In Vitro Activity of Ceftaroline against Clinical Isolates of Streptococcus pneumoniae Recovered in 43 U.S. Medical Centers during 2010-2011

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The in vitro activity of ceftaroline, a recently introduced parenteral cephalosporin, was assessed versus 1,750 isolates of Streptococcus pneumoniae recovered from patients with a variety of pneumococcal infections in 43 U.S. medical centers during 2010-2011. Using a breakpoint of ≤0.5 μg/ml for susceptibility, all of the isolates were found to be susceptible to ceftaroline. Ceftaroline MICs were consistently 16-fold lower than ceftriaxone MICs. Among the isolates characterized in this investigation, 38.9% were found to be nonsusceptible to penicillin (oral penicillin breakpoints) and 9.1% were nonsusceptible to ceftriaxone (nonmeningitis breakpoints).

Streptococcus pneumoniae is an important cause of a variety of human infections. These include community-acquired pneumonia (CAP), acute maxillary sinusitis, acute otitis media, and bacterial meningitis. Indeed, S. pneumoniae remains the most common bacterial cause of all of these infectious diseases, at least in developed parts of the world.

As with most bacterial pathogens of humans, antimicrobial resistance has emerged as a major problem with S. pneumoniae (5, 12, 20). In response to increasing rates of antimicrobial resistance with S. pneumoniae during the 1990s, the 7-valent conjugate-antigen pediatric pneumococcal vaccine, Prevnar (PCV-7; Wyeth), was introduced in February 2000 with the aim of preventing invasive pneumococcal infections and otitis media in children. It was inclusive of those pneumococcal serotypes that were most often resistant. Widespread use of the PCV-7 vaccine initially seemed to have the desired effect, leading to a diminishing prevalence of pneumococcal infections in children, and perhaps adults, and a concomitant decrease in resistance (1, 4, 13, 15, 19). However, the positive impact of PCV-7 was transient. Largey as a consequence of capsular switching and as a result of the emergence of pneumococcal serotypes that had existed previously but at low levels, new antimicrobial-resistant serotypes, in particular serotypes 19A and 6C, soon emerged that escaped the effect of the vaccine, and the problem of antimicrobial resistance with S. pneumoniae again began to grow (6, 7, 8, 9, 17, 21). This cycle has prompted the development of a second, 13-valent pediatric pneumococcal vaccine, PCV-13 (Pfizer), which was introduced into clinical practice in March 2010. It is reasoned that this vaccine, which is inclusive of serotypes contained in the 7-valent vaccine plus those that have emerged since its introduction, will have a positive impact on resistance rates. Clearly, however, irrespective of advances in vaccine immunoprophylaxis, there remains a need for antimicrobial agents that effectively treat pneumococcal infections, particularly those caused by antimicrobial-resistant strains.

In March of 2011, ceftaroline fosamil (Teflaro; Forest Laboratories), a parenteral broad-spectrum cephalosporin, was introduced into clinical practice in the United States. It has FDA-approved indications for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia (CAP) in patients requiring hospitalization but not admission into an intensive care unit setting. Its use is currently restricted to patients 18 years of age and older. Ceftaroline is not yet indicated for use in treating CAP caused by MRSA, as patients with MRSA bronchopulmonary infections were specifically excluded from the phase III clinical trials of CAP which led to its approval. That said, ceftaroline is clearly of some consideration in the treatment of CAP caused by S. pneumoniae.

Among 1,337 isolates of S. pneumoniae recovered from patients with bacteremic pneumonia from multiple European medical centers during 2007-2008, the highest ceftaroline MIC was 0.5 μg/ml (18). The same observation was made in a survey of 891 S. pneumoniae isolates obtained from patients in 22 U.S. medical centers during 2008 (10) and in a study of 1,340 pneumococcal isolates recovered from patients in numerous medical centers in the United States and Europe in 2008-2009 (11). McGee and colleagues examined the activity of ceftaroline against an international collection of 120 strains of S. pneumoniae, all with cefotaxime MICs of ≥4 μg/ml, and 18 laboratory-derived mutants of S. pneumoniae R6 with various penicillin binding protein (PBP) alterations and found ceftaroline to be consistently more active than either cefotaxime or ceftriaxone, i.e., a MIC90 of 0.5 μg/ml versus a MIC90 of 8 μg/ml (16). These results are consistent with the observations of Kosowska-Shick and coworkers, who demon-
TABLE 1 In vitro activities of penicillin, ceftaroline, and ceftriaxone against 1,750 isolates of Streptococcus pneumoniae recovered from 43 U.S. medical centers in 2010-2011

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>No. (%) of isolates with the indicated MIC (µg/ml):</th>
<th>0.008</th>
<th>0.015</th>
<th>0.03</th>
<th>0.06</th>
<th>0.125</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td></td>
<td>138 (7.9)</td>
<td>590 (33.7)</td>
<td>224 (13.9)</td>
<td>94 (5.4)</td>
<td>130 (7.4)</td>
<td>81 (4.6)</td>
<td>50 (2.8)</td>
<td>91 (5.2)</td>
<td>102 (5.8)</td>
<td>224 (12.8)</td>
<td>6 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Ceftaroline</td>
<td></td>
<td>976 (55.8)</td>
<td>162 (9.3)</td>
<td>96 (5.5)</td>
<td>170 (9.7)</td>
<td>295 (16.9)</td>
<td>38 (2.2)</td>
<td>13 (0.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>85 (4.9)</td>
<td>280 (16)</td>
<td>588 (33.6)</td>
<td>166 (9.5)</td>
<td>103 (5.9)</td>
<td>88 (5.0)</td>
<td>72 (4.1)</td>
<td>211 (12.1)</td>
<td>122 (7.0)</td>
<td>24 (1.4)</td>
<td>8 (0.5)</td>
<td>3 (0.2)</td>
</tr>
</tbody>
</table>

strated the remarkable binding affinities of ceftaroline for the PBPs of S. pneumoniae that are most often responsible for β-lactam antimicrobial resistance (14).

In view of these observations, it was of interest to systematically examine the profile of in vitro activity of ceftaroline against a large, nationally representative collection of current S. pneumoniae isolates from the United States.

During the 6-month period of October 2010 through March 2011, a total of 1,750 isolates of S. pneumoniae were obtained in 43 medical centers distributed throughout the United States (see the Acknowledgments) and shipped to the University of Iowa for further characterization. Isolates were recovered from unique patients who had pneumococcal infection. Blood cultures were the source of 428 isolates (24.5%), 16 were recovered from cerebrospinal fluid (CSF) (0.9%), 840 were recovered from lower respiratory tract specimens (48.0%), 110 were recovered from sinus specimens (6.3%), 147 were recovered from middle ear fluid (6.3%), and 209 were from unknown sources (11.9%). The ages of patients from whom the isolates were recovered were as follows: 5 years old (y/o), 367 (20.1%); 6 to 20 y/o, 173 (9.9%); 21 to 64 y/o, 367 (20.1%); 65 y/o, 376 (21.5%). Isolates were recovered from unique patients (45.7%) and 942 male patients (53.8%).

All isolates were identified as S. pneumoniae by conventional microbiology procedures. MICs of penicillin, ceftaroline, and ceftriaxone were determined by broth microdilution in Mueller- Hinton broth supplemented with 5% horse blood (100-µl final volume) with an inoculum size of 1 × 10⁵ to 5 × 10⁵ CFU/ml according to the guidelines of the Clinical and Laboratory Standards Institute (2). Streptococcus pneumoniae ATCC 49619 was used as a quality control strain for all MIC determinations.

MIC distributions for the S. pneumoniae isolates examined in this investigation are presented in Table 1. There appeared to be a distinct bimodal distribution of ceftaroline MICs. The majority of isolates (55.8%) had MICs of ≤0.008 µg/ml; the highest MIC, of 0.5 µg/ml, occurred in only 13 isolates (0.7%). For purposes of comparison, penicillin and ceftriaxone MICs are also depicted in Table 1. Ceftaroline was consistently found to be ca. 16-fold more active on a per-weight basis than ceftriaxone.

In Table 2, ceftaroline and ceftriaxone MICs are sorted according to the penicillin MIC category of the S. pneumoniae isolates characterized in this study. Generally, the higher the penicillin MICs, the higher the ceftaroline and ceftriaxone MICs. Note that based on MIC breakpoints intended to predict the clinical activity of parenterally administered penicillin for the treatment of nonmeningeal infections (3), only 6 isolates (0.3%) were found to be high-level penicillin resistant, with a MIC of 8 µg/ml, and 1,520 isolates (86.9%) were found to be susceptible. However, given that parenteral penicillin is rarely used these days to treat pneumococcal infections in any site, arguably a more relevant assessment of penicillin effect is provided by an analysis which is based on orally administered penicillin breakpoints. Using the CLSI breakpoints for oral penicillin (3), 1,066 isolates (60.9%) were classified as being penicillin susceptible, 352 (20.1%) were classified as being intermediate, and 332 (19.0%) were classified as being resistant.

The CLSI has not yet established breakpoints for use in interpreting MIC values with ceftaroline against S. pneumoniae. The FDA, however, has established a breakpoint of ≤0.25 µg/ml for classifying S. pneumoniae isolates as being susceptible. Given the absence of pneumococcal isolates with higher ceftaroline MICs in phase III clinical trials, no breakpoints have been promulgated for classifying isolates as intermediate or resistant. Based on an FDA breakpoint of ≤0.25 µg/ml for the susceptible category, 99.3% of isolates were classified as being susceptible (see Table 2).

TABLE 2 In vitro activities of ceftaroline and ceftriaxone against 1,750 recent clinical isolates of Streptococcus pneumoniae sorted according to penicillin resistance category

<table>
<thead>
<tr>
<th>Penicillin resistance category</th>
<th>MIC (µg/ml)</th>
<th>No. of isolates</th>
<th>Ceftaroline MIC (µg/ml)</th>
<th>Ceftriaxone MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral administration</td>
<td></td>
<td></td>
<td>MIC₅₀</td>
<td>MIC₉₀</td>
</tr>
<tr>
<td>Susceptible</td>
<td>≤0.06</td>
<td>1,066</td>
<td>0.008</td>
<td>0.008</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.12–1</td>
<td>352</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Resistant</td>
<td>≥2</td>
<td>332</td>
<td>0.12</td>
<td>0.25</td>
</tr>
<tr>
<td>Parenteral administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td>≤2</td>
<td>1,520</td>
<td>0.008</td>
<td>0.06</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4</td>
<td>224</td>
<td>0.12</td>
<td>0.25</td>
</tr>
<tr>
<td>Resistant</td>
<td>≥8</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a CLSI MIC interpretive criteria for penicillin against Streptococcus pneumoniae when administered orally (3).
b CLSI MIC interpretive criteria for penicillin against Streptococcus pneumoniae when administered parenterally in the treatment of nonmeningeal infections (3).
c The ceftaroline MICs of these six strains were as follows: 0.12 µg/ml (n = 1), 0.25 µg/ml (n = 1), and 0.5 µg/ml (n = 4).
d The ceftriaxone MICs of these six strains were as follows: 2 µg/ml (n = 2), 8 µg/ml (n = 2), and 16 µg/ml (n = 2).

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the isolates examined in this study would thus have been classified as being susceptible to ceftaroline.

In conclusion, in this systematic assessment of the in vitro activity of ceftaroline against a large and nationally representative collection of *S. pneumoniae* isolates obtained during 2010, ceftaroline was found to be nearly uniformly active irrespective of the degree of penicillin resistance present among test strains. Further, ceftaroline was consistently 16 times more active than ceftriaxone. Based on these observations, it is likely that this agent would be of utility in the treatment of pneumococcal bronchopulmonary infections.

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REFERENCES