Comparative In Vitro Inhibitory and Killing Activity of Cefpirome, Ceftazidime, and Cefotaxime Against *Pseudomonas aeruginosa*, Enterococci, *Staphylococcus epidermidis*, and Methicillin-Susceptible and -Resistant and Tolerant and Nontolerant *Staphylococcus aureus*

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With a macrotube dilution method, MICs and MBCs were determined for three aminothiazolyl cephalosporins, cefpirome (HR 810), ceftazidime, and cefotaxime, against *Pseudomonas aeruginosa*, enterococci, *Staphylococcus epidermidis*, and methicillin-resistant, -susceptible, and -tolerant strains of *Staphylococcus aureus*. Comparatively, cefpirome was the most active agent against all gram-positive cocci, including enterococci and methicillin-resistant *S. aureus*, and was as active as ceftazidime against *P. aeruginosa*. MBCs of cefpirome were within two dilutions of the MICs for 91% of *P. aeruginosa* and 90% of gram-positive cocci strains tested, except methicillin-resistant *S. aureus*, for which the MBCs were within three dilutions for 90% of strains.

Although numerous cephalosporins have been developed recently, there remain wide gaps in their in vitro activity and therapeutic efficacy. Most third-generation agents have expanded activity against aerobic gram-negative rods, including *Pseudomonas aeruginosa* (1, 2, 15). However, resistance to and enterococcal superinfections associated with many of these agents have developed (3, 14). With their structural alteration, these agents have less activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* than the first-generation cephalosporins (2, 4, 8, 9). In addition, the emergence and increasing frequency of methicillin-resistant *S. aureus* (MRSA) strains (7) have led to therapeutic dilemmas. Some of these strains appear to be susceptible to cephalosporins by the disk method but resistant by quantitative dilution testing (16). Generally, the use of cephalosporins against MRSA and enterococci in humans has been discouraged because of inconsistent therapeutic results (4–7, 16). The clinical significance of tolerance in *S. aureus* strains has also led to diverse therapeutic approaches with more limited roles for the cephalosporins (12).

Cefpirome (HR 810) is a new cefotaxime-like aminothiazolyl cephalosporin. It has been reported to have an expanded spectrum of activity which includes problem pathogens such as *P. aeruginosa*, enterococci, and staphylococci (1, 10, 11, 13). These studies used various methods, including broth microtitre and agar dilution, to determine MICs, but do not report MBCs and therefore do not give information about tolerance (MBC/MIC, >32) or the bactericidal activity of these agents.

Consequently, we studied the inhibitory and bactericidal activity of cefpirome, ceftazidime, another new aminothiazolyl cephalosporin, and cefotaxime by a macrotube dilution method against these problem pathogens.

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allowed no visible growth. A 0.05-ml portion was carefully
removed from each tube and subcultured onto a blood agar
plate to determine the MBC (99.9% kill). All plates were
incubated overnight, and colony counts were performed.

Growth control cultures and broth and drug sterility tests
were included in each run. In addition, S. aureus ATCC
25923, S. aureus RMA096, and P. aeruginosa ATCC 27853
were included as controls. The MICs of cefpirome, cefotax-
ine, and ceftazidime for S. aureus ATCC 25923 were 0.25 to
0.5, 1, and 8 μg/ml, respectively; the MBCs were 1 to 8, 2,
and 32 μg/ml, respectively. For P. aeruginosa the MICs
were 4 to 8, 8 to 16, and 2 μg/ml and the MBCs were 4 to 16,
32, and 2 μg/ml of cefpirome, cefotaxime, and ceftazidime,
respectively. S. aureus RMA096 was tested seven times to
study the reproducibility of the results from the method. The
MICs were within one dilution in all instances. MBCs were
within one dilution in 19 of 22 tests, within three dilutions in
two instances, and within five dilutions in one instance.

The activity of cefpirome, ceftazidime, and cefotaxime
against the test strains is shown in Table 1. In general,
cefpirome was much more active than cefotaxime and
ceftazidime against all gram-positive bacteria tested. All S.
epidermidis, MSSA, and MRSA-T strains tested were highly
susceptible (MIC for 90% of strains [90% MIC], <0.5 μg/ml)
to cefpirome. All MRSA strains and enterococci tested were
inhibited (90% MIC, <8 μg/ml) by cefpirome, but nine
MRSA strains and five enterococci had MBCs of 32 to 128
μg/ml. The addition of 5% NaCl to the medium increased
MICs and MBCs of cefpirome against MRSA by one to two
dilutions. The clinical and biological significance of this
effect of salt is unclear. In general, ceftazidime had rela-
tively poor activity against all gram-positive cocci tested.
Cefotaxime had good activity against S. epidermidis, MSSA,
and MSSA-T strains but poor activity against MRSA and
enterococci. Cefpirome was more active than cefotaxime
and comparable in activity to ceftazidime against P. aeruginosa. MBCs were within two dilutions of the MIC for
cefpirome, indicating bactericidal activity, for 91% of P.
aeruginosa and 90% of MSSA and S. epidermidis strains,
including those previously found to be tolerant to a variety of antimicrobial agents.

Our results showed that cefpirome has good activity
against P. aeruginosa and excellent activity against gram-
positive organisms. It was active against S. aureus, including
MSSA, MSSA-T, and MRSA strains, S. epidermidis, and
enterococci, but was less active against enterococci and
MRSA than against MSSA isolates. Only one enterococcal
(MIC, 16 μg/ml; MBC, 64 μg/ml) and one MRSA strain
(MIC, 16 μg/ml; MBC, 128 μg/ml) were relatively resistant
to cefpirome. By comparison, these isolates are usually not
susceptible to cephalosporins. This is in accord with the
MIC determinations reported by other investigators (1, 10,
13). In addition, our results showed that cefpirome was
bactericidal, with MBCs within two dilutions of the MICs for
almost all isolates tested except MRSA. Although the bacte-
ricidal levels were usually higher than the inhibitory levels,
25% of enterococci and 10% of MRSA isolates were still
susceptible (≤8 μg/ml), and 50% of enterococci were in the
moderately susceptible range (<16 μg/ml) (11). Although the
clinical significance of tolerance in S. aureus remains un-
clear, these isolates were more susceptible to cefpirome
(MIC range, 0.25 to 2 μg/ml) than to cefotaxime (MBC
range, 2 to 64 μg/ml) or ceftazidime (MBC range, 8 to 16
μg/ml).

This in vitro activity has been correlated with in vivo
activity in laboratory animals (13). Kiesel et al. (13) studied
the comparative activity of cefpirome in the prevention and
treatment of localized and systemic infections in both mice
and rats. Cefpirome was found to be superior to ceftazidime,
cefotaxime, ceftriaxone, cefoperazone, and moxalactam,
with a 50% effective dose of 0.8 to 6.3 μg/ml against
experimental MSSA infections. They also found it to be

### Table 1. Activity of cefpirome, cefotaxime, and ceftazidime against P. aeruginosa, enterococci, S. epidermidis, and S. aureus

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of strains</th>
<th>Agent</th>
<th>MIC (μg/ml)</th>
<th>MBC (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range</td>
<td>90%*</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>11</td>
<td>Cefpirome</td>
<td>1-16</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefotaxime</td>
<td>8-256</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td>1-8</td>
<td>8</td>
</tr>
<tr>
<td>Enterococci</td>
<td>10</td>
<td>Cefpirome</td>
<td>0.5-16</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefotaxime</td>
<td>8-&gt;256</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td>2-&gt;256</td>
<td>256</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>10</td>
<td>Cefpirome</td>
<td>0.125-0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefotaxime</td>
<td>0.125-4</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td>0.125-32</td>
<td>16</td>
</tr>
<tr>
<td>MSSA</td>
<td>10</td>
<td>Cefpirome</td>
<td>0.25-0.5</td>
<td>0.5</td>
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<tr>
<td></td>
<td></td>
<td>Cefotaxime</td>
<td>1-2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td>4-8</td>
<td>8</td>
</tr>
<tr>
<td>MSSA-T</td>
<td>12</td>
<td>Cefpirome</td>
<td>0.125-0.5</td>
<td>0.5</td>
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<tr>
<td></td>
<td></td>
<td>Cefotaxime</td>
<td>1-2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td>4-8</td>
<td>8</td>
</tr>
</tbody>
</table>
| MRSA (24-h incuba-
| 10            | Cefpirome | ≤1-16      | 8           | 8-128       | 128         |
| tion)            |               | Cefotaxime | 8-256      | 128         | 32->256     | >256        |
|                   |               | Ceftazidime | 32-128     | 128         | 32->256     | >256        |

* 90%, MIC for 90% of the isolates.  
* 90%, MBC for 90% of the isolates.
effective against experimental enterococcal, MRSA, and P. aeruginosa infections. Clinical evaluation of cefpirome seems warranted.

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LITERATURE CITED