Introduction

One of the prominent challenges in managing community-acquired bacterial skin and skin structure infections (ABSSSI) in today’s healthcare system is the changing pattern of causative pathogens and antibiotic susceptibilities. In recent years, there has been a significant increase in the prevalence of community-acquired MRSA requiring hospital intervention caused by antibiotic-resistant pathogens, in particular methicillin-resistant Staphylococcus aureus (MRSA) strains (or strains resistant to previously available ß-lactam antibiotics).1-3 Beginning in the mid-1990s, the prevalence of MRSA shifted from healthcare-associated MRSA (HA-MRSA) to community-associated MRSA (CA-MRSA) strains. CA-MRSA is now the leading identifiable cause of purulent skin and soft tissue infections (SSTIs) in emergency department (ED) patients in the United States.4-6 The primary cause of MRSA in noncultivable skin and soft tissue infections are MRSA strains resistant to ß-lactams (i.e., ß-lactamase-mediated resistance to ß-lactams such as ß-lactamase ß-hemolytic streptococci (mostly Streptococcus pyogenes).7-9

New Broad-Spectrum Cephalosporin for Monotherapy of ABSSSI

Cefozopran fosamil is a novel, broad-spectrum cephalosporin approved in October 2010 for protracted treatment of ABSSSI in adults 18 years and older caused by:11-20

• Susceptible gram-positive S. aureus (MSSA and MRSA), ß-hemolytic streptococci, S. pyogenes, and S. agalactiae bacteria
• Susceptible gram-negative Klebsiella pneumoniae, K. oxytoca, and Echerichia coli bacteria

Cefozopran fosamil is not active against gram-negative bacteria producing extended-spectrum ß-lactamases from the TEM, SHV, or CTX-M families, 99% of the MRSA strains (causing >95% of all-cause mortality with tigecycline versus comparable antibiotics in a pooled analysis of clinical trials). However, the greatest increase in risk of death with tigecycline was seen in patients with ventilator-associated pneumonia—an uncommon occurrence—and there were no significant differences in mortality in complicated skin infection trials (1.4% vs 0.7%; 95% CI: 4.3–1.7). Similarly, although the novel cephalosporin cefozopran fosamil was non-inferior to tigecycline by the FDA at the time of writing, the IDSA Guidelines recognized it as a potential option pending its approval.

Finally, and of high importance, the IDSA Guidelines re-emphasize the principle that MSSA should preferably be treated with a ß-lactam agent, which has been known to be more effective than vancomycin for infections due to susceptible isolates.11-20

Antibiotic Choices

In determining the appropriate antibiotic choice, one should consider the likely causative microorganism(s), the site and severity of the infection, and adequate coverage based on the IDSA 2010 Guidelines for skin and soft tissue infections susceptibilities. Given the high and growing prevalence of CA-MRSA in ABSSSI, empirical use of agents active against CA-MRSA is suitable for all patients with SSTIs who have normal renal function and are not obese.

Table 4. Clinical Outcomes: Ceftaroline

<table>
<thead>
<tr>
<th>Infection type</th>
<th>Overall clinical cure (%)</th>
<th>Overall microbiological cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline</td>
<td>93.6%</td>
<td>93.7%</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>92.3%</td>
<td>93.7%</td>
</tr>
</tbody>
</table>

A higher microbiological response was observed with vancomycin plus aztreonam against gram-negative infections. Cefozopran fosamil was comparable to aztreonam against E. coli and K. pneumoniae, but was more active against Pseudomonas aeruginosa and Proteus mirabilis than ceftaroline.21-25

Cefozopran monotherapy is as effective and well tolerated as ceftaroline plus aztreonam in the management of patients with Absssi,24 with a clinical cure rate comparable to that of vancomycin plus aztreonam.22,23 The most common adverse events seen with cefozopran, occurring in ≤2% of patients, include diarrhea, nausea, and vomiting.21-23 Treatment of difficult-dosed diarrheas has been reported with cefozopran.21-23 Cefazopran represents an important addition to the armamentarium of anti-microbial active against pathogens that commonly cause ABSSSI.14-20

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Cefozopran, a prodigiously converted to the active form following administration by 1-hour IV infusion, has been shown in vitro to act by inhibiting penicillin binding protein 2a (PB2a), the PB2a of PBP unique to MRSA strains.24 In vivo, cefozopran has demonstrated initial potency and coverage against multidrug-resistant gram-positive bacteria, including MRSA strains, VISA or VRSA strains, PRE-producing strains, strains resistant to other classes of antimicrobial agents (such as glycopeptides, ß-lactamase ß-hemolytic streptococci, TMP-SMX, and linezolid), and strains with extended-spectrum ß-lactamase and ß-lactamase ß-hemolytic streptococci species is the more predominant pathogen. Acidification of the urine to urinary tract infections with vancomycin-resistant enterococci (VRE) and organisms that have altered the principle that MSSA should preferably be treated with a ß-lactam agent, which has been known to be more effective than vancomycin for infections due to susceptible isolates.11-20

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Table 2. Antibiotics Commonly Employed to Treat ABSSSI

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Group</th>
<th>Agent</th>
<th>Commonly employed for skin and soft tissue infections in ABSSSI</th>
<th>Susceptibility breakpoint MIC ≤1 µg/mL</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Glycopeptide</td>
<td>Vancomycin</td>
<td>Commonly used for skin and soft tissue infections in ABSSSI</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>
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