Clinical development of CEM-102 (fusidic acid) has recently begun in the United States for chronic oral treatment of prosthetic joint infections. To support this development, the in vitro activity of fusidic acid against important Staphylococcus aureus clones and resistance phenotypes was determined. Against 51 such isolates, the modal fusidic acid MIC was 0.12 μg/ml (range, 0.06 to 0.25 μg/ml for 49 isolates). This level of in vitro fusidic acid activity underscores the potential clinical utility of this compound in the United States.

Staphylococcus aureus is a prominent pathogen of both community- and hospital-acquired infections worldwide and is the most common pathogen isolated from skin and skin structure infections (1). Treatment of S. aureus infections has become more complicated with the increasing frequency of methicillin-resistant S. aureus (MRSA) since 1990 and, though rare, the emergence of S. aureus with reduced susceptibility to other first-line agents (vancomycin, linezolid, daptomycin) (2–6).

Fusidic acid has been approved for use in Europe to treat skin infections such as impetigo and dermatitis since the 1960s (7, 8). However, a number of European countries have seen increases in fusidic acid resistance among S. aureus isolates over the past few decades largely mediated by acquisition of fusB and/or fusC (which can be plasmid associated) and, depending on the geographic area, mutations within fusA (8–10). Until recently, fusidic acid had not been proposed for use in the United States, though current surveillance has shown that fusidic acid is potent against staphylococci in the United States and resistance to fusidic acid among S. aureus isolates in the United States is currently rare (less than 0.3% among S. aureus isolates) (10, 11). Fusidic acid is now in clinical development in the United States for chronic oral treatment of prosthetic joint infections. The strategy for this development utilizes a novel oral dosing regimen design that maximizes bioavailability to increase coverage and minimize the potential for resistance development (2, 12, 13). In support of fusidic acid’s development, it is important to establish the activity of fusidic acid against prominent MRSA clones and isolates of S. aureus resistant to other key therapeutic agents.

(This study was presented in part at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, MA, September 2010.)

In this study, single patient S. aureus isolates not susceptible to various key antimicrobial agents were selected from the Eurofins repository (Chantilly, VA) and the Network on Antimicrobial Resistance in S. aureus (NARSA; developed and supported by NIAID) repository. Among those from the Eurofins repository, eight were isolated from the bloodstream, five were isolated from respiratory tract infections, three were isolated from skin/wound infections, and four were isolated from other body sites. In addition, strains of the following prominent clones were randomly selected and tested: USA300 (n = 7) and USA400 (n = 3), prevalent among community-associated strains, and USA100 (n = 8), USA600 (n = 1), and USA800 (n = 1), prevalent among hospital-associated strains. The Iberian, Brazilian/Hungarian, UK-EMRSA-15, UK-EMRSA-16, and Berlin clones and a south German clone were also selected from the Eurofins and NARSA repositories. Susceptibility testing of the S. aureus isolates was conducted in accordance with the CLSI M7-A8 and CLSI M100-S20 methods (14, 15). Fusidic acid quality control MIC ranges were monitored on the basis of the EUCAST-recommended ranges for fusidic acid against S. aureus ATCC 29213 (16).

The profiles of the 51 strains tested in this study are summarized in Table 1. Although the fusidic acid results are displayed according to key phenotype or clonal groups, certain strains may be represented in more than one group. For example, 4 of the 13 vancomycin-intermediate S. aureus (VISA) strains were also nonsusceptible to daptomycin, so they also comprised 4 of the 7 daptomycin-nonsusceptible strains. Nonetheless, among the 51 S. aureus strains, 49 (96%) demonstrated fusidic acid MICs that were ≤0.25 μg/ml, with the majority of MICs (90%) falling within the range of 0.06 to 0.12 μg/ml. This range of fusidic acid MICs was maintained across all resistant phenotypes and clonal groups. The two strains that had higher fusidic acid MICs (4 and 8 μg/ml) were two VISA strains also nonsusceptible to daptomycin. According to current EUCAST fusidic acid interpretive breakpoints for Staphylococcus spp. (≤1 μg/ml for susceptible, >1 μg/ml for resistant; EUCAST clinical breakpoints—bacteria, v.1.3), these were the only two strains that would be considered resistant to fusidic acid at European doses. It is of interest to note that these two strains with elevated fusidic acid MICs were also relatively refractory to the in vitro activities of both vancomycin and daptomycin. Whether this is coincidence or is due to some related mechanism is uncertain, although this seems unlikely, as fusidic acid targets protein synthesis and the other two agents target the cell wall.

The findings of this study demonstrate that fusidic acid maintained potent in vitro activity against selected S. aureus strains, including those from Europe, with resistance to currently utilized
TABLE 1 Distribution of fusidic acid MICs against S. aureus

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>0.03</th>
<th>0.06</th>
<th>0.12</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>51</td>
<td>12</td>
<td>34</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>VISA</td>
<td>13</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRSA</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin NS</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epidemic MRSA</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>USA300, USA400</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA100, USA600, USA800</td>
<td>10</td>
<td>1</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Fifty-one strains were tested.
b VISA, vancomycin-intermediate S. aureus; VRSA, vancomycin-resistant S. aureus; NS, nonsusceptible; R, resistant.
c MICs for a subset of evaluated isolates are represented in more than one group due to overlap (e.g., coreistance; the two strains with fusidic acid MICs of 4 and 8 μg/ml were both VISA and nonsusceptible to daptomycin).
d UK-EMRSA-15, UK-EMRSA-16, Iberian, Brazilian/Hungarian, Berlin, and south German clones (Health Protection Agency, United Kingdom).
e Pulsotype characterized by NARSA (NIAID) to be associated with community-acquired S. aureus.
f Pulsotype characterized by NARSA (NIAID) to be associated with hospital-acquired S. aureus.

agents and representatives of the most common clones currently encountered in the United States. This level of activity is consistent with the high level of activity found in generalized surveillance initiatives for U.S. S. aureus isolates (11, 17) and underscores the potential that this compound has for the management of acute bacterial skin and skin structure infections encountered in the United States.

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