The Infamous Oral Cephalosporins – A Step Up or a Step Down?
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Consider the following patient case:

A 5 year old female is admitted with community-acquired pneumonia and placed on intravenous ceftriaxone for antimicrobial management. A culture returns with *Streptococcus pneumoniae*. Sensitivities return, and both ceftriaxone and penicillin are reported as sensitive. Based on her improvement on ceftriaxone, she is transitioned to oral cefdinir. She fails this oral transition with return of fever and an increased respiratory requirement 3 days later….. Why did this happen?!

Providers consider transition to oral cephalosporin therapy in the treatment of many pediatric infectious conditions. Although they may appear as attractive options due to dosing, taste, allergy, or even price, the suboptimal exposure of drug to susceptible organisms (specifically for *Streptococcus pneumoniae*) in comparison to amoxicillin is subpar and unacceptable.

Many of the oral cephalosporins gained FDA approval in the 1970-80s, with cefdinir coming to the market in the late 1990s (Table 1). These agents caught the attention of many practitioners, offering options for treatment for many pediatric illnesses including otitis media, urinary tract infections, and pneumonia among others; however; the pharmacokinetic profile of these agents needs to be carefully examined to bring to light the general drawbacks of this drug class – poor absorption, high protein binding, and short half-life. Each of these items will be examined here to further clarify the role of these antimicrobials in treatment of infection.

Cephalosporins are active against a variety of gram positive and gram negative organisms by disrupting cell wall synthesis due to inhibition of penicillin binding proteins (PBPs). Their activity and killing is defined best by maintaining antibiotic concentrations above the minimum inhibitory concentration (MIC) of the bacteria for longer periods of the day. This is termed “time-dependent” pharmacodynamics and described by time over the MIC (T>MIC) (Figure 1).

*S. pneumoniae* is a gram positive coccus that is considered part of normal respiratory flora, and as such can in certain conditions cause serious disease. It is the most common bacteria implicated in bacterial otitis media and pneumonia in children. Both otitis media and pneumonia are amongst the most common indications for antimicrobial treatment in children. Amoxicillin remains to be the treatment of choice in both otitis media and pneumonia. This is largely due to amoxicillin’s ability to provide more suitable drug levels at the site of infection versus oral cephalosporins.

When evaluating the preferred pharmacodynamic parameter for cephalosporins and penicillins, T>MIC, it is clear that amoxicillin provides greater coverage than the oral cephalosporins for *S. pneumoniae* (Figure 2). We target T>MIC of 30-40% of the day in a patient well enough to be managed outpatient, 60-80% in an inpatient, and greater than 90% in an immunocompromised patient. High dose amoxicillin (90mg/kg/day) divided in 3 doses provides 12 hours of time above the MIC of a sensitive *S. pneumoniae* isolate (Panel A). Comparatively, high dose cefdinir (30mg/kg/day) divided in 2 doses, and the ever-popular standard dose cefdinir (14mg/kg/day) administered once daily only provide 5 hours and 2 hours of time above the MIC of the same *S. pneumoniae* isolate, respectively (Panel C). Thus though cefdinir is a third generation cephalosporin, its killing power is really not at all comparable to ceftriaxone, a common misconception. Note amoxicillin in high dose divided three times daily provides more killing time than divided twice daily for treatment of infections outside the ear; within the ear the half-life is longer, so killing time is extended.
The subpar exposure of the cephalosporin at the site of infection is largely related to the specific pharmacokinetics of each oral cephalosporin (Table 1). Only unbound drug is active, making the poor oral absorption and the high protein binding of cefuroxime, cefpodoxime, and cefdinir their detriment. The short half-lives also contribute to the inability of oral cephalosporins to provide optimal T>MIC. Truly, cephalexin is the only cephalosporin that offers the pharmacokinetic parameters to lend itself to treatment; however, its activity against \textit{S. pneumoniae} is debated, again making it an undesirable option for treatment of otitis media and pneumococcus. It is, however, a great option in treatment of musculoskeletal infections due to its coverage of methicillin-susceptible \textit{Staphylococcus aureus} (amoxicillin does not provide coverage of MSSA).

Consider the same patient mentioned earlier. Based on the inferior pharmacokinetics of cefdinir in comparison to amoxicillin for treatment of \textit{S. pneumoniae} pneumonia, the most appropriate choice for an oral transition is amoxicillin. In conclusion, although providers may think that “broadening” to an oral cephalosporin provides better coverage of \textit{S. pneumoniae}, the pharmacokinetics show that indeed it is a step down of amoxicillin therapy.

<table>
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<th>Drug (Brand)</th>
<th>Generation</th>
<th>Available As</th>
<th>Generic Available?</th>
<th>Cost</th>
<th>Oral Absorption</th>
<th>Protein Binding</th>
<th>Half-Life (hours)</th>
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<td>$</td>
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**Figure 1: Different Pharmacodynamic Targets of Antimicrobials**

Abbreviations: AUC = antibiotic area under the curve; AUC/MIC = the ratio of the antibiotic area under the curve to the time above the minimum inhibitory concentration needed to inhibit microorganisms; Cmax = the maximum serum concentration needed to inhibit microorganisms; Cmax/MIC = ratio of maximum serum concentration (or peak) to the time above the minimum inhibitory concentration needed to inhibit microorganisms; MIC = minimal inhibitory concentration; T = time.
Figure 2: Pharmacokinetic Modeling of Amoxicillin and Oral Cephalosporins Against Sensitive *Streptococcus pneumoniae*

Panel A: Amoxicillin Modeling Against Sensitive *Streptococcus pneumoniae* (MIC = 2 mcg/mL)

Amox HD-TID = amoxicillin 90mg/kg/day divided in 3 doses; Amox HD-BID = amoxicillin 90mg/kg/day divided in 2 doses; Amox LD-TID = amoxicillin 45mg/kg/day divided in 3 doses.

Panel B: Cefuroxime Modeling Against Sensitive *Streptococcus pneumoniae* (MIC = 1 mcg/mL)

Cefuroxime = cefuroxime 30 mg/kg/day divided in 2 doses.

Panel C: Cefpodoxime and Cefdinir Modeling Against Sensitive *Streptococcus pneumoniae* (MIC = 0.5 mcg/mL)

Cefdinir HD-BID = cefdinir 30mg/kg/day divided in 2 doses; Cefdinir SD-BID = 14mg/kg/day divided in 2 doses; Cefdinir SD-QD = cefdinir 14mg/kg/day administered once daily; Cefpodoxime = cepodoxime 10mg/kg/day divided in 2 doses.
References:


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