



# Comparative activity of newer antibiotics against gram-negative bacilli

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■ The in vitro activities of cefoperazone, cefotaxime, ceftriaxone, ceftazidime, azlocillin, mezlocillin, piperacillin, ticarcillin/clavulanate, aztreonam, imipenem, and ciprofloxacin were concurrently determined against over 1,000 isolates of gram-negative bacilli from clinical specimens of patients at the Cleveland Clinic. Cephalosporins, penicillins, and aztreonam were active against species of Enterobacteriaceae other than *Citrobacter freundii*, *Enterobacter aerogenes*, and *Enterobacter cloacae*. Ceftazidime was the most active cephalosporin against *Pseudomonas aeruginosa*. Against the Enterobacteriaceae, the rank order of activity of penicillins was ticarcillin/clavulanate > piperacillin > mezlocillin > azlocillin. Against *P. aeruginosa*, the rank order of activity of penicillins was piperacillin > ticarcillin/clavulanate > azlocillin > mezlocillin. Aztreonam was less active *v* *P. aeruginosa* than ceftazidime, cefoperazone, or piperacillin. The most active antimicrobials against all isolates tested were imipenem and ciprofloxacin.

□ INDEX TERMS: ANTIBIOTICS, LACTAM; GRAM-NEGATIVE BACTERIA □ CLEVE CLIN J MED 1989; 56:161-166

THE RECENT introduction of ciprofloxacin for clinical use follows closely a period of active research in and development of expanded spectrum  $\beta$ -lactam antibiotics, including cephalosporins, penicillins, monobactams, and carbapenems. Although numerous published studies compare the activity of ciprofloxacin with other quinolones, only a limited number of studies compare the activity of ci-

and penicillins, as well as the monobactam, aztreonam, and the carbapenem, imipenem.<sup>1-3</sup>

We compared the susceptibility of more than 1,000 clinical bacterial isolates to four expanded spectrum cephalosporins (cefoperazone, cefotaxime, ceftriaxone, and ceftazidime), four expanded spectrum penicillins (azlocillin, mezlocillin, piperacillin, and ticarcillin/clavulanate), aztreonam, imipenem, and ciprofloxacin.

■ See also the editorial by Rehm (pp 119-121)

profloxacin concurrently with the activities of parenterally administered expanded spectrum cephalosporins

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## MATERIALS AND METHODS

Minimal inhibitory concentrations (MIC) were determined by the microdilution method according to procedures described by the National Committee for Clinical Laboratory Standards (NCCLS).<sup>4</sup> All organisms tested represented gram-negative bacteria from clinical specimens of both inpatients and outpatients at the Cleveland Clinic. Specimen sources represented blood, respiratory and urinary tracts, skin, and soft tissue.

TABLE 1  
ACTIVITIES OF CEPHALOSPORINS

Organism (no.)	Cefoperazone			Cefotaxime			Ceftriaxone			Ceftazidime		
	MIC range	MIC <sub>90</sub>	S (%)	MIC range	MIC <sub>90</sub>	S (%)	MIC range	MIC <sub>90</sub>	S (%)	MIC range	MIC <sub>90</sub>	S (%)
<i>Branhamella catarrhalis</i> (17)	≤8	≤8	—	≤2	≤2	—	≤1	≤1	—	2	2	—
<i>Haemophilus influenzae</i> (33)	≤8–128	≤8	—	≤2	≤2	100	<1–4	≤1	97	2–4	2	93
<i>Acinetobacter anitratus</i> (46)	16–64	32	80	≤2–16	16	84	4–16	8	93	2–4	4	100
<i>Citrobacter diversus</i> (11)	≤8	≤8	100	≤2	≤2	100	≤1	≤1	100	2	2	100
<i>Citrobacter freundii</i> (37)	≤8–>128	>128	51	≤2–>16	>16	52	≤1–>64	64	62	2–16	16	54
<i>Enterobacter aerogenes</i> (52)	≤8–64	32	88	≤2–>16	16	64	≤1–32	16	71	2–32	32	35
<i>Enterobacter cloacae</i> (78)	≤8–>128	>128	78	≤2–>16	>16	68	≤1–>64	64	75	2–32	32	70
<i>Escherichia coli</i> (354)	≤8–>128	≤8	98	≤2–>16	≤2	99	≤1–>64	≤1	99	2–32	2	99
<i>Klebsiella oxytoca</i> (42)	≤8–128	≤8	97	≤2	≤2	100	≤1	≤1	100	2	2	100
<i>Klebsiella pneumoniae</i> (127)	≤8–64	≤8	96	≤2–4	≤2	100	≤1–8	≤1	100	2–8	2	100
<i>Morganella morganii</i> (42)	≤8–>128	16	95	≤2–>16	8	92	≤1–8	≤1	100	2–32	16	87
<i>Proteus mirabilis</i> (74)	≤8–64	≤8	98	≤2	≤2	100	≤1–>64	≤1	98	2	2	100
<i>Proteus vulgaris</i> (7)	≤8	≤8	100	≤2	≤2	100	≤1–64	64	83	2	2	100
<i>Serratia marcescens</i> (37)	≤8–16	≤8	100	≤2–8	≤2	100	≤1–8	2	100	2–4	2	100
<i>Pseudomonas aeruginosa</i> (212)	≤8–>128	32	87	≤2–16	>16	17	≤1–>64	32	70	2–32	8	91
<i>Pseudomonas maltophilia</i> (19)	≤8–>128	128	57	≤2–16	>16	21	4–>64	>64	21	2–32	16	73

MIC = minimal inhibitory concentration in µg/mL; MIC<sub>90</sub> = MIC for 90% of isolates tested; and S (%) = percent of isolates susceptible at breakpoints: cefoperazone, ≤16 µg/mL; other cephalosporins, 8 µg/mL.

Ranges of concentrations of antimicrobials tested were chosen to bracket concentrations ("breakpoints") used to define susceptibility and resistance according to recommendations made by the NCCLS.<sup>4</sup>

## RESULTS

The results for each antimicrobial agent are given by species in Tables 1–3 as the MIC ranges, minimal concentrations inhibiting 90% of isolates (MIC<sub>90</sub>), and the percentages of isolates inhibited by concentrations equivalent to susceptibility according to guidelines published by the NCCLS<sup>4</sup> and, when different from those of the NCCLS, those approved by the Food and Drug Administration for the product's package insert.

Results for all three parameters in Tables 1–3 are not listed for all species for the following reasons:

1. Since neither the carboxypenicillins nor the ureidopenicillins are considered drugs of first choice or as alternatives to drugs of first choice for the treatment of serious *Haemophilus influenzae* infections, none was tested at concentrations below the MIC equivalent of susceptibility for the Enterobacteriaceae, and no results are shown for these β-lactams *v* *H. influenzae*.

2. Of all of the antimicrobials tested, only cefotaxime, ceftriaxone, and cefotaxime, ceftriaxone, and ceftazidime have undergone sufficient clinical trials to warrant their use, even preferentially, in children with bacterial meningitis.<sup>5</sup> Resistance of *H. influenzae* to these cephalosporins has not yet been reported in sus-

ceptibility tests performed with conventional methodology so that an MIC equivalent for resistance has not yet been defined.

3. The roles of aztreonam and imipenem in the treatment of serious *H. influenzae* infections is as yet undefined, and it is unlikely that ciprofloxacin or, for that matter, any quinolone will have any approved indications for treatment of infections in children. Thus, although susceptibility data are shown for aztreonam, imipenem, and ciprofloxacin, one should not infer that presentation of the data indicates clinical activity or indications for use of these antimicrobials in serious *H. influenzae* infections.

Against the Enterobacteriaceae, ciprofloxacin and imipenem were the most active (Table 3). Ciprofloxacin inhibited all Enterobacteriaceae at a concentration of ≤1 µg/mL. Except against *Citrobacter freundii*, imipenem inhibited all Enterobacteriaceae at ≤4 µg/mL. The cephalosporins and aztreonam were active against all Enterobacteriaceae except *Citrobacter freundii*, *Enterobacter aerogenes*, and *Enterobacter cloacae* (Table 1). The activities of cefoperazone, cefotaxime, ceftriaxone, and ceftazidime were very similar against the Enterobacteriaceae. Ceftazidime was the most active cephalosporin against *Pseudomonas aeruginosa*, *Pseudomonas maltophilia*, and *Acinetobacter anitratus*.

Activities among the broad spectrum penicillins against the Enterobacteriaceae varied somewhat. Based on MIC<sub>90</sub> values, their rank order of activity was ticarcillin/clavulanate > piperacillin > mezlocillin > azlocillin.

**TABLE 2**  
ACTIVITIES OF PENICILLINS

Organism (no.)	Azlocillin			Mezlocillin			Piperacillin			Ticarcillin/Clavulanate		
	MIC range	MIC <sub>90</sub>	S (%)	MIC range	MIC <sub>90</sub>	S (%)	MIC range	MIC <sub>90</sub>	S (%)	MIC range	MIC <sub>90</sub>	S (%)
<i>Branhamella catarrhalis</i> (17)	≤16	≤16	—	≤16	≤16	—	≤16	≤16	—	4	4	—
<i>Haemophilus influenzae</i> (33)	—	—	—	—	—	—	—	—	—	—	—	—
<i>Acinetobacter anitratus</i> (46)	≤16–128	64	100	≤16–64	32	100 ( 50)	≤16–32	≤16	100 ( 95)	4–16	16	100 ( 82)
<i>Citrobacter diversus</i> (11)	≤16–64	32	100	≤16	≤16	100 (100)	≤16	≤16	100 (100)	4	4	100 (100)
<i>Citrobacter freundii</i> (37)	≤16–>256	>256	48	≤16–>256	256	64 ( 48)	≤16–>256	>256	59 ( 51)	4–>128	>128	62 ( 51)
<i>Enterobacter aerogenes</i> (52)	≤16–>256	>256	51	≤16–128	64	92 ( 59)	≤16–128	64	94 ( 61)	4–>128	128	72 ( 54)
<i>Enterobacter cloacae</i> (78)	≤16–>256	>256	65	≤16–256	128	87 ( 75)	≤16–>256	256	81 ( 74)	4–>128	>128	66 ( 54)
<i>Escherichia coli</i> (354)	≤16–>256	>256	78	≤16–>256	128	87 ( 78)	≤16–>256	128	89 ( 81)	4–>128	32	94 ( 86)
<i>Klebsiella oxytoca</i> (42)	≤16–>256	>256	81	≤16–>256	128	83 ( 78)	≤16–>256	64	90 ( 81)	4–>128	32	92 ( 81)
<i>Klebsiella pneumoniae</i> (127)	≤16–>256	256	79	≤16–>256	128	88 ( 71)	≤16–>256	128	89 ( 86)	2–>128	16	94 ( 90)
<i>Morganella morganii</i> (42)	≤16–>256	>256	71	≤16–>256	64	90 ( 76)	≤16–>256	64	95 ( 81)	4–>128	16	97 ( 92)
<i>Proteus mirabilis</i> (74)	≤16–128	≤16	98	≤16–256	≤16	98 ( 98)	≤16–>256	≤16	98 ( 98)	4	4	100 (100)
<i>Proteus vulgaris</i> (7)	≤16–>256	>256	71	≤16–>256	>256	85 ( 71)	≤16–>256	>256	85 ( 85)	4–16	16	100 (100)
<i>Serratia marcescens</i> (37)	≤16–>256	256	86	≤16–128	32	94 ( 86)	≤16–128	16	97 ( 91)	4–>128	32	94 ( 70)
<i>Pseudomonas aeruginosa</i> (212)	≤16–>256	128	86	≤16–>256	256	76	≤16–>256	64	92	2–>128	128	87
<i>Pseudomonas maltophilia</i> (19)	≤16–>256	>256	68	≤16–>256	>256	63 ( 21)	≤16–>256	>256	36 ( 5)	4–128	128	88 ( 77)

MIC = minimal inhibitory concentration in µg/mL; MIC<sub>90</sub> = MIC for 90% of isolates tested; and S (%) = percent of isolates susceptible at FDA (and NCCLS) approved breakpoints: azlocillin, ≤64 µg/mL; mezlocillin, piperacillin, and ticarcillin, ≤64 (FDA) or ≤16 (NCCLS) µg/mL.

**TABLE 3**  
IN VITRO ACTIVITIES OF AZTREONAM, IMIPENEM, AND CIPROFLOXACIN

Organism (no.)	Aztreonam			Imipenem			Ciprofloxacin		
	MIC range	MIC <sub>90</sub>	S (%)	MIC range	MIC <sub>90</sub>	S (%)	MIC range	MIC <sub>90</sub>	S (%)
<i>Branhamella catarrhalis</i> (17)	1–4	4	—	≤0.12	0.12	—	<0.06–0.12	0.12	—
<i>Haemophilus influenzae</i> (33)	1–8	2	93	≤0.12–1	1	100	0.12	0.12	100
<i>Acinetobacter anitratus</i> (46)	8–>64	64	13	≤0.12–0.5	0.25	100	≤0.06–2	0.25	97
<i>Citrobacter diversus</i> (11)	1	1	100	≤0.12–0.5	0.25	100	0.12	0.12	100
<i>Citrobacter freundii</i> (37)	1–>64	64	56	<0.12–>32	2	89	0.12–1	0.12	100
<i>Enterobacter aerogenes</i> (52)	1–>64	32	71	≤0.12–4	2	100	0.12	0.12	100
<i>Enterobacter cloacae</i> (78)	1–>64	64	74	≤0.12–4	1	100	0.12–0.25	0.12	100
<i>Escherichia coli</i> (354)	1–>64	1	98	≤0.12–>32	0.25	99	0.12–1	0.12	100
<i>Klebsiella oxytoca</i> (42)	1–16	1	97	≤0.12–0.5	0.25	100	0.12	0.12	100
<i>Klebsiella pneumoniae</i> (127)	1–32	1	99	<0.12–16	0.25	98	0.12–0.5	0.12	100
<i>Morganella morganii</i> (42)	1–>64	2	97	0.25–4	4	100	0.12–0.25	0.12	100
<i>Proteus mirabilis</i> (74)	1–>64	1	97	≤0.12–8	4	97	0.12–1	0.12	100
<i>Proteus vulgaris</i> (7)	1	1	100	≤0.12–4	2	100	0.12–0.25	0.12	100
<i>Serratia marcescens</i> (37)	1–8	2	97	0.25–4	2	100	0.12–0.25	0.25	100
<i>Pseudomonas aeruginosa</i> (212)	1–>64	16	76	0.25–>32	4	90	0.12–2	0.5	99
<i>Pseudomonas maltophilia</i> (19)	4–>64	>64	15	0.5–>32	>32	5	0.25–>8	8	42

MIC = minimal inhibitory concentration in µg/mL; MIC<sub>90</sub> = MIC for 90% of isolates tested; and S (%) = percent of isolates susceptible at breakpoints: aztreonam, 8 µg/mL; imipenem, 4 µg/mL; ciprofloxacin, 1 µg/mL.

Activity was moderate to poor against *C. freundii*, *E. aerogenes*, and *E. cloacae*, depending on whether the FDA (<64 µg/mL) or NCCLS (<16 µg/mL) breakpoint for defining susceptibility was used. Against *P. aeruginosa*, the rank order of activity was piperacillin > ticarcillin/clavulanate > azlocillin > mezlocillin. Among penicillins, ticarcillin/clavulanate was the most active against *P. maltophilia*, while piperacillin was the most active against *A. anitratus*.

## DISCUSSION

All of the β-lactams tested in this study have been used alone or in combination with an aminoglycoside for the empirical therapy of the febrile neutropenic patient. The reported use of ceftazidime alone v the combination of cephalothin, carbenicillin, and gentamicin<sup>6</sup> has sparked a lively debate over the efficacy of monotherapy v combination therapy.<sup>7</sup> Subsequent stu-

dies by the European Organization for Research on Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group comparing the combinations of azlocillin plus amikacin with ceftazidime plus either a short or long course of amikacin have not only raised further questions about the efficacy of ceftazidime as monotherapy for the febrile neutropenic patient but have also emphasized the important relationship between resistance to the  $\beta$ -lactam antibiotic and overall outcome.<sup>8</sup> In the EORTC study, the outcome of patients receiving the long course of amikacin with ceftazidime was significantly better than that of patients receiving the long course of amikacin with azlocillin. This difference in outcome reflected the higher rate of resistance to azlocillin (31%) than to ceftazidime (2%) among infecting organisms.<sup>8</sup> Resistance to the  $\beta$ -lactam was reported to be important in overall outcome even when the organism was susceptible to amikacin.

The activities of the penicillins, cephalosporins, and aztreonam in our study were moderate to poor against isolates of species in which mutants selected for derepressed class I  $\beta$ -lactamase occur with some frequency, i.e. *C. freundii*, *E. aerogenes*, and *E. cloacae*.<sup>9,10</sup> These data differ substantively from those published in reviews that demonstrated potent in vitro activity of cefotaxime, ceftriaxone, ceftazidime, penicillins, and aztreonam against these species.<sup>11-15</sup> The discrepancy between our data and those cited above could be due to either of two reasons:

1. Resistance to  $\beta$ -lactams by species producing the chromosomal class I  $\beta$ -lactamase is inoculum-dependent. Therefore, resistance may not be evident in broth dilution studies in which the final inoculum has not been documented to approximate  $5 \times 10^5$  CFU/mL, as recommended in the NCCLS procedure.<sup>4</sup>

2. The increasing clinical use of broad spectrum cephalosporins, ureidopenicillins, and aztreonam has fostered the selection of stable mutants with derepressed class I  $\beta$ -lactamase among clinical isolates of *C. freundii*, *E. aerogenes*, *E. cloacae*, *S. marcescens*, and *P. aeruginosa* during therapy, and adverse clinical consequences have resulted.<sup>9,16,17</sup> The mutants resulting from this selection are cross-resistant to other cephalosporins, ureidopenicillins, and aztreonam but not to imipenem.<sup>10</sup> Although imipenem is a potent inducer of the class I  $\beta$ -lactamase, it is stable in the presence of this  $\beta$ -lactamase.<sup>10,18</sup> The typical scenario is a patient infected with a "susceptible" class I  $\beta$ -lactamase producing organism (e.g., *E. cloacae*, *P. aeruginosa*) and treated with a newer-generation cephalosporin, a ureidopenicillin, or a monobactam and from whom stable derepressed resistant mutants are sub-

sequently isolated. These eventually constitute the entire population of organisms at the infected site.<sup>10</sup>

The high level of activity of imipenem in our study reflects that reported in multiple studies reviewed by Birnbaum et al<sup>19</sup> and Jones.<sup>20</sup> Emergence of resistance among aerobic gram-negative bacilli during imipenem therapy remains limited to *P. aeruginosa* due to decreased penetration of imipenem across the outer membrane.<sup>21-23</sup> The incidence of emergence of imipenem-resistant *P. aeruginosa* during therapy remains unclear but was reported to be 19% in a review by Acar<sup>24</sup> of the worldwide experience of therapy of lower respiratory tract infections with imipenem and as high as 37% in a study by Krilov et al<sup>25</sup> of imipenem in acute pulmonary exacerbations of cystic fibrosis. Thus far, resistance appears to occur infrequently during imipenem therapy of nonrespiratory infections. Also unknown at this time is whether the combination of imipenem with an aminoglycoside or with ciprofloxacin, which is often synergistic with imipenem in vitro,<sup>26</sup> might reduce the frequency of emergence of resistance during imipenem therapy.

Comparison of the relative activities of the *Pseudomonas*-active penicillins is complicated by three factors:

1. The MIC equivalents of susceptibility of the Enterobacteriaceae to mezlocillin, piperacillin, and ticarcillin/clavulanate differ between the NCCLS (<16  $\mu$ g/mL) and the FDA (<64  $\mu$ g/mL).

2. Although azlocillin plus amikacin resulted in a significantly greater response rate than did ticarcillin plus amikacin in an EORTC prospective randomized study of empirical therapy of suspected bacteremias in febrile granulocytopenic patients,<sup>27</sup> few other studies have demonstrated any significant differences in outcome between regimens consisting of various penicillins plus and aminoglycoside. In the EORTC study, outcome appeared to be correlated with the lower rate of resistance of multiple *E. coli* isolates to azlocillin than to ticarcillin. An earlier study by Wade et al<sup>28</sup> of piperacillin or ticarcillin plus amikacin in febrile granulocytopenic patients is an example of a comparison that failed to demonstrate any clinically significant difference between the two regimens, despite the greater in vitro spectrum of activity of piperacillin.

3. Penicillin monotherapy for serious gram-negative infections is not recommended.<sup>29</sup> Therefore, the penicillins are administered with an aminoglycoside, perhaps minimizing the clinical importance of differences in the activities of the penicillins in vitro.

Clavulanic acid inhibits  $\beta$ -lactamases (including staphylococcal) other than the class I chromosomal  $\beta$ -



lactamase. Thus, the activity of ticarcillin/clavulanate against *C. freundii*, *E. aerogenes*, and *E. cloacae* is only moderate, though lower than that published in a review by Fuchs et al<sup>30</sup> of the combination's activity in vitro. Once again, however, there has been no clear-cut demonstration of a statistically significant difference in outcome between ticarcillin/clavulanate plus aminoglycoside and another penicillin, such as piperacillin, plus an aminoglycoside in a variety of infections.<sup>31</sup>

In the final analysis, the most active compounds evaluated in this study were imipenem and ciprofloxacin. Our data are comparable to those published by Birnbaum et al<sup>19</sup> and Jones<sup>20</sup> for imipenem and by Sanders et al<sup>32</sup> and Wolfson and Hooper<sup>33</sup> for ciprofloxacin. As mentioned previously, imipenem is active against most gram-negative bacilli that are resistant to cephalosporins, penicillins, and monobactams. To date, experience with imipenem monotherapy of febrile granulocytopenic cancer patients is limited,<sup>34</sup> and as already discussed, emergence of resistance in *P. aeruginosa* during therapy is a concern of uncertain magnitude.

Since ciprofloxacin initially has been approved only

for oral administration, most published experience with this quinolone is in the treatment of urinary tract, skin and skin structure, tissue, gastrointestinal, and respiratory tract infections, as well as in osteomyelitis.<sup>35</sup> Experience with either oral or intravenous quinolones in the treatment of serious infections is still limited but suggests performance equivalent with currently recommended therapy.<sup>36</sup> Obviously, the availability of a potent antibacterial compound that can be administered orally as an alternative to one or two compounds that must be administered parenterally can have a substantial economic impact on hospital costs. Resistance to ciprofloxacin has been reported among isolates of *P. aeruginosa* from patients with cystic fibrosis and, to a less frequent extent, among isolates of *S. marcescens*, *P. aeruginosa*, and *Staphylococcus aureus* from wound infections.<sup>37</sup>

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