSP:	penicillin-resistant *Streptococcus pneumoniae*
UTI:	urinary tract infection

Background

The cephem antibiotics were first deployed in the 1960s but did not expand into broad use until the 1970s with the development of useful semisynthetic derivatives. The cephem class includes the cephalosporins and the cephamycins, of which more than 22 antibiotics are now in clinical use (Table 1). There is no doubt that the cephem antibiotics are important weapons in a practitioner's armamentarium; they are the most widely prescribed and largest selling class of antibiotics, with $8.5 billion spent yearly worldwide. (1)

That said, cephems are also arguably the most inappropriately used antibiotics in pediatrics. Approximately 40% of pediatric antibiotic use is inappropriate. This overuse drives resistance on patient and community levels. The observation that methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) are much lower in countries where cephem use is restricted is likely not a coincidence, indicating that prevention of indiscriminant use warrants consideration. (2,3,4,5)

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Table 1. **Compiled Cephem and Comparative Penicillin Agent Pharmacokinetic and Pharmacodynamic Data**

Antibiotic (Year Approved)	Absorption, %/Protein Binding, %/Half-life, h	Recommended maximum adult dose (mg/d)/pediatric dose (mg/kg/d)	Dose evaluated	Peak Dose, μg/mL (Total dose is bound and unbound)	Time That the Antibiotic Plasma Concentration (Active, Unbound Drug) for a Single Dose Remains Above a Certain MIC, h[a]				
					Time Above an MIC of 0.5 μg/mL	Time Above an MIC of 1.0 μg/mL	Time Above an MIC of 2.0 μg/mL	Time Above an MIC of 4.0 μg/mL	Time Above an MIC of 8.0 μg/mL
Comparative Oral Penicillin									
Amoxicillin[b] (1970s)	89/20/1.2-2	4,000/90 given 2 to 3 times daily	500 mg	9.0	6	4.5	2.5	1	-
			875 mg	11.6	6.5	5	3.5	2	-
			15 mg/kg	7.9	5.5	4	2.5	1	-
			25 mg/kg	10.6	6	4.5	3	1.5	-
			45 mg/kg	15.7	7	5.5	4	2.5	1
Oral First-Generation Agent									
Cephalexin[c] (1971)	90/10-20/ 0.5-0.6	4,000/150 given 4 times daily	250 mg	9	2	1.5	1	-	-
			500 mg	18	2.5	2	1.5	1	-
			1,000 mg	32	3	2.5	2	1	-
Oral Second-Generation Agent									
Cefuroxime (1987)	37-52 with food/33-50/ 1.2-1.9	1,000/30 given 2 times daily	10 mg/kg	3.3	2.5	1	-	-	-
			15 mg/kg	5.1	3.5	2	-	-	-
			20 mg/kg	7.0	4.5	3	1.5	-	-
			500 mg	7.0	4.5	3	1.5	1.5	-
			1,000 mg	13.6	6	4.5	3	-	-
Cefprozil[c] (1991)	95/36/1.3	1,000/30 given 2 times daily	250 mg	6.1	3.5	2.5	1	-	-
			500 mg	10.5	4.5	3.5	2	-	-
			1,000 mg	18.3	5.5	4.5	3	2	-
Oral Third-Generation Agent									
Cefixime (1989)	40-50/65/ 1.5-4	400/8 –given 1-2 times daily	200 mg (suspension)	3	3.5	-	-	-	-
			400 mg (suspension)	4.6	5.5	2	-	-	-
			200 mg (capsule)	2	1.5	-	-	-	-
			400 mg (capsule)	3.7	4.5	1	-	-	-
			7 mg/kg (suspension)	2.3	2	-	-	-	-
			14 mg/kg (suspension)	3.8	4.5	1	-	-	-

Continued

Table 1. (Continued)

Antibiotic (Year Approved)	Absorption, %/Protein Binding, %/Half-life, h	Recommended maximum adult dose (mg/d)/pediatric dose (mg/kg/d)	Dose evaluated	Peak Dose, μg/mL (Total dose is bound and unbound)	Time That the Antibiotic Plasma Concentration (Active, Unbound Drug) for a Single Dose Remains Above a Certain MIC, h[a]				
					Time Above an MIC of 0.5 μg/mL	Time Above an MIC of 1.0 μg/mL	Time Above an MIC of 2.0 μg/mL	Time Above an MIC of 4.0 μg/mL	Time Above an MIC of 8.0 μg/mL
Cefpodoxime (1992)	50/14-24/ 2.09-2.84	400/10 given 2 times daily	200 mg	2.3	4.5	2	-	-	-
			400 mg	3.9	6.5	4	1.5	-	-
			5 mg/kg	2.1	4	1.5	-	-	-
			10 mg/kg	5.3	7.5	5	2.5	-	-
Ceftibuten (1995)	80/65/2-2.4	400/9 given once daily	9 mg/kg	13.4	6	4	1.5	-	-
			400 mg	15	6.5	4.5	2	-	-
Cefdinir (1997)	16-25/73/ 1.4-1.8	600/25 given 1-2 times daily	300 mg	1.6	-	-	-	-	-
			600 mg	2.87	1	-	-	-	-
			7 mg/kg	2.3-2.56	-	-	-	-	-
			14 mg/kg	2.07-3.86	1	-	-	-	-
			25 mg/kg	4.42	2	-	-	-	-
Comparative IV Penicillin Agents									
Ampicillin[c] (<1965?)	NA/15-25/ 0.8-1.9	12,000/400 given every 4-6 h	44 mg/kg	177-200	10.5	9	8	6.5	5.5
Nafcillin[c,d] (1970)	NA/70-90/ 0.5-1.9	12,000/200 given every 4-6 h	37.5 mg/kg[c]	48.1	5	3.5	2.5	1.5	
IV First-Generation Agent									
Cefazolin[c,d] (1973)	NA/80-86/ 1.5-1.7	12,000/150 given every 6-8 h	25 mg/kg[c]	150-247	9.5	8.5	6.5	4.5	3**#
IV Second-Generation Agent									
Cefoxitin (1978)	NA/65-80/ 0.68-0.98	12,000/160 given every 4-8 h	1,000 mg	110	4.5	4	3	2	1.5
			37.5 mg/kg	82	4.5	3.5	2.5	2	1
Cefuroxime (1983)	NA/33-50/ 1.5	6,000/240 given every 6-8 h	50 mg/kg	105	10	8.5	7	5.5	4

Continued

Table 1. (Continued)

Antibiotic (Year Approved)	Absorption, %/Protein Binding, %/Half-life, h	Recommended maximum adult dose (mg/d)/pediatric dose (mg/kg/d)	Dose evaluated	Peak Dose, μg/mL (Total dose is bound and unbound)	Time That the Antibiotic Plasma Concentration (Active, Unbound Drug) for a Single Dose Remains Above a Certain MIC, h[a]				
					Time Above an MIC of 0.5 μg/mL	Time Above an MIC of 1.0 μg/mL	Time Above an MIC of 2.0 μg/mL	Time Above an MIC of 4.0 μg/mL	Time Above an MIC of 8.0 μg/mL
Cefotetan[c] (1985)	NA/88/3-4.6	6,000/100 given every 12 h	1,000 mg 2,000 mg 20 mg/kg[c]	158 237 216	19.5 22 21.5	16 18 17.5	12 14.5 14	8.5 10.5 10	4.5 6.5 6
IV Third-Generation Agent									
Cefotaxime (1981)	NA/30-35/ 0.8-1.5	12,000/300 given every 4-8 h	50 mg/kg	142	9	7.5	6.5	5.5	4
Ceftriaxone[c] (1984)	NA/86-96/ 4.2-6.5	4,000/100 given every 12-24 h	50 mg/kg[c]	230	27.5	23	17.5	12	7
Ceftazidime[c] (1985)	NA/10-17/ 1.2-2	6,000/300 given every 8 h	35 mg/kg[c] 1,000 mg 2,000 mg	110 60 129	12 10.5 12	10.5 9 10.5	8.5 7.5 9	7 5.5 7.5	5.5 4 6
IV Fourth-Generation Agent									
Cefepime[d] (1996)	NA/16-19/ 1.5-1.9	6,000/150 given every 8 h	50 mg/kg	184	14	12	10.5	8.5	7
IV Fifth-Generation Agent (MRSA)									
Ceftaroline[d] (2010)	NA/14.5-28/ 1.6-2.6	1,200 given every 12 h	600 mg	19-21	10	8	6	4	2

MIC=mean inhibitory concentration; NA=not Applicable.

[a]Pharmacokinetic and pharmacodynamic efficacy is supported if the serum level is above the MIC for 30% to 40% of the day (7.2-9.6 hours) and, for more serious infection treated intravenously, 60% to 90% (14.4 hours).

[b]For amoxicillin, although peak concentrations for the common dose, 90 mg/kg per day (30 mg/kg per dose), were not found, Monte Carlo simulation supports pharmacokinetic and pharmacodynamic efficacy for MICs of 2 μg/mL in 90% of children (compared with 65% if the dose is divided into twice daily administrations). Peak information for the 2- to 5-mg/kg dose approximates this.

[c]Single doses used in clinical practice for these agents are often higher than those for which peak levels are reported or evidence with pediatric dosing not found.

[d]If antibiotic is administered more than once daily, calculate the total daily time above the MIC by multiplying hours for that dose by number of doses per day. Rough time above MIC is calculated as described in the article, using serum peak, percentage of protein binding, and serum half-life for dose to left. Information was obtained from referenced sources, package inserts, and the Food and Drug Administration website. Estimates reported here are rough and do not take into account time for oral absorption to keep the model simple. Because of some postantibiotic effects, agents active against *Staphylococcus aureus* need less time above the MIC for efficacy (25%-35% per day for treatment orally, 50% for more serious infection treated intravenously).

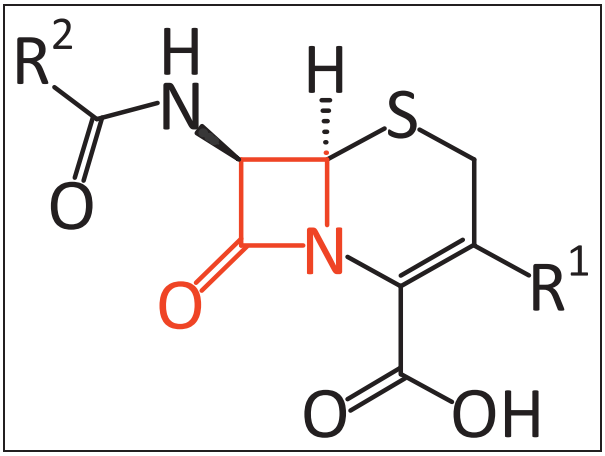

Figure 1. The core structure of cephem antibiotics. The square in the center is the β-lactam ring. The R groups represent the arms.

In outpatient pediatrics, cephem overuse is driven by ease of dosing, palatability, and strategic marketing techniques that highlight the positive aspects of noninferiority trials (the Pollyanna phenomenon) while ignoring pharmacokinetic (PK) and pharmacodynamic (PD) principles. (6,7) This review emphasizes the concepts necessary to understand the PK and PD principles of cephem antibiotics to encourage their selective use, rather than overuse, thereby improving the care of patients and our microbial community and preserving cures for tomorrow. (8,9,10) The sections on mechanisms of action and PK and PD principles are followed by sections on allergy and clinical indications.

Cephem Structure, Mechanism of Action, and Microbial Resistance

Structurally, the cephems are β-lactam antibiotics and thus related to the penicillins, monobactams (aztreonam), carbapenems, and β-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam). (1,11,12) The 4-membered β-lactam ring is present in all of these groups (Figure 1) and is central to their activity. In the cephems, this β-lactam ring is connected to a 6-membered dihydrothiazine ring. Chemical substitutions at the 2 cephem arms confer differences in spectra of antibacterial activity, susceptibility to β-lactamases, and PK and PD properties.

The mechanism of antibacterial activity of the cephems involves synthesis inhibition and disruption of the bacterial cell wall. The bacterial cell wall is a crucial framework that provides both structure and protection. The basic interlocking unit of the cell wall is cross-linked peptidoglycan. Below this layer, within the cytoplasmic membrane, are a heterogeneous group of proteins called the penicillin-binding proteins (PBPs), which are mostly involved in microbial cell wall maintenance. Certain types of PBPs called *transpeptidases* perform the cross-linking of the peptidoglycan layer. These are the key PBPs inhibited by β-lactam antibiotics, including the cephems. Microbes have multiple PBP transpeptidases, some of which are more essential than others, and they are differentially targeted by the β-lactam antimicrobials. The PBP transpeptidases essentially mistake the β-lactam antibiotic for the yet to be cross-linked peptidoglycan and are rendered inactive, leaving the microbial cell wall weakened.

The cephems are not classified on structural similarity but on their spectra of antibacterial activity (see the "Common Indications" section below and Table 1). The spectra are determined by a drug's ability to (1) penetrate the organism's outer structure to reach the PBP transpeptidase, (2) bind the particular PBP transpeptidase essential to that pathogen, and (3) escape the activity of native or acquired β-lactamase enzymes. These spectral activity determinants are also the areas exploited by the microbes to develop their main mechanisms of resistance. Thus, understanding resistance mechanisms helps one understand spectrum of activity and generation classification, important concepts to the judicious use of these drugs.

The first mechanism of bacterial resistance is alteration of the gene encoding the PBP transpeptidase or its expression. This is common in gram-positive organisms and is responsible for resistance in MRSA and PRSP. When *S aureus* acquires the new gene (named *mecA* or *pbp2a*), it encodes a novel PBP transpeptidase that replaces the function of all 4 native PBP transpeptidases, and methicillin resistance is acquired. As a result, MRSA is not inhibited by any of the approved β-lactam drugs, with the exception of ceftaroline (not yet approved in pediatrics). PRSP is the result of a *S pneumoniae* and *Streptococcus viridans* genetic recombination event, creating a novel PBP transpeptidase that is less susceptible to β-lactam drugs. However, at high drug levels, the resistance can be overwhelmed by clinically relevant doses. Unlike gram-positive organisms that acquire new genetic information, the gram-negative organisms tend to have a larger number of genes encoding PBP transpeptidases, with the ability to substitute one for the other (functional redundancy). Gram-negative organisms prefer to alter expression of their various PBPs rather than create novel PBPs (ie, if one is inhibited, the bacterium will just increase production of one of its alternative PBPs).

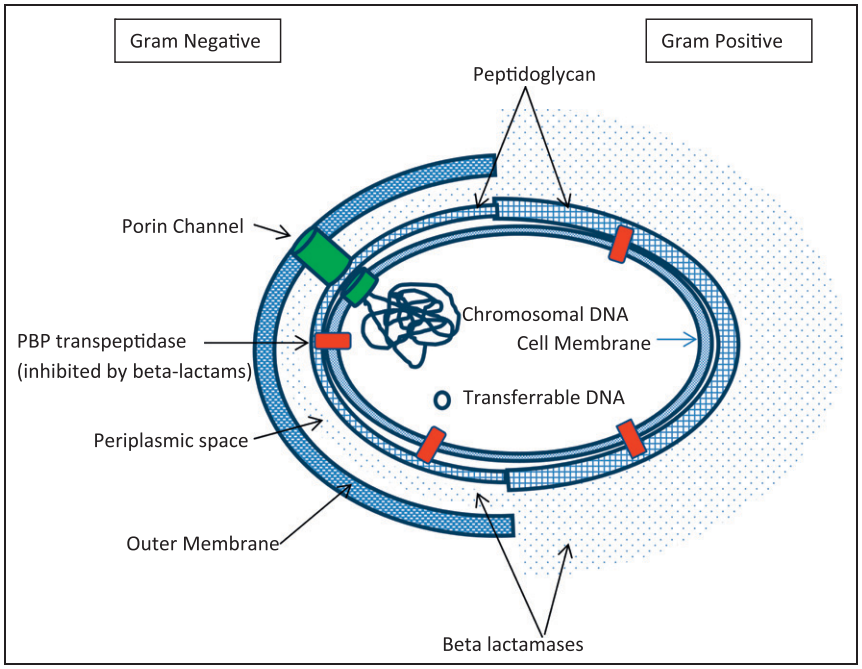

Figure 2. Schematic of gram-negative and gram-positive cell walls. PBP = peptide-binding protein.

The second common resistance mechanism is expression of β-lactamase enzymes that inactivate the β-lactam antibiotic. Gram-negative bacteria concentrate β-lactamases in the periplasmic space, which is coated with an outer membrane (Figure 2). Thus, relatively little needs to be produced to result in highly effective resistance. Gram-positive bacteria also produce β-lactamases but lack the outer membrane, forcing them to produce voluminous quantities to compensate for dilution loss to the environment. Nevertheless, this mechanism is responsible for nearly universal resistance of *S aureus* to penicillin and ampicillin. There are currently more than 927 β-lactamase enzymes described, most of which are in gram-negative bacteria. (13) The 927 β-lactamases range from relatively simple and narrow enzymes to complex inducible β-lactamases, extended-spectrum β-lactamases, and the emerging carbapenemases. The genes encoding these enzymes are located on the chromosome or on transferrable pieces of DNA (and thus easily and frighteningly shared with other microbes), and organisms can harbor more than one type. For a deeper understanding of the complexities, the reader is referred to the articles by Jacoby and Paterson and Bonomo. (14,15) It is essential for the general pediatric practitioner to know that the cephems are not often the drugs of choice for children severely ill with organisms that have complex types of β-lactamases. Help in drug choice and dosing is advised in these situations in consultation with an infectious diseases specialist or pharmacist or an antimicrobial steward because microbes with these resistance mechanisms often harbor resistance to multiple classes of drugs, need optimized drug and dosing strategies, and are of emerging concern. (16)

The third common mechanism of resistance is for the microbe to decrease penetration of the drug. Cephems reach the PBP transpeptidase targets by passive diffusion or, in the case of gram-negative organisms, through small channels in the outer membrane called *porins*. The genes that encode these porins, or genes that control their overall presence in the cell wall, can be altered by the microbe to prevent drug entrance. The microbe can also decrease penetration by thickening its peptidoglycan layer. In this case, the drug only reaches the outer portion, leaving an inner portion functional. If a drug penetrates, the microbe can also pump it out by efflux. (1)

Cephem Pharmacokinetics and Pharmacodymics

Among the 3 basic elements of clinical antibiotic decision making are the practitioner's experience and clinical sense in assessing the need for antibiotics and the clinical studies supporting an antibiotic's efficacy. Unfortunately, most antibiotic studies in pediatrics are noninferiority trials in diseases with high spontaneous remission rates (otitis media, community-acquired pneumonia [CAP], and sinusitis). Noninferiority trials are designed to demonstrate that a drug is not unacceptably worse than a standard, although they are often erroneously interpreted as equivalence. In these studies, the efficacy of the studied drug is not even clear because poor adherence to study reporting and misleading conclusions plague such trials. (17,18,19,20,21,22) Furthermore, the bar is perpetually lowered when a drug gains approval with a noninferiority trial by comparing it to a standard that also gained approval in a noninferiority trial. This is the Pollyanna phenomenon and leads to inappropriate confidence in the oral cephems. (6) To balance these studies, the third

element of antibiotic decision making, PK and PD assessment, can be helpful. For the β-lactam class of antibiotics, including the cephems, there are some easy rules of thumb that make a PK and PD assessment practical for all prescribers. (23,24,25,26,27) This section will require extended attention, using the tables and figures for reference, but will instill prescribing confidence for those ready to make a shift from oral cephalosporins to more judicious alternatives; discussion of allergy and clinical indications follows.

Oral cephems are attractive for many reasons. However, as a class, oral cephems are generally not well absorbed, are highly protein bound (bound drug is not active), and have short half-lives. Thus, peak levels of active (unbound) drug decrease below the mean inhibitory concentrations (MIC) of common pathogens relatively quickly, leaving suboptimal and subinhibitory levels of drug, subsequently encouraging the development of resistance on a patient and community level. (8) A relative exception to this is cephalexin, which can be used in high doses divided 4 times daily successfully in the treatment of pediatric osteomyelitis.

The cephems (and all β-lactams) display time-dependent bactericidal activity, meaning free drug concentrations higher than the MIC of the pathogen for an adequate percentage of the day (time above the MIC) must be maintained for efficacy. For the oral cephems, this is defined as at least 30% to 40% of the day; for inpatient infections requiring intravenous (IV) therapy, this goal should be increased to more than 60% to 80% and ideally more than 90% for immunocompromised patients. (28) If favorable PK and PD profiles cannot be achieved in the serum, they are unlikely to be achieved at the site of infection, resulting in suboptimal treatment and resistance. Because postantibiotic effect (continued killing when the drug concentration is below the MIC) for the cephems is minimal (though described for *S aureus*) and they do not regularly accumulate in tissue to levels higher than in the serum, clinically relevant approximations can be made for β-lactam antimicrobials using a simple method of rough PK and PD modeling in serum.

Rough PK and PD profiles can be calculated using the dose, serum peak, percentage of protein binding, serum half-life, dosing interval, and the MIC of the target pathogen. The use of this information is demonstrated in Figures 3 and 4. The example in Figure 3 is for oral amoxicillin, chosen for comparison to the oral cephems. It also highlights the advantage to using amoxicillin divided 3 times daily rather than 2 (more time achieved above the MIC). Using this method to compare oral cephems to high-dose oral amoxicillin demonstrates that oral cephems are never superior in PK and PD for susceptible pathogens. The PK and PD assessment can be performed with the cephem of choice by following the directions in Figure 5 (for more examples see the article by Prober). (27) Clinical MICs are available from the Clinical Laboratory Standards Institute (CLSI), (29) and relevant MICs for the cephems are listed in Table 3. The PK drug information for adults is easily available from the Sanford guide; (30) pediatric PK data are difficult to find but are available on the Food and Drug Administration (FDA) website either publicly or on request and for common cephems are compiled and referenced in Table 1. (31) As a rule, the most favorable PK and PD profiles for the cephems will be achieved with the highest allowable dose given as frequently as possible to the point of continuous infusion. (32) Please note this rough PK and PD assessment applies to the β-lactam antibiotics only because other antimicrobial classes display other PK properties. We have chosen to model free (not protein-bound) drug because studies support bound drug is not active, although this model approach is not performed in all studies. (33)

In contrast to the oral cephems, IV cephems generally achieve favorable PK and PD profiles, despite some being highly protein bound. However, these levels are not necessarily superior to those achieved by narrower agents; a similar strategy for a rough PK and PD assessment is presented in Figure 4 for ceftriaxone and ampicillin. Unfortunately, achieving favorable PK and PD profiles in serum does not necessarily mean they are achieved at the site of infection due to drug penetration. For example, first- and second-generation cephems do not generally achieve therapeutic levels in the cerebral spinal fluid (CSF).

Use of Tables 1 and 3 with a rough PK and PD assessment helps to put clinical studies in context and allows practitioners to make more informed antibiotic decisions. However, it may lead to confusion because of perceived contradiction with clinical susceptibility reports. The microbial MIC breakpoints of susceptible, intermediate, and resistant for a specific pathogen are determined by the CLSI in the United States and by the European Committee on Antimicrobial Susceptibility Testing in Europe and are further complicated by FDA breakpoints with which a laboratory must be compliant. (8) These breakpoints do not always agree, exemplifying that they are both oversimplified and controversial.

Take for example a common susceptibility report on a child with CAP yielding *S pneumoniae*; the laboratory reports the strain's nonmeningeal susceptibility as having

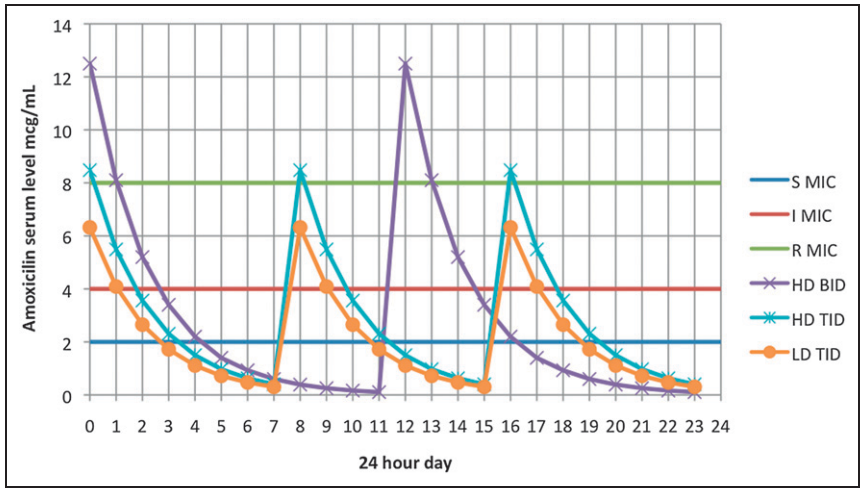

Figure 3. Rough pharmacokinetic (PK) and pharmacodynamic (PD) example for low-dose amoxicillin at 45 mg/kg daily divided 3 times daily (LD TID), high-dose amoxicillin at 90 mg/kg daily divided twice daily (HD BID), or high-dose amoxicillin at 75 mg/kg daily divided 3 times daily (HD TID) (approximates common dosage of 90 mg/kg daily), with a serum half-life of 1.2 hours and protein binding of 20%. Horizontal lines are the mean inhibitory concentrations (MICs) considered susceptible (S), intermediate (I), or resistant (R) for nonmeningeal *Streptococcus pneumoniae*. For PK- and PD-predicted efficacy, the drug level must be over the MIC for at least 30% to 40% of the day (ie >7.2 hours per day). For susceptible *S pneumoniae* (MIC <2 μg/mL), this is achieved with all of these dosing strategies. Note that for susceptible *S pneumoniae* with higher (approximately 2 μg/mL) MICs, the most favorable PK and PD profiles are achieved with HD TID. Compared with all oral cephems, the PK and PD profiles for amoxicillin is superior.

a penicillin MIC of 2 μg/mL and a ceftriaxone MIC of 0.5 μg/mL or less. According to the CLSI guidelines for nonmeningeal isolates, and thus reported by the laboratory, this is susceptible to IV penicillin (susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; and resistant, ≥8 μg/mL), resistant to oral penicillin (susceptible, ≤0.06 μg/mg; intermediate, 0.12-1 μg/mL; resistant, ≥2 μg/mL), and susceptible to ceftriaxone (susceptible, ≤0.5 μg/mL; intermediate 1 μg/mL; resistant, ≥2 μg/mL). A practitioner might conclude that treatment with ceftriaxone is superior when the PK and PD profiles and clinical studies equally support the use of the narrower ampicillin agent (Fig 4) (34) for nonmeningeal infection, which has resistance and cost advantages. When ready to switch to an oral agent, the practitioner may further conclude that this *S pneumoniae* must also be susceptible to oral cephems and that these agents will be "better" than oral amoxicillin. This is erroneous. First, the isolate is likely susceptible to oral amoxicillin per the CLSI guidelines (amoxicillin CLSI break points: susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; resistant, ≥8 μg/mL; amoxicillin susceptibilities are not commonly performed, but penicillin and amoxicillin MICs largely correlate). Second, ceftriaxone susceptibility does not predict oral cephem susceptibility, (35,36) and third, the PK and PD profiles would support the opposite conclusion, that amoxicillin is superior to oral cephems (see Tables 1 and 3 for time above the MIC predictions). Amoxicillin, particularly at a high dose divided 3 times daily for optimal PK and PD profiles, can clearly treat nonmeningeal *S pneumoniae* with an MIC of 2 μg/mL or less, and some argue also an MIC of 4 μg/mL or less. (37,38,39,40) Although local antibiograms may report high levels of *S pneumoniae* resistance, for empiric treatment, amoxicillin remains the drug of choice for oral therapy, with a high dose divided 3 times daily best for isolates with higher MICs. With known isolates of very high MICs (≥4 μg/mL, per some authors, MIC ≥8 μg/mL), rather than an oral cephalosporin, one is best leaving the β-lactam class. (41,42,43) Because oral cephems achieve relatively low free serum levels, they are inferior for oral treatment of *S pneumoniae* and many other pathogens; prescribing them should be the exception and reserved for particular clinical entities (below) or for those who are truly penicillin allergic.

Allergy, Cross-reactivity and Adverse Effects

Mechanisms underlying allergic reactions to the cephalosporins are poorly understood, but some points are clinically helpful, beginning with an understanding of penicillin allergy. (44,45,46,47,48,49) Most allergic reactions to penicillin are not to the compound penicillin but rather a degradation product attached to host tissues (usually the penicilloyl group) (ie, a hapten-protein conjugate), although less frequently to other minor determinants. There is no known equivalent to the penicilloyl hapten in cephems, so the issue of cross-reactivity between penicillins and cephems remains unsettled. It is suspected that in cephalosporin allergy, the immunogen is one of the side chains (Fig 1). Allergy to all agents is increased in penicillin allergic patients and thus not technically a cross-reaction. Although penicillin allergy is reported in 5% to 10% of the population, only

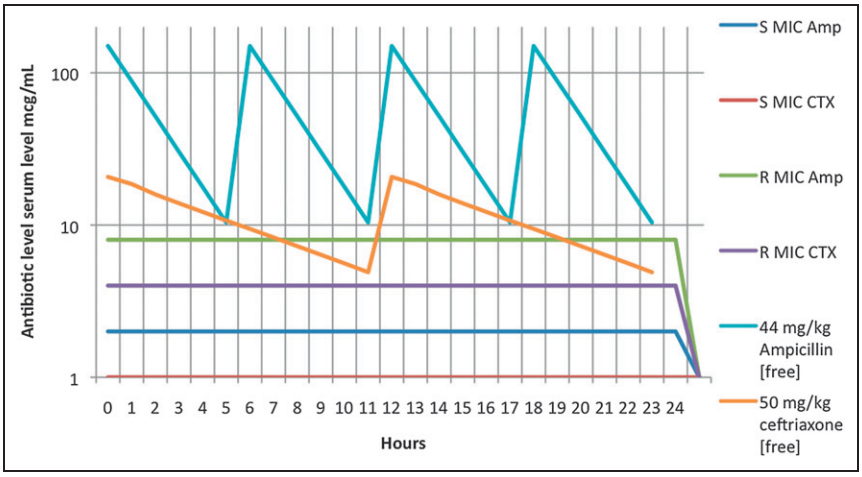

Figure 4. Rough pharmacokinetic (PK) and pharmacokinetic (PD) example for ampicillin (Amp) at 44 mg/kg per dose every 6 hours intravenously with a half-life of 1.3 hours and protein binding of 20% and 50 mg/kg per dose of ceftriaxone (CTX) every 12 hours with a half-life of 5.3 hours and protein binding of 91%. Horizontal lines are the mean inhibitory concentrations (MICs) considered susceptible (S) or resistant (R) for each drug for nonmeningeal *Streptococcus pneumoniae*. The PK and PD efficacy is predicted for both drugs, even with resistant *S pneumoniae* MICs, for nonmeningeal infections.

approximately 5% of those will have a positive skin test result, indicating the misdiagnosing of many people as being penicillin allergic. This results in suboptimal treatment and excessive costs. (48) Cephem allergy in the population is approximately 10-fold lower than to the penicillins. True cross-reactivity is probably approximately 0.1% of those with a self-reported, unconfirmed allergy and 2% to 3% of those with an allergist-confirmed penicillin allergy. (49) All of this translates into a general rule of thumb that if an allergy to penicillin is not consistent with an IgE-mediated reaction, a clinician may reasonably prescribe a cephem. If history is consistent with an IgE-mediated reaction or if the child is known to have a positive penicillin skin test result, a clinician has various options. These options include graded oral challenge, full dose oral challenge, or desensitization when clinically indicated, all under appropriate observation; useful algorithms are published. (46,48) Skin testing with other agents is possible in some research settings but largely unavailable. Indefinite avoidance of β-lactams is not preferred to prevent life-long suboptimal treatment common to those diagnosed as being penicillin or cephem allergic; instead, referral to an allergist for formal diagnosis of β-lactam allergy and counseling is recommended. Notably, there are shared side chains between some penicillins and some cephems, for example, ampicillin and cephalexin, where more care in cross-use should be taken. (50) There is no known cross-reactivity between the cephems and aztreonam (with the exception of ceftazidime, which shares a common side chain). Cross-reactivity of the carbapenems with penicillins is less well studied, although very low in recent publications (<1%), and because there is less shared structure between carbapenems and cephems, cross-reaction between these should be even less likely. If a child has had a severe systemic reaction to a cephem, IgE mediated or not (Table 2), avoidance of the cephem class until the child can be evaluated by an allergist is warranted. Other adverse effects reported with the cephems (and all β-lactams) are listed in Table 2.

Use Table 1 for relevant PK/PD information and Table 3 for MICs of common pediatric pathogens to answer the following questions below for the particular antibiotic:

1. Is the peak serum level for the desired dose (Table 1) above the MIC of the organism (Table 3) of concern?
2. *When I account for the % protein binding, is the unbound level still over the MIC?
3. *When I lower the free drug level by half for each half-life of the drug, does the drug level stay over the MIC for at least 30-40% of the dosing interval?
4. Is the drug expected to penetrate the space of the infection?

* These steps are done for you in Table 1, under MIC values.

If the answer to any of the above is NO, PK/PD efficacy is not supported. If all answers are yes, PK/PD efficacy may be supported.

Figure 5. Directions for performing a pharmacokinetic (PK) and pharmacodynamic (PD) assessment. MIC = mean inhibitory concentration.

Use of Cephems in Common Clinical Situations: Common Indications and Choices

Cephem antibiotics are helpful antibiotics in certain clinical situations.

Table 2. Common and Serious Adverse Effects of Cephem Antimicrobials

Gastrointestinal
- Gastrointestinal upset
- Antibiotic-associated diarrhea
- *Clostridium difficile* and pseudomembranous colitis
- Biliary sludging and bilirubin displacement (ceftriaxone; thus, its use is not advised in neonates younger than 1 month)

Dermatologic reactions and systemic illness (often hand-in-hand)
- IgE mediated: anaphylaxis, laryngeal and angioedema, bronchospasm, urticaria (consider evaluation for hereditary angioedema)
- Antibiotic rash
- Drug fever
- Erythema multiforme
- Stevens-Johnson syndrome, toxic epidermal necrolysis spectrum illness
- Drug-induced hypersensitivity syndrome
- Serum sickness

Hematologic
- Bone marrow suppression (most common is neutropenia)
- Eosinophilia (eosinophils, ≥00.5 × 10^9/L)
- Coomb positivity and hemolysis

Renal
- Most cephems are excreted renally, and all require some adjustment for renal impairment
- Renal impairment (interstitial nephritis and renal tubular necrosis)

Other
- Neurotoxicity (very high doses)
- Yeast infections
- Precipitation when coadministered with calcium (ceftriaxone; thus, its use is not advised in neonates younger than 1 month)

(51) However, they are rarely considered first-line options by experts, particularly for oral treatment. This is largely reflected in national guidelines for common clinical pediatric entities. Indications for IV choices are clearer, but IV cephems should be used more judiciously than current practice to avoid emerging resistance.

Cephems are often broken down into generations based on spectra of antimicrobial activity (Table 1). The first-generation cephems are most active against gram-positive (methicillin-susceptible *S aureus* [MSSA], groups A and B streptococci) and some limited aerobic gram-negative activity, although resistance in common urinary tract infection (UTI) pathogens is increasing. Second-generation cephems have aerobic gram-positive and negative activity, although overall they have less gram-positive activity than the first-generation cephems and less gram-negative activity than the third-generation cephems. The first- and second-generation cephems do not penetrate the CSF at levels above the MICs of common pathogens, and first-generation cephems do not penetrate the middle ear well. (52) Some second-generation cephems have some anaerobic coverage (cefotetan and cefoxitin), and cefoxitin has some antimycobacterial activity. The third-generation cephems are largely geared to gram-negative pathogens, including *Escherichia coli*, *Neisseria* spp, and *Haemophilus influenzae* coverage. Importantly, some IV formulations (cefotaxime and ceftriaxone) have good *S pneumoniae* and groups A and B streptococcal coverage, and therapeutic penetration of the CSF and middle ear. Ceftazidime penetrates CSF, but because of the higher susceptible MIC to *S pneumoniae* it cannot be used for that pathogen. The third-generation cephems have less MSSA coverage than the first-generation cephems, and utility of ceftriaxone for MSSA is controversial in pediatrics. Fourth-generation cephems, namely cefepime, have MSSA, expanded aerobic gram-negative, and antipseudomonal coverage. The other cephem with antipseudomonal coverage is ceftazidime. Ceftaroline is a recently developed fifth-generation cephem with MRSA activity (but no pseudomonal activity) in clinical use in adults, but no dosing is established yet in pediatrics. None of the pediatric-approved cephems have either MRSA or enterococcal coverage.

Oral Cephalosporins

1. Outpatient UTI and pyelonephritis: Oral cephalosporins of all generations have a place in the treatment of UTI in infants and children. Most oral cephems are excreted largely unchanged by the kidneys, so levels are higher in the urine than in the serum (although not necessarily in renal parenchyma), and thus PK and PD assessment often predicts efficacy, even for some laboratory-reported nonsusceptible pathogens. (53) Chosen agent and route should be driven by degree of illness, therapy compliance of the patient, local antibiograms, and culture results. (54,55)
2. Outpatient CAP, acute otitis media, group A streptococcal pharyngitis, and sinusitis for penicillin allergic patients: Because of high spontaneous remission rates in these entities, they are particularly susceptible to the

Table 3. Nonmeningeal MICs of Common Organisms to Common Cephems and Comparator to Common Penicillin Agents[a] (29)

Antibiotic	MIC of Oral Agents, μg/mL								MIC of Intravenous Agents, μg/mL[b]								
Organism	Cephalothin[c]	Cefuroxime	Cefprozil	Cefpodoxime	Cefdinir	Cefixime	Amoxicillin	Amoxicillin–clavulanic acid	Cefazolin	Cefuroxime	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Ampicillin	Ampicillin–sulbactam	Oxacillin[d]
Staphylococcus aureus	S: ≤8 I: 16 R: ≥ 32	S: ≤4 I: 8–16 R: ≥32	S: ≤8 I: 16 R: ≥32	S: ≤2 I: 4 R: ≥8	S: ≤1 I: 2 R: ≥4	~~CLSI~~	~~CLSI~~	S: ≤4/2 I: - R: ≥8/4	S: ≤ 8 I: 16 R: ≥32	S: ≤8 I: 16–32 R: ≥64	S: ≤8 I: 16–32 R: ≥64	S: ≤8 I: 16–32 R: ≥64	S: ≤8 I: 16 R: ≥32	S: ≤ 8 I: 16 R: ≥32	S: ≤0.25 I: - R: 0.5	S: ≤8/4 I: 16/8 R: 32/16	S: ≤0.25 I: - R: ≥0.5
Streptococcus pneumoniae	~~CLSI~~	S: ≤1 I: 2 R: ≥4	S: ≤2 I: 4 R: ≥8	S: ≤0.5 I: 1 R: ≥2	S: ≤0.5 I: 1 R: ≥2	~~CLSI~~	S: ≤2 I: 4 R: ≥8	As for amoxicillin component	~~CLSI~~	S: ≤0.5 I: 1 R: ≥2	S: ≤1 I: 2 R: 4	S: ≤1 I: 2 R: 4	~~CLSI~~	S: ≤1 I: 2 R: 4	S: ≤2 I: 4 R: ≥8	As for ampicillin component	Disk diffusion zone >20 mm
Haemophilus influenzae	~~CLSI~~	S: ≤4 I: 8 R: ≥16	S: ≤8 I: 16 R: ≥32	S: ≤2	S: ≤1	S: ≤1	Use ampicillin susceptibility	S: ≤4/2 I: - R: ≥8/4	~~CLSI~~	S: ≤4 I: 8 R: ≥16	S: ≤2	S: ≤2	S: ≤2	S: ≤2	S: ≤1 I: 2 R: ≥4	S: ≤2/1 I: - R: ≥4/2	
Escherichia coli	S: ≤8 I: 16 R: ≥32	S: ≤4 I: 8–16 R: ≥32	S: ≤8 I: 16 R: ≥32	S: ≤2 I: 4 R: ≥8	S: ≤1 I: 2 R: ≥4	S: ≤1 I: 2 R: ≥4	Use ampicillin susceptibility	S: ≤8/4 I: 16/8 R: ≥32/16	S: ≤2 I: 4 R: ≥8	S: ≤8 I: 16 R: ≥32	S: ≤ I: 2 R: ≥4	S: ≤1 I: 2 R: ≥ 4	S: ≤4 I: 16 R: ≥32	S: ≤8 I: 16 R: ≥32	S: ≤8 I: 16 R: ≥32	S: ≤8/4 I: 16/8 R: ≥32/16	
Pseudomonas aeruginosa	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	~~CLSI~~	S: ≤8 I: 16 R: ≥32	S: ≤8 I: 16 R: ≥32	~~CLSI~~	~~CLSI~~	~~CLSI~~

~~CLSI~~ : no CLSI susceptibility break points I=intermediate; MIC, mean inhibitory concentration; R=resistance; S=susceptible.

[a]Lower MICs do not imply increased sensitivity, as the MIC must be interpreted with achievable levels of free antibiotic in serum/site of infection. The *Streptococcus pneumoniae* MIC in this table is for nonmeningeal isolates; meningeal MICs for penicillin are 0.06 or less for susceptible and 0.12 or greater for resistant.

[b]Susceptibility to intravenous cephem agents does not imply susceptibility to oral cephem agents

[c]Cephalothin interpretive criteria are used to interpret results of oral agents cefadroxil, cefpodoxime, cephalexin, and loracarbef.

[d]If susceptible to oxacillin, also considered susceptible to nafcillin and anti-staphylococcal cephems

Pollyanna phenomenon, leaving many practitioners with the erroneous impression they are equivalent or worse yet better than narrower drugs. (6) If dosing is optimized, using the maximum dose and highest allowable frequency of administration, some oral cephem agents achieve adequate PK and PD support, but they are still inferior pharmacokinetically to high-dose amoxicillin and amoxicillin-clavulanate for susceptible pathogens. This inferior PK and PD profile further suggests that resistance is likely to develop. (8,9) Thus, a practitioner should not consider the oral cephems first-line agents for these entities unless a child is suspected of being allergic to penicillin or the expanded spectrum of activity is clinically indicated. (42,56) For GAS pharyngitis, some studies have demonstrated benefit of cephems, but the number needed to treat for benefit approximates 50 patients, and relevance to prevention of rheumatic fever is unclear. Given the disadvantages from a cost and resistance perspective, oral cephems are not recommended for first-line treatment, except in those that are allergic to penicillin or in whom the expanded microbiologic profile is indicated. (57,58)

3. Outpatient treatment of skin and musculoskeletal infections: Unlike other oral cephems, cephalexin is relatively well absorbed and not highly protein bound. Clinical studies support efficacy of cephalexin to treat susceptible pathogens in these infections (when oral therapy is appropriate) if used in high doses and given 4 times daily. (59) In addition to MSSA and GAS coverage, cephalexin also has activity against *Kingella kingae*, a common cause of osteoarticular infections in young children. (60)
4. Oral second-line therapy of selected sexually transmitted diseases: Cefixime, 400 mg orally, in a single dose in combination with azithromycin or doxycycline is a second-line option for uncomplicated gonococcal infections of the cervix, urethra, and rectum in patients, but only when intramuscular (IM) ceftriaxone is unavailable. (61) It has limited efficacy compared with ceftriaxone for treatment of gonococcal infections, and there are no data available regarding its use for this indication in children. Importantly, because of the development of antimicrobial resistance in *Neisseria gonorrhoeae*, a test of cure at the site of infection should be performed 1 week after treatment with cefixime. Particular caution should be taken with oral infections, which are often asymptomatic, unrecognized, and more difficult to eradicate than anorectal or urogenital infections. (61,62)

IV Cephems

IV cephem use is largely supported by PK and PD assessment for susceptible organisms, although it is not necessarily superior and is often more broad than necessary. Considerations in their use include appropriate penetration into the infected space (particularly CSF), spectra of activity, and whether a narrower agent can logically be chosen to alleviate development of antibiotic resistance and the development of *Clostridium difficile* colitis. Second-generation IV cephems (cefuroxime), because of inferior PK and PD profiles to first- and third-generation agents for common pathogens, have limited uses in pediatrics. Suggested considerations include the following:

1. IV and IM treatment of UTI and pyelonephritis: Ceftriaxone and cefotaxime are among first-line agents for empiric therapy while cultures are pending. However, as previously noted, none of the cephems have enterococcal coverage. (54,55,63)
2. Treatment of bacterial meningitis and CNS infections: High-dose cefotaxime in combination with ampicillin is a first-line option for empiric therapy in infants younger than 1 month, with consideration of vancomycin if *S pneumoniae* is suspected. Cefotaxime or ceftriaxone in combination with vancomycin is first-line therapy in children older than 1 month; ceftriaxone use is not preferred in young infants because of adverse effects (Table 2). Cefotaxime and ceftriaxone can also be used in combination with other agents (metronidazole and vancomycin initially) for brain abscess or other intracranial infections not associated with trauma, shunts, or postneurosurgical infections, in which one should consider a cephem with expanded resistant gram-negative coverage (cefepime) in combination with vancomycin empirically. (25,52,64)
3. Inpatient treatment of CAP in select circumstances: Ceftriaxone or cefotaxime should only be used in cases where infants and children are not fully immunized or are otherwise at risk for gram-negative pathogens, regions where local epidemiology of invasive pneumococcal strains document high-level penicillin resistance, cases of life-threatening infection, including empyema, or cases of penicillin allergy. In circumstances of severe illness, coverage should be expanded to include MSSA and MRSA, and this is not adequately provided by these cephalosporins. (25,34,41,42) Ceftaroline has MRSA coverage, but dosing in pediatrics is not yet established. (65,66) IV cefuroxime has some MSSA coverage but decreased *S pneumoniae* coverage and no MRSA coverage, so it is not included in

national guidelines for the empiric IV treatment of CAP. (40,42,67,68)

4. Otitis media: A 3-day course of IM or IV ceftriaxone is recommended for therapy for refractory acute otitis media unresponsive to amoxicillin-clavulanate or in situations where an oral antibiotic is not a good option. (56) Notably, no oral cephalosporin provides broader coverage than amoxicillin-clavulanate for refractory otitis media pathogens. The advantage of IM ceftriaxone is the increased period achieved above the MIC for common otitis media pathogens.
5. Inpatient treatment of skin and musculoskeletal infections: cefazolin, alone or in combination with other agents, is an acceptable first-line option in musculoskeletal infection. Choice should also be driven by concern for MRSA clinically and based on local epidemiologic findings, exposures or history concerning for other organisms, and severity of disease, with expanded coverage if concern for these entities exists while cultures are pending. In addition to MSSA and GAS, cefazolin also has *K kingae* coverage, a common cause of osteoarticular infections in young children. (59,60,69)
6. Appendicitis and other intra-abdominal infections: Cefotaxime and ceftriaxone are considered first-line options in combination with metronidazole for appendicitis. (70) Ceftriaxone in combination with metronidazole (both once daily) is demonstrated to be a cost-effective, efficacious, and easily administered regimen. (71,72,73) Older literature supports the use of first- and second-generation cephalosporins, particularly those with anaerobic coverage, such as cefoxitin or cefotetan for appendicitis; however, resistance of *E coli* in recent years has outdated these regimens for cases of perforated appendicitis. Notably, these regimens do not have enterococcal or pseudomonal coverage, but this is not generally necessary in appendicitis.
7. Treatment of selected sexually transmitted infections: Because of increasing resistance, single-dose ceftriaxone, 250 mg IV or IM, in combination with azithromycin or doxycycline is first-line therapy for uncomplicated gonococcal urogenital, anorectal, and pharyngeal infections. Alternatives include ceftizoxime, 500 mg IM, cefoxitin, 2 g IM (with probenecid, 1 g orally), and cefotaxime, 500 mg IM, although their efficacy for pharyngeal infections is less established. Ceftriaxone is also the first-line agent in disseminated gonococcal infections and in conjunctivitis and ophthalmia neonatorum (unless the infant has hyperbilirubinemia, in which case use cefotaxime; Table 2). For parenteral treatment of pelvic inflammatory disease, cefotetan or cefoxitin is recommended in combination with doxycycline for the added anaerobic coverage. Use of other second- or third-generation cephems may also be effective, but there are limited data on their use, and they are less active against anaerobic bacteria. IM ceftriaxone is also recommended in combination with doxycycline for treatment of epididymitis and proctitis. (61,62)
8. Treatment of fever and neutropenia: Cefepime monotherapy is among the first-line agents for fever during chemotherapy-induced neutropenia because of its expanded coverage for *Pseudomonas* spp and other Enterobacteriaceae, as well as gram-positive coverage, including MSSA. Initial concerns over increased mortality with cefepime have largely been mitigated. (74) Some centers use ceftazidime for initial gram-negative coverage. Expanded gram-positive, highly resistant gram-negative, and antifungal coverage should be considered in certain circumstances, in accordance with national fever and neutropenia guidelines. (75,76)
9. Treatment of multidrug-resistant gram-negative infections: Treatment of multidrug-resistant gram-negative infections with cephems is a controversial area because all cephems are at least partially susceptible to inactivation by these β-lactamases. There are usually superior choices available, although in some circumstances, with care to MICs, particular resistance mechanisms, and combination therapy options, cephems may play a role; (14,15,16) consultation with an infectious diseases specialist or pharmacist or an antimicrobial steward may be warranted.
10. Surgical prophylaxis: Cefazolin is used for prevention of postsurgical MSSA infection with certain operations and cefoxitin for prevention of gut and urogenital flora postsurgical infections. These therapies should not continue more than 24 hours, per national guidelines. (77)

Summary

- Cephems are commonly used in pediatrics, and overuse drives microbial resistance (based on strong evidence, epidemiologic observation, laboratory studies, and expert opinion). (2,3,4,8,78)
- For most pediatric pathogens, oral cephems are not pharmacokinetically and pharmacodynamically superior to oral amoxicillin or amoxicillin–clavulanic acid, and for many pathogens they are inferior. Informed use and use of pharmacokinetic and pharmacodynamic assessment in addition to clinical trials and experience can preserve the effectiveness of our antimicrobials (based on some research evidence and consensus). (7,8,9,43,79,80,81,82,83,84)

- National guideline recommendations, which rarely recommend oral cephems, are pharmacokinetically well founded and should be heeded, as should recommendations for antimicrobial stewardship (based on some research evidence and consensus). (41,42,54,56,57,61,62,85,86,87)
- Except for certain clinical entities, cephems should largely be reserved for patients allergic to penicillin or those in whom expanded coverage is indicated based on suspected pathogens and clinical scenario (based on some research evidence and consensus). (44)

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(NOTE: Selected references appear below. Numbers correspond to the references in the article. The complete list of references is available online at: http://pedsinreview.aappublications.org/content/34/11/510/suppl/DCSupplementary_Data.

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1. Cephems have developed a number of ways to confer resistance to antimicrobials. The mechanism of bacterial resistance that is common in gram-positive organisms and is responsible for methicillin-resistant *Staphylococcus aureus* is:
   - A. Expression of β-lactamase enzymes.
   - B. Microbial decrease in penetration of the drug.
   - C. Thickening of the peptidoglycan layer.
   - D. Alteration of the encoded PBP (penicillin binding protein) transpeptidase gene.
   - E. Increased production of efflux pumps.

2. A 2-week-old infant is brought into the hospital with a fever. Blood, urine, and cerebrospinal fluid samples are obtained. Of the following, which is the most appropriate therapy for empiric treatment?
   - A. Ampicillin plus cefotaxime.
   - B. Ampicillin plus cefazolin.
   - C. Cefotaxime plus gentamicin.
   - D. Ampicillin plus vancomycin.
   - E. Ceftriaxone alone.

3. Cephems display time-dependent bactericidal activity. For inpatient infections that require intravenous therapy, the goal should be to keep free drug concentrations higher than the mean inhibitory concentration of the pathogen for:

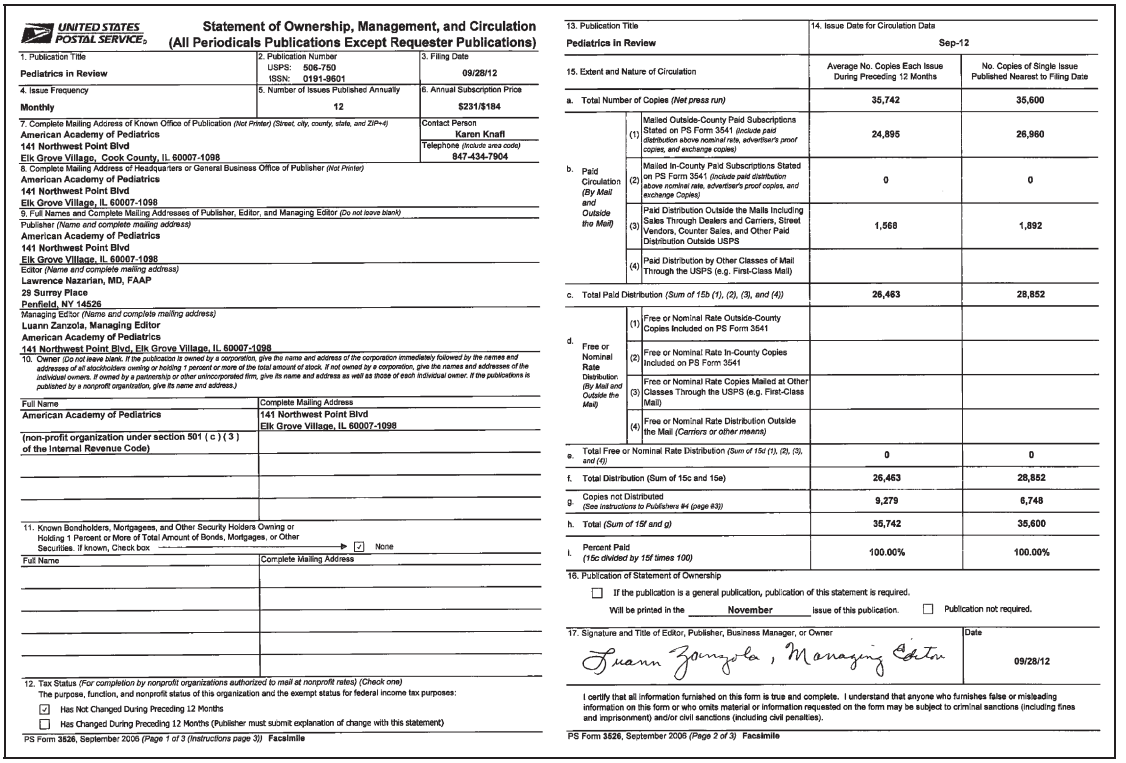
A. 5% to 10% of the day.
B. 30% to 40% of the day.
C. 50% of the day.
D. 60% to 80% of the day.
E. More than 90% of the day.

4. You are admitting a 4-year-old unimmunized child to the hospital with acute onset of fever and cough. There is a right lower lobe infiltrate apparent on the chest radiograph. You suspect community-acquired pneumonia. Which of the following is the most appropriate empiric therapy?

A. Ceftazidime.
B. Ceftriaxone.
C. Cefazolin.
D. Cefepime.
E. Ceftaroline.

5. A 3-year-old child comes to your office with ear pain and fever. You diagnose acute otitis media. The mother tells you that the child has an allergy to penicillin. When you ask about the allergic reaction, she tells you that the last time the child took amoxicillin symptoms included abdominal pain and diarrhea. The best choice of therapy for the child's acute otitis media at this time is:

A. Cefazolin.
B. Clindamycin.
C. Cefepime.
D. Cefixime.
E. Amoxicillin-clavulanate.



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15. Extent and Nature of Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies (Net press run)	35,742	35,600
b. Paid Circulation (By Mail and Outside the Mail) (1) Mailed Outside-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)	24,895	26,960
(2) Mailed In-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange Copies)	0	0
(3) Paid Distribution Outside the Mails Including Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid Distribution Outside USPS	1,568	1,892
(4) Paid Distribution by Other Classes of Mail Through the USPS (e.g. First-Class Mail)		
c. Total Paid Distribution (Sum of 15b (1), (2), (3), and (4))	26,463	28,852
d. Free or Nominal Rate Distribution (By Mail and Outside the Mail) (1) Free or Nominal Rate Outside-County Copies included on PS Form 3541		
(2) Free or Nominal Rate In-County Copies included on PS Form 3541		
(3) Free or Nominal Rate Copies Mailed at Other Classes Through the USPS (e.g. First-Class Mail)		
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e. Total Free or Nominal Rate Distribution (Sum of 15d (1), (2), (3), and (4))	0	0
f. Total Distribution (Sum of 15c and 15e)	26,463	28,852
g. Copies not Distributed (See instructions to Publishers #4 (page #3))	9,279	6,748
h. Total (Sum of 15f and g)	35,742	35,600
i. Percent Paid (15c divided by 15f times 100)	100.00%	100.00%

16. Publication of Statement of Ownership
☐ If the publication is a general publication, publication of this statement is required.
Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Luann Zanzola, Managing Editor — Date: 09/28/12

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