1994-03-01

# Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. The Severe Pneumonia Study Group

Mitchell P. Fink
*University of Massachusetts Medical School*

*Et al.*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1994, p. 547–557
0066-4804/94/$04.00+0

Vol. 38, No. 3

# Treatment of Severe Pneumonia in Hospitalized Patients: Results of a Multicenter, Randomized, Double-Blind Trial Comparing Intravenous Ciprofloxacin with Imipenem-Cilastatin

MITCHELL P. FINK,[1]* DAVID R. SNYDMAN,[2] MICHAEL S. NIEDERMAN,[3] KENNETH V. LEEPER, JR.,[4] ROYCE H. JOHNSON,[5] STEPHEN O. HEARD,[1] RICHARD G. WUNDERINK,[4] JOHN W. CALDWELL,[5] JEROME J. SCHENTAG,[6] GHODRAT A. SIAMI,[7] RICKI L. ZAMECK,[8] DANIEL C. HAVERSTOCK,[8] HARALD H. REINHART,[8] ROGER M. ECHOLS,[8] AND THE SEVERE PNEUMONIA STUDY GROUP†

*Department of Surgery, University of Massachusetts Medical Center, Worcester, Massachusetts 01655[1]; Departments of Medicine and Pathology, New England Medical Center, Boston, Massachusetts 02111[2]; Pulmonary and Critical Care Medicine Division, Winthrop University Hospital, Mineola, New York 11501[3]; Division of Pulmonary and Critical Care Medicine, University of Tennessee, Memphis, Tennessee 38163-2116[4]; UCLA Department of Medicine, Kern Medical Center, Bakersfield, California 93305[5]; State University of New York at Buffalo and Millard Fillmore Hospital, Buffalo, New York 14209[6]; Department of Medicine, VA Medical Center, Vanderbilt University, Nashville, Tennessee 37212-2637[7]; and Pharmaceutical Division, Miles Inc., West Haven, Connecticut 06516[8]*

Received 29 July 1993/Returned for modification 24 November 1993/Accepted 3 January 1994

**Intravenously administered ciprofloxacin was compared with imipenem for the treatment of severe pneumonia. In this prospective, randomized, double-blind, multicenter trial, which included an intent-to-treat analysis, a total of 405 patients with severe pneumonia were enrolled. The mean APACHE II score was 17.6, 79% of the patients required mechanical ventilation, and 78% had nosocomial pneumonia. A subgroup of 205 patients (98 ciprofloxacin-treated patients and 107 imipenem-treated patients) were evaluable for the major efficacy endpoints. Patients were randomized to receive intravenous treatment with either ciprofloxacin (400 mg every 8 h) or imipenem (1,000 mg every 8 h), and doses were adjusted for renal function. The primary and secondary efficacy endpoints were bacteriological and clinical responses at 3 to 7 days after completion of therapy. Ciprofloxacin-treated patients had a higher bacteriological eradication rate than did imipenem-treated patients (69 versus 59%; 95% confidence interval of −0.6%, 26.2%; $P = 0.069$) and also a significantly higher clinical response rate (69 versus 56%; 95% confidence interval of 3.5%, 28.5%; $P = 0.021$). The greatest difference between ciprofloxacin and imipenem was in eradication of members of the family *Enterobacteriaceae* (93 versus 65%; $P = 0.009$). Stepwise logistic regression analysis demonstrated the following factors to be associated with bacteriological eradication: absence of *Pseudomonas aeruginosa* ($P < 0.01$), higher weight ($P < 0.01$), a low APACHE II score ($P = 0.03$), and treatment with ciprofloxacin ($P = 0.04$). When *P. aeruginosa* was recovered from initial respiratory tract cultures, failure to achieve bacteriological eradication and development of resistance during therapy were common in both treatment groups (67 and 33% for ciprofloxacin and 59 and 53% for imipenem, respectively). Seizures were observed more frequently with imipenem than with ciprofloxacin (6 versus 1%; $P = 0.028$). These results demonstrate that in patients with severe pneumonia, monotherapy with ciprofloxacin is at least equivalent to monotherapy with imipenem in terms of bacteriological eradication and clinical response. For both treatment groups, the presence of *P. aeruginosa* had a negative impact on treatment success. Seizures were more common with imipenem than with ciprofloxacin. Monotherapy for severe pneumonia is a safe and effective initial strategy but may need to be modified if *P. aeruginosa* is suspected or recovered from patients.**

Despite improvements in antimicrobial chemotherapy and supportive care, bacterial pneumonia, whether nosocomial or community acquired, remains an infection with substantial mortality. Nosocomial pneumonia accounts for about 15% of

* Corresponding author. Present address: Beth Israel Hospital, 330 Brookline Avenue, Boston, MA 02215. Phone: (617) 735-4710. Fax: (617) 735-2978.

† The members of the Severe Pneumonia Study Group are as follows: Study Coordinators Cathleen Helsmoortel and Donna Soja-Strzepa, University of Massachusetts Medical Center, Worcester; Coinvestigator Steven Schwaitzberg and Study Coordinator Laurie Barefoot, New England Medical Center, Boston, Mass.; Coinvestigators Alan M. Fein, Steven H. Feinsilver, and Jonathan S. Ilowite and Study Coordinators Nancy Clare and Debra Schulman, Winthrop University Hospital, Mineola, N.Y.; Study Coordinator Carol B. Jones, University of Tennessee Medical Center, Memphis; Study Coordinator Renee I. Griffin and Major Contributor Charles W. Wrobel, Kern Medical Center, University of California at Los Angeles, Bakersfield; Coinvestigators Charles H. Ballow and Guy Amsden and Study Coordinator Patricia Mitchell, State University of New York at Buffalo and Millard Fillmore Hospital, Buffalo, N.Y.; Study Pharmacist Todd Bess and Study Coordinator Walter Wilkins, VA Medical Center, Vanderbilt University, Nashville, Tenn.; Principal Investigator Richard B. Brown, Coinvestigator William McGee, and Study Coordinator Mary Jo Safford, Baystate Medical Center, Springfield, Mass.; Principal Investigator Donald P. Levine, Coinvestigators Stephen A. Lerner, James A. Kruse, and Joseph J. Bander and Study Coordinators Pamela McNeil and Michele Munkarah, Detroit Receiving Hospital and University Health Center, Wayne State University, Detroit, Mich.; Principal Investigators Warren R. Summer and Bennett deBoisblanc, Louisiana State University Medical Center, New Orleans; Principal Investigator Matthew E. Levison, Coinvestigators Oksana Korzeniowski, Allison Sigler, and James Baldassarre, and Study Coordinators Patricia Walsh and Carol Samel, Medical College of Pennsylvania, Philadelphia; Principal Investigator Curtis N. Sessler, Coinvestigators Ronald E. Polk and Debra S. Israel, and Study Coordinator Janet

all hospital-acquired infections (20) and is the most common nosocomial infection among patients cared for in intensive care units (10). In several recent reviews, mortality due to nosocomial pneumonia has been estimated to be 30 to 70% (6, 11, 12, 26). However, most prospective antimicrobial clinical trials have been conducted in patient populations with mortality rates ranging from 4 to 33% (23, 28, 29, 31). Severe cases of community-acquired pneumonia usually necessitate hospitalization and have been associated with a mortality rate as high as 21%, even among patients without obvious preexisting immune deficits (37, 47).

A key component of the treatment for severe bacterial pneumonia is administration of an appropriate parenteral antibacterial regimen. The initial choice of agents is typically empiric, since the results of sputum and blood cultures are usually not available when therapy is started. The clinical diagnosis of pneumonia based upon conventional criteria only (i.e., fever, leukocytosis, new infiltrates on chest roentgenogram, and purulent sputum) may be inaccurate (2, 7, 12, 14, 44, 53). Moreover, results obtained by culturing sputum aspirated from the airways of endotracheally intubated, mechanically ventilated patients may lack specificity compared with results obtained by more invasive means of sampling bronchial secretions (2, 12, 42, 45, 46). In addition, pneumonia in mechanically ventilated patients is often polymicrobial (18). For example, Fagon et al. found that multiple organisms were isolated from 40% of study patients (12). Consequently, broad-spectrum antimicrobial coverage is generally recommended for the empirical or initial treatment of severe bacterial pneumonia (18).

Imipenem and ciprofloxacin are two broad-spectrum antimicrobial agents belonging to different chemical classes which have been evaluated as single agents for the treatment of pneumonia (19, 21, 23, 27, 38–40, 43, 49, 50). Imipenem is a carbapenem antibiotic which possesses excellent in vitro activity against a wide range of pathogens implicated in the etiology of severe pneumonia, including methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae*, members of the family *Enterobacteriaceae*, and *Haemophilus influenzae* (34). This drug also manifests good in vitro activity against *Pseudomonas aeruginosa* (34). Ciprofloxacin is a fluorinated quinolone antimicrobial agent which demonstrates excellent in vitro activity against *H. influenzae*, members of the family *Enterobacteriaceae*, including *Enterobacter cloacae*, methicillin-susceptible *S. aureus*, and *P. aeruginosa*, and moderate activity against *S. pneumoniae* (51, 52). Ciprofloxacin, unlike β-lactam antibiotics, reaches levels in bronchial secretions above those in serum (5), a property that might enhance its therapeutic efficacy in the treatment of pneumonia.

Intravenous (i.v.) ciprofloxacin is indicated for the treatment of mild-to-moderate lower respiratory tract infections at a dosage of 400 mg every 12 h. Our study was designed to assess treatment of patients with severe nosocomial or community-acquired pneumonia based on stringent entry criteria. In patients with severe pneumonia, because of the severity of the illness or the possible presence of pulmonary pathogens that may be only moderately susceptible to ciprofloxacin, administration of a higher dose might be warranted (38). Therefore, the goal of the present study was to compare the efficacy and safety of ciprofloxacin (400 mg every 8 h) with those of imipenem (1,000 mg every 8 h), an antibiotic frequently used in the treatment of patients hospitalized with severe pneumonia (39).

Previous clinical trials conducted to assess the efficacy of antibiotics for the treatment of pneumonia have been difficult to evaluate. Flaws of these studies have included lack of a double-blind design, exclusion of patients with underlying conditions associated with higher mortality, small sample sizes, and absence of intent-to-treat analyses (15–17, 27, 39–41, 43, 44). Other trials allowed inclusion of patients with a variety of lower respiratory tract infections and therefore did not enroll a clearly defined patient population (15, 17, 21, 23, 37, 41, 43, 48, 49). In the present study, we sought to avoid these criticisms and, accordingly, enrolled a relatively homogeneous population in which severity of illness measured by objective indices of respiratory dysfunction served as the entry criterion. The study was conducted and analyzed under fully blind conditions.

(This work was presented in part at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., 17 to 20 October 1993.)

## MATERIALS AND METHODS

**Study design.** This was a multicenter, double-blind, randomized trial comparing i.v. ciprofloxacin with i.v. imipenem for the treatment of patients hospitalized (usually in intensive care units) with severe pneumonia. Twenty medical centers in the United States participated in the study and enrolled patients from May 1990 through July 1992. The study was approved by the institutional review board at each participating center. Informed consent was obtained from each patient (or an appropriate third party).

The objective of the study was to compare ciprofloxacin with imipenem for the treatment of severe pneumonia, with therapeutic equivalence being defined as a difference in bacteriological eradication rates of less than 10 percentage points (10%). The sample size objective to test this hypothesis for efficacy was 100 evaluable patients in each treatment group.

With a computer-generated code, patients were randomized to receive either i.v. imipenem-cilastatin or i.v. ciprofloxacin. Prior to randomization, patients were stratified on the basis of whether pneumonia was nosocomial or community acquired. Nosocomial pneumonia was defined as pneumonia developing after 48 or more h of hospitalization for another problem. All other cases of pneumonia, including those acquired in nursing homes, were considered community acquired.

**Patient selection.** The study inclusion criteria were as follows: ≥18 years of age; compromised respiratory function requiring a fractional inspired oxygen concentration of ≥0.35 to maintain an arterial oxygen tension of ≥60 mm Hg or being on mechanical ventilation at any oxygen concentration; at least

Toner, Medical College of Virginia, Virginia Commonwealth University, Richmond; Principal Investigator Scott L. Traub, Coinvestigator George Karras, Jr., and Research Coordinator Dorothy Tourville, Mercy Hospital Center for Health, Springfield, Mass.; Principal Investigator Faroque Khan and Coinvestigator Ashok Karnik, Nassau County Medical Center, East Meadow, N.Y.; Principal Investigator Philip B. Schworer, Coinvestigator Roy J. Moser III, and Study Coordinator Daniel J. Lageman, St. Elizabeth Hospital, Fort Mitchell, Ky.; Principal Investigator William H. Greene, Coinvestigators Susan V. Donelan and Lonnie Frei, and Study Coordinator Susan Vitale, Stony Brook Health Sciences Center, State University of New York at Stony Brook; Principal Investigator Vincent G. Pons and Study Coordinator Jacqueline Octavio, University of California Medical Center, San Francisco; Principal Investigator Lewis J. Rubin, University of Maryland School of Medicine, Baltimore; Principal Investigator Sheldon R. Braun, Coinvestigator James M. Hinson, and Study Coordinator Sue Prenger, University of Missouri-Columbia; and Principal Investigator Randy D. Pryka, Coinvestigators Ronald Wainz and Frank Horton and Study Coordinator George M. Haig, University of Toledo, Toledo, Ohio.

one symptom of bronchopulmonary infection (dyspnea; fever, hypothermia, or rigors; increase or new onset of cough; pleuritic chest pain; increase in sputum production or purulent sputum); new pulmonary infiltrate on chest roentgenogram thought to be due to infection; sputum Gram stain showing >25 polymorphonuclear neutrophils and <10 squamous cells and potentially pathogenic bacteria. The study exclusion criteria were as follows: allergy to a fluoroquinolone or β-lactam; pregnancy or nursing mother status; concurrent treatment with antimicrobial agents with activity spectra similar to those of the study drugs; absolute neutrophil count of ≤1,000 cells per $mm^3$; prior antimicrobial treatment of the study infection for more than 24 h unless a persistent positive culture is documented; treatment with an investigational drug within 30 days prior to study enrollment or previous enrollment in this study. These criteria were designed to selectively enroll critically ill patients with pneumonia caused by identifiable pathogens.

**Treatment.** A high-dosage regimen of imipenem-cilastatin (1,000 mg every 8 h) and ciprofloxacin (400 mg every 8 h) was designed for the treatment of susceptible pathogens. A lower-dosage schedule of the study agents (400 mg/12 h for ciprofloxacin and 500 mg/6 h for imipenem) was designed for the treatment of highly susceptible pathogens (imipenem dosing was based on package insert information). All patients were to be started on the high-dosage schedule. However, once susceptibility data were available, patients could be changed to the lower-dosage schedule at the discretion of the principal investigator at each center. Only a single change in the schedule (i.e., from the high to the lower dosage) was permitted by the protocol. Both schedules allowed for adjustment of the study medication dose for patients with renal impairment. This was performed by the study pharmacist (unblinded) on the basis of estimated creatinine clearance.

The study antibiotics were diluted by the research pharmacist to a volume of at least 150 ml with normal saline or a 5% dextrose solution. The study drug was infused i.v. over a period of 40 to 60 min.

Administration of antifungal agents, antiviral agents, topical antimicrobial agents, and oral vancomycin was permitted by the protocol. If aspiration was suspected as the etiology of pneumonia or if the sputum Gram stain suggested the presence of anaerobic bacteria, then administration of metronidazole was permitted for those patients randomized to ciprofloxacin treatment. Patients randomized to imipenem received a placebo infusion to maintain the blind condition. Use of i.v. vancomycin was permitted at the investigator's discretion for patients in both treatment groups with sputum cultures showing mixed gram-positive and gram-negative organisms or in patients with gram-positive bacteremia. If i.v. vancomycin was utilized, then the bacteriologic response to the study drug of any gram-positive organisms was excluded from efficacy analyses. The administration of other systemically active antimicrobial chemotherapy was prohibited by the protocol.

**Bacteriological procedures.** Appropriate cultures for isolation, identification, and susceptibility testing of organisms thought to be involved in the infectious process were obtained no more than 48 h prior to initiation of treatment. Sputum was the primary sample used for bacteriological documentation of pneumonia, although blood cultures were also obtained to document bacteremia. Susceptibility of bacterial isolates to the study drugs was determined by standard methods, and the results were assessed in accordance with published guidelines of the National Committee for Clinical Laboratory Standards (32, 33). Routine cultures for *Legionella pneumophila* were not required by the protocol.

**Evaluations for efficacy and safety.** Patients were considered evaluable for both bacteriological and clinical responses if they met inclusion criteria, had at least one pretreatment pathogenic organism susceptible to both of the study drugs, and satisfied other evaluability criteria.

The primary measure of study drug efficacy was bacteriological response at the end of therapy, which was defined as the time between days 3 and 7 posttherapy to allow for elimination of any residual antimicrobial drug which might prevent detection of persisting pathogenic bacteria. Bacteriological responses were classified as eradication (elimination of pretherapy organisms), presumed eradication (no material available for culture), persistence (continued isolation of the causative organisms), superinfection (acquisition of a new pathogen requiring treatment during study therapy), and indeterminate (bacteriological response to the study drug was not evaluable) (4, 8).

Clinical response to therapy was a major secondary endpoint of the trial. Clinical response at 3 to 7 days after completion of therapy was assessed by each principal investigator. Clinical responses were classified as resolution (disappearance of signs and symptoms related to the infection), failure (insufficient lessening of the signs and symptoms of infection such that additional therapy was necessary), and indeterminate (no evaluation possible) (4, 8). If during therapy the infection was improving but a patient died as a result of another disease process or study treatment of a patient was prematurely discontinued because of an adverse event, then the clinical response was considered improvement. If the infection was not improving or was thought to have contributed to the patient's demise, then the clinical response was graded as failure.

All adverse clinical events or laboratory abnormalities occurring during treatment or within 7 days of discontinuation of study medication were recorded and assessed by the principal investigator with regard to the relationship to the study drug and the severity of the event. Theophylline concentrations in serum were routinely monitored in patients receiving concomitant theophylline. Patient survival was recorded during therapy and for 30 days following drug discontinuation.

**Premature termination of treatment.** Any patient who received the study drug for less than 5 full days of treatment was not considered in the efficacy-evaluable analyses unless there was clear evidence of therapeutic failure. If the patient did not respond clinically or if a superinfection developed, treatment with the study drug was discontinued and other appropriate therapy was instituted. Patients dying within the first 48 h of therapy were classified as indeterminate, not as treatment failures, and were included in the analyses performed on the intent-to-treat population. These decisions were made before unblinding of the study.

**Statistical analyses.** Results were analyzed to determine the comparative efficacy and safety of the two study drugs. Primary efficacy analyses were performed on only those cases meeting predetermined criteria for evaluability (efficacy-evaluable population). In addition, the same analyses for efficacy and all safety analyses were performed on the intent-to-treat population. All patients who received at least one dose of the study drug were included in the intent-to-treat population. No interim analysis was performed, and all data were processed by Miles Inc. All major variables were defined explicitly in the protocol, and no changes in the data base were made subsequent to breaking of the treatment allocation code.

The primary efficacy variable was bacteriological response at 3 to 7 days posttherapy. Clinical response at the same time point was considered a secondary outcome variable. For these two variables, 95% confidence intervals (CI) were constructed for the differences in eradication rates or resolution rates

between the two treatment groups, respectively. A CI that did not include −10% would indicate treatment equivalence; a lower limit greater than 0% would indicate ciprofloxacin superiority. Indeterminate responses were not included in the calculation of either eradication rates or resolution rates.

Overall tests of baseline comparability between the two treatment groups were conducted for several categorical variables by using the Cochran-Mantel-Haenszel test to adjust for the multicenter nature of the trial. Cochran-Mantel-Haenszel tests were also used for the efficacy variables. A Mantel-Haenszel weighting scheme was used to compute the CI (30). This method requires at least one evaluable patient per treatment group per center, resulting in the exclusion of five centers from the primary analyses; this decision was made prior to breaking of the treatment allocation code. To determine whether bacteriological and clinical response results were poolable across centers, a treatment-by-center interaction test was performed by the method of Zelen (54).

Logistic regression was used to determine whether the treatment group or any clinical factor was a significant predictor of bacteriological and clinical responses. First, each variable that potentially affected eradication or resolution rates was included in logistic regression models to assess the ability of that variable to predict outcome (univariate model). Then, a stepwise logistic regression procedure was used to identify the best combination of variables by utilizing those variables that were significant predictors of outcome in the univariate model. Finally, treatment group was added to the best model selected by this stepwise procedure to determine whether it had significant explanatory value.

TABLE 1. Reasons for exclusion from efficacy-evaluable analysis

| Reason for exclusion | No. (%) of patients treated with: | |
|---|---|---|
| | Ciprofloxacin[a] | Imipenem[b] |
| No causative organism isolated pretherapy | 36 (17.6) | 23 (11.5) |
| Organism resistant to study drug | 9 (4.4) | 10 (5.0) |
| Five study sites excluded because of Mantel-Haenszel statistical requirements | 4 (2.0) | 4 (2.0) |
| Patients with indeterminate responses for both bacteriological and clinical efficacy endpoints | 3 (1.5) | 8 (4.0) |
| Protocol violations | | |
| Inclusion or exclusion criteria | 20 (9.8) | 9 (4.5) |
| Required cultures not obtained | 11 (5.4) | 13 (6.5) |
| Inadequate duration of treatment | 7 (3.4) | 12 (6.0) |
| Antimicrobial therapy within pretreatment window | 7 (3.4) | 5 (2.5) |
| No susceptibility testing done pretherapy | 4 (2.0) | 4 (2.0) |
| Concomitant antimicrobial therapy (other than pretreatment) | 2 (1.0) | 4 (2.0) |
| Randomization error | 1 (0.5) | 1 (0.5) |
| Total patients excluded from efficacy-evaluable population[c] | 104 (51.5) | 93 (46.5) |

[a] $n$ = 202. Three patients randomized to the ciprofloxacin treatment group never received the study medication and are not included.
[b] $n$ = 200.
[c] $P$ = 0.094 (not significant). The $P$ value was calculated with a chi-square test.

## RESULTS

**Patient characteristics.** Twenty centers contributed to the study, enrolling 405 patients (205 in the ciprofloxacin treatment group and 200 in the imipenem treatment group). Three patients never received study medication after being randomized; the other 402 patients received either ciprofloxacin ($n$ = 202) or imipenem ($n$ = 200), and these patients constituted the intent-to-treat population. One patient was randomized to the imipenem treatment group but actually received ciprofloxacin; this patient was analyzed as part of the ciprofloxacin treatment group.

Of the 402 patients in the intent-to-treat population, 205 (98 in the ciprofloxacin treatment group and 107 in the imipenem treatment group) met the predetermined criteria for the efficacy-evaluable population. The reasons for excluding patients from the primary efficacy analyses are shown in Table 1. All determinations of evaluability were made prior to unblinding.

Overall, the ciprofloxacin and imipenem treatment groups were statistically comparable with respect to almost all demographic variables (Table 2). This was true for both the efficacy-evaluable and the intent-to-treat populations. At the time of enrollment, both treatment groups were similar with respect to severity of illness, as quantitated by APACHE II scores (23a), and degree of pulmonary dysfunction, as estimated by the arterial oxygen tension/fractional inspired oxygen concentration ratio and the alveolar-arterial oxygen tension gradient. Approximately four-fifths of both the efficacy-evaluable and intent-to-treat patients were classified as having nosocomial pneumonia and were being mechanically ventilated at the time of randomization.

**Treatment.** Among patients considered to be efficacy evaluable, the mean durations of treatment were 10.5 days in the ciprofloxacin group and 10.1 days in the imipenem group ($P$ = 0.703). Eighty percent of ciprofloxacin-treated patients and 82% of imipenem-treated patients in the intent-to-treat population received the high-dosage regimen throughout the entire study. In the efficacy-evaluable population, 76% of ciprofloxacin-treated and 78% of imipenem-treated patients received the high-dosage regimen throughout the study. The mean durations of the high-dosage regimen in the ciprofloxacin and imipenem treatment groups were 9.5 and 8.8 days, respectively ($P$ = 0.809). Among the patients considered for the intent-to-treat analyses, the mean durations of treatment were approximately 1 day shorter for both treatment groups.

In the efficacy-evaluable population, 58 (59.2%) of the patients in the ciprofloxacin treatment group and 71 (66.4%) of the patients in the imipenem treatment group had been treated with nonstudy antimicrobial agents prior to enrollment. Concomitant antimicrobial agents were employed by 42 (43%) ciprofloxacin-treated patients and 50 (47%) imipenem-treated patients in the efficacy-evaluable population. The concomitant antibacterial agents permitted by the protocol included vancomycin (27 patients) and metronidazole (11 patients) in the ciprofloxacin treatment group. In the imipenem treatment group, 31 patients received vancomycin and 16 received a placebo for metronidazole to maintain the blind condition. Both gram-positive and gram-negative organisms were isolated from all of the efficacy-evaluable patients who received vancomycin (11 in the ciprofloxacin treatment group and 8 in the imipenem treatment group). A few patients in both treatment groups concomitantly received antibiotics excluded by the protocol. These patients were evaluated on an individual basis prior to breaking of the treatment allocation code and were considered valid for the analyses of efficacy if at least one pretreatment respiratory pathogen was not susceptible to the concomitantly administered antibiotic (4, 8).

TABLE 2. Demographic data of study population[a]

| Variable | Intent-to-treat population data | |
|---|---|---|
| | Ciprofloxacin group ($n$ = 202) | Imipenem group ($n$ = 200) |
| No. (%) of: | | |
| Males | 140 (69.3) | 142 (71.0) |
| Females | 62 (30.7) | 58 (29.0) |
| Mean age (yr)[b] ± SD | 59.9 ± 17.9 | 59.6 ± 17.6 |
| Mean weight (kg)[b] ± SD | 72.7 ± 18.7 | 71.8 ± 17.8 |
| No. (%) of: | | |
| Caucasians | 153 (75.7) | 155 (77.5) |
| Noncaucasians | 49 (24.3) | 45 (22.5) |
| Duration of hospital stay prior to enrollment (days)[b] | | |
| Median | 7.0 | 7.0 |
| Range | 0–259 | 0–508 |
| Mean P(A-a)$O_2$[c] ± SD | 222.9 ± 135.6 | 233.4 ± 139.4 |
| Mean $PaO_2/FIO_2$[d] ratio[b] ± SD | 208.2 ± 96.2 | 202.8 ± 84.7 |
| Mean APACHE II score[b] ± SD | 17.7 ± 6.5 | 17.6 ± 6.4 |
| No. (%) of patients with: | | |
| Assisted ventilation | 154 (80.6) | 150 (76.9) |
| Unassisted ventilation | 37 (19.4) | 45 (23.1) |
| Mean leukocyte count/$mm^3$[b] ± SD | 15.0 ± 7.5 | 14.7 ± 7.0 |
| Mean creatinine concn (mg/dl)[b] ± SD | 1.28 ± 1.0 | 1.45 ± 1.3 |
| No. (%) of patients with[e]: | | |
| Nosocomial pneumonia | 156 (78.0) | 156 (78.0) |
| Community-acquired pneumonia | 44 (22.0) | 44 (22.0) |
| No. (%) of patients in ICU or SICU[f] | 160 (79.2) | 161 (80.5) |
| No. (%) of patients from whom *P. aeruginosa* isolated[g] | 47 (23.3) | 44 (22.0) |
| No. (%) of patients with: | | |
| Bacteremia | 35 (17.3) | 29 (14.5) |
| No. (%) of patients with: | | |
| No previous antimicrobial treatment | 75 (37.1) | 73 (36.5) |
| Previous antimicrobial treatment | 127 (62.9) | 127 (63.5) |

[a] Demographic data of study population at the time of randomization into the study. None of the differences between the treatment groups were statistically significant.

[b] Treated as a continuous variable.

[c] P(A-a)$O_2$, alveolar-arterial oxygen tension gradient.

[d] $PaO_2$, arterial oxygen tension; $FIO_2$, fractional inspired oxygen concentration.

[e] Two patients in the ciprofloxacin treatment group had nonpulmonary infection sites.

[f] ICU, intensive care unit; SICU, surgical intensive care unit.

[g] Represents the number of patients from whom *P. aeruginosa* was isolated.

**Bacteriological and clinical responses.** The bacteriological and clinical efficacy assessments are presented in Table 3. There were 3 (of 98) ciprofloxacin and 13 (of 107) imipenem indeterminate outcomes for bacteriological eradication and 0 (of 98) ciprofloxacin and 3 (of 107) imipenem indeterminate responses for clinical resolution in the efficacy-evaluable population.

In the efficacy-evaluable population, ciprofloxacin-treated patients had a bacteriological eradication rate of 69%, compared with 59% for imipenem-treated patients (95% CI of −0.6%, 26.2%; $P$ = 0.069; Table 3). The difference in eradication rate between the two treatment groups was not statistically significant but did show ciprofloxacin to be statistically equivalent to imipenem.

The clinical resolution rates, also shown in Table 3, demonstrate that in the efficacy-evaluable population, ciprofloxacin-treated patients had a statistically significantly better clinical response rate (69%) than the imipenem-treated patients (56%) (95% CI of 3.5%, 28.5%; $P$ = 0.021). The clinical response rate in the ciprofloxacin treatment group was higher but not significantly different from that in the imipenem treatment group for the intent-to-treat population (64 versus 56%, 95% CI of −2.1%, 19.6%; $P$ = 0.123). These trends were maintained whether patients had community-acquired or nosocomial pneumonia. Of the clinical treatment failures, two-thirds of both the ciprofloxacin and imipenem treatment groups were still clinical failures at a 14- to 28-day posttherapy follow-up evaluation, despite treatment with alternative antimicrobial agents (data not shown).

Multiple organisms were isolated from half of the efficacy-evaluable patients in both the ciprofloxacin and imipenem treatment groups. Bacteriological and clinical response rates were consistently better in both study groups when only a single respiratory pathogen was isolated. However, presence of multiple organisms on initial sputum culture was not a significant predictor of poor outcome on logistic regression analysis (Table 4). Not unexpectedly, 80% of patients still had persistent infiltrates on chest X-ray at the end of therapy.

**Univariate and multiple logistic regression analyses of efficacy parameters.** Bacteriological eradication rates in the efficacy-evaluable population were further analyzed to examine the effects of potentially confounding factors on the comparison between ciprofloxacin and imipenem. When potential risk factors for treatment failure were analyzed in a univariate fashion, three variables were found to have a statistically significant effect on the eradication rate (Table 4). The presence of *P. aeruginosa*, lower body weights, and higher APACHE II scores at entry all adversely affected the eradication rate. By using these three variables, stepwise logistic regression was employed to develop the most predictive model for response to treatment. The final model chosen by the stepwise procedure included all three variables which were predictive in the univariate analyses. When treatment group was added to this model, ciprofloxacin therapy resulted in a bacteriological eradication rate significantly superior ($P$ = 0.039) to that of imipenem therapy (Table 4).

Clinical resolution rates in the efficacy-evaluable population also were analyzed by logistic regression to determine whether ciprofloxacin was statistically superior to imipenem, even when other potentially confounding factors were simultaneously considered. In the univariate analyses, the requirement for mechanical ventilation, a higher leukocyte count, a higher APACHE II score, and presence of *P. aeruginosa* at entry all were found to have a statistically significant adverse impact on the resolution rate. Since leukocyte count is a component of the APACHE II score, only the APACHE II score was

TABLE 3. Efficacy assessments

| Population and treatment group | No. of patients with respiratory bacteriological eradication[a,b]/total (%) | | | 95% CI (%) for all pneumonia[c] (*P* value)[d] | No. of patients with clinical resolution[b,e]/total (%) | | | 95% CI for all pneumonia[c] (*P* value)[d] |
|---|---|---|---|---|---|---|---|---|
| | Nosocomial pneumonia | Community-acquired pneumonia | All pneumonia | | Nosocomial pneumonia | Community-acquired pneumonia | All pneumonia | |
| Efficacy evaluable | | | | | | | | |
| Ciprofloxacin | 57/83 (69) | 9/12 (75) | 66/95 (69) | −0.6, 26.2 (0.069) | 58/86 (67) | 10/12 (83) | 68/98 (69) | 3.5, 28.5 (0.021) |
| Imipenem | 44/76 (58) | 11/18 (61) | 55/94 (59) | | 44/83 (53) | 14/21 (67) | 58/104 (56) | |
| Intent to treat | | | | | | | | |
| Ciprofloxacin | 63/97 (65) | 13/18 (72) | 76/115 (66) | −0.9, 24.2 (0.077) | 74/121 (61) | 18/23 (78) | 92/144 (64) | −2.1, 19.6 (0.123) |
| Imipenem | 53/96 (55) | 13/20 (65) | 66/116 (57) | | 71/130 (55) | 19/32 (59) | 90/162 (56) | |

[a] Eradication rate = (number of patients with eradication + presumed eradication)/(number of patients with eradication + presumed eradication + persistence) (4).
[b] These data do not include indeterminate responses; therefore, the denominators differ for different parameters.
[c] CI, 95% CI for difference in eradication (or resolution) rates (ciprofloxacin minus imipenem).
[d] *P* values (two tailed) were calculated by the Cochran-Mantel-Haenszel method.
[e] Resolution rate = (resolution + improvement)/(resolution + improvement + failure) (8).

considered in the development of the stepwise logistic regression model. The final model chosen by the multivariate procedure included all three variables which were significant univariate predictors. When treatment group was added to this multiple logistic regression model, it continued to have a statistically significant effect on the resolution rate (Table 4). Thus, even after adjustment for confounding variables, clinical outcome in the ciprofloxacin treatment group was statistically superior to that in the imipenem treatment group ($P = 0.016$).

**Pathogenic organisms.** The spectrum of organisms isolated from the respiratory tract at study entry was similar in the two treatment groups for both the efficacy-evaluable and the intent-to-treat populations (data not shown). The most common isolates encountered in the intent-to-treat population were *P. aeruginosa* ($n = 91$), *H. influenzae* ($n = 72$), methicillin-susceptible *S. aureus* ($n = 60$), *Klebsiella pneumoniae* ($n = 46$), and *Escherichia coli* ($n = 30$). The frequency of *E. cloacae* and *K. pneumoniae* isolates was greater in the imipenem treatment group than in the ciprofloxacin treatment group (16 versus 7 for *E. cloacae* and 29 versus 17 for *K. pneumoniae*, respectively); these differences were not statistically significant. In the intent-to-treat population, 94.1% of the organisms isolated at study entry were susceptible in both the ciprofloxacin and imipenem treatment groups, and in the efficacy-evaluable population, 98.6 and 96.5% of the organisms isolated from ciprofloxacin- and imipenem-treated patients, respectively, were susceptible at entry (32, 33).

The bacteriological eradication rates for each causative organism at the respiratory site are shown in Table 5. Overall, the ciprofloxacin treatment group showed a higher rate of

TABLE 4. Analysis of risk factors for favorable bacteriological and clinical responses in efficacy-evaluable patients: a logistic regression model

| Risk factor[a] | Bacteriological response | | | | Clinical response | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | Stepwise logistic regression | | | Univariate | Stepwise logistic regression | | |
| | *P* value[b] | *P* value[b] | Odds ratio[c] | 95% CI for odds ratio | *P* value[b] | *P* value[b] | Odds ratio[c] | 95% CI for odds ratio |
| Age[d] | 0.829 | | | | 0.816 | | | |
| Sex | 0.366 | | | | 0.920 | | | |
| Higher body wt[d] | 0.010 | 0.011 | 1.03 | 1.01, 1.05 | 0.628 | | | |
| Race | 0.824 | | | | 0.581 | | | |
| Diagnosis of nosocomial pneumonia | 0.742 | | | | 0.183 | | | |
| Days in hospital prior to enrollment[d] | 0.294 | | | | 0.322 | | | |
| Mechanical ventilation not required | 0.637 | | | | 0.001 | 0.001 | 8.06 | 2.31, 28.06 |
| Lower APACHE II score[d] | 0.007 | 0.027 | 1.07 | 1.01, 1.13 | 0.019 | 0.058 | 1.05 | 0.99, 1.11 |
| Alveolar-arterial oxygen tension gradient[d] | 0.470 | | | | 0.859 | | | |
| $PaO_2/FIO_2$ ratio[d,e] | 0.379 | | | | 0.266 | | | |
| PEEP[d,f] | 0.734 | | | | 0.150 | | | |
| Serum creatinine[d] | 0.919 | | | | 0.371 | | | |
| Lower leukocyte count[d] | 0.129 | | | | 0.021 | | | |
| Multiple respiratory pathogens | 0.141 | | | | 0.204 | | | |
| Absence of *P. aeruginosa* | 0.0001 | 0.0001 | 7.12 | 3.35, 15.14 | 0.008 | 0.011 | 2.38 | 1.22, 4.65 |
| Treatment with ciprofloxacin | | 0.039 | 2.08 | 1.04, 4.16 | | 0.016 | 2.16 | 1.15, 4.03 |

[a] Variable as present at study randomization.
[b] *P* value (two-tailed) calculated by the Wald chi-square method.
[c] By definition, an odds ratio of 1.0 means the two groups are equal. An odds ratio of >1.0 means that the chance of bacteriological or clinical success is greater for the situation described.
[d] Treated as a continuous variable.
[e] $PaO_2$, arterial oxygen tension; $FIO_2$, fractional inspired oxygen concentration.
[f] PEEP, positive end-expiratory pressure.

TABLE 5. Bacteriological eradication rates for each causative organism at respiratory site[a]

| Organism | No. of organisms eradicated/total (%) | | | |
|---|---|---|---|---|
| | Efficacy-evaluable population | | Intent-to-treat population | |
| | Ciprofloxacin group ($n$ = 152)[b] | Imipenem group ($n$ = 155)[b] | Ciprofloxacin group ($n$ = 177)[b] | Imipenem group ($n$ = 182)[b] |
| *S. aureus* | | | | |
| Methicillin susceptible | 13/20 (65) | 11/17 (65) | 15/26 (58) | 14/20 (70) |
| Methicillin resistant | 0/0 (0) | 1/1 (100) | 0/0 (0) | 2/2 (100) |
| *S. pneumoniae* | 8/8 (100) | 5/5 (100) | 9/9 (100) | 9/9 (100) |
| *H. influenzae* | 25/25 (100) | 18/18 (100) | 29/29 (100) | 22/24 (92) |
| *Acinetobacter* species | 5/6 (83) | 4/5 (80) | 5/6 (83) | 4/5 (80) |
| *E. coli* | 10/10 (100) | 11/14 (79) | 10/10 (100) | 11/14 (79) |
| *Klebsiella* species | 10/11 (91) | 12/18 (67) | 13/17 (76) | 13/21 (62) |
| *Proteus* species | 6/6 (100) | 2/5 (40) | 6/6 (100) | 2/5 (40) |
| *Enterobacter* species | 10/10 (100) | 13/21 (62) | 10/10 (100) | 13/22 (59) |
| *P. aeruginosa* | 11/33 (33) | 11/27 (41) | 13/38 (34) | 11/32 (34) |
| *X. maltophilia* | 0/2 (0) | 0/2 (0) | 0/2 (0) | 0/2 (0) |
| Other gram-positive cocci[c] | 3/4 (75) | 2/2 (100) | 4/6 (67) | 2/2 (100) |
| Other gram-negative bacilli[d] | 11/13 (85) | 10/14 (71) | 12/14 (86) | 12/16 (75) |
| Other[e] | 4/4 (100) | 5/6 (83) | 4/4 (100) | 5/8 (63) |
| Total | 116/152 (76) | 105/155 (68) | 130/177 (73) | 120/182 (66) |

[a] The data do not include indeterminate responses; therefore, denominators change for different parameters. Eradication rate = (eradication + presumed eradication)/(eradication + presumed eradication + persistence) (4).

[b] $n$, number of organisms at entry; one patient may have had more than one type of bacteria isolated.

[c] *Enterococcus* and other *Streptococcus* species.

[d] *Citrobacter* species, *Hafnia alvei*, *Morganella morganii*, *Providencia* species, *Serratia marcescens*, *Aeromonas hydrophila*, *Pseudomonas fluorescens*, *P. paucimobilis*, *Eikenella corrodens*, and *Haemophilus parainfluenzae*.

[e] *Neisseria*, *Moraxella*, and *Corynebacterium* species.

pathogen eradication than did the imipenem treatment group for both the efficacy-evaluable population (76 versus 68%, respectively) and the intent-to-treat population (73 versus 66%, respectively). This was primarily due to the statistically superior ability of ciprofloxacin to eradicate members of the family *Enterobacteriaceae* (41 of 44 [93%] for ciprofloxacin versus 45 of 68 [66%] for imipenem; $P$ = 0.001) in the efficacy-evaluable population. The two antimicrobial agents were comparable with regard to eradication of *S. aureus*, *H. influenzae*, *S. pneumoniae*, and *P. aeruginosa*, for both the efficacy-evaluable and the intent-to-treat populations. In both treatment groups, bacteriological failure was common when *P. aeruginosa* was a pretreatment respiratory pathogen. In the efficacy-evaluable population, bacteriological eradication of *P. aeruginosa* was greater, but not significantly so, in the imipenem group than in the ciprofloxacin group (11 [41%] versus 11 [33%], respectively; $P$ = 0.559).

**Development of resistance.** The development of bacteriological resistance by organisms that were initially susceptible to the study antimicrobial agents is shown in Table 6. In the intent-to-treat population, both treatment groups exhibited similar rates of development of resistance: 9% for the ciprofloxacin treatment group and 11% for the imipenem treatment group. There were 23 isolates from 20 ciprofloxacin-treated patients and 27 isolates from 27 imipenem-treated patients that developed resistance during the course of the study in the intent-to-treat population. *P. aeruginosa* was the predominant pathogen developing resistance to ciprofloxacin or imipenem in both the intent-to-treat and efficacy-evaluable patients. For this organism, 13 (28%) of 47 isolates in the ciprofloxacin treatment group and 22 (50%) of 44 isolates in the imipenem treatment group developed resistance in the intent-to-treat population. Resistance to *P. aeruginosa* did not develop before day 3 of treatment, but by day 7 of therapy, 6 (of 13) isolates in the ciprofloxacin treatment group and 13 (of 22) isolates in the imipenem treatment group had become resistant.

**Superinfection.** Superinfection was caused by 21 isolates in 18 ciprofloxacin-treated patients and by 37 isolates in 30 imipenem-treated patients in the efficacy-evaluable population. In the intent-to-treat population, superinfection was caused by 32 isolates in 28 ciprofloxacin-treated patients and caused by 53 isolates in 41 imipenem-treated patients. Although certain species of superinfecting organisms seemed to be study drug specific, *P. aeruginosa*, *K. pneumoniae*, and *Xanthomonas maltophilia* were the primary pathogens causing superinfection in the efficacy-evaluable population (Table 6).

**Premature discontinuation from study treatment.** Treatment with the study drug was discontinued prematurely for 192 of 402 patients; of these, 96 were in the ciprofloxacin treatment group and 96 were in the imipenem treatment group. Reasons for premature drug discontinuation were as follows (the percentages of all patients in the ciprofloxacin and imipenem treatment groups, respectively, are in parentheses): failure to respond clinically (12 and 20% [$P$ = 0.032]), violation of inclusion or exclusion criteria (14 and 7% [$P$ = 0.020]), death (5 and 3% [$P$ = 0.332]), adverse reaction (3 and 5% [$P$ = 0.575]), and miscellaneous factors (12 and 14% [$P$ = 0.695]).

**Adverse events.** Adverse events were reported for 132 (65%) of 202 patients in the ciprofloxacin treatment group and for 148 (74%) of 200 patients in the imipenem treatment group, a difference that was not statistically significant ($P$ = 0.059). However, seizures occurred in only 3 (1%) of 202 patients in the ciprofloxacin treatment group, compared with 11 (6%) of 200 patients in the imipenem treatment group ($P$ = 0.028). In two ciprofloxacin-treated patients, seizures occurred more than a week after the study drug was discontinued. In contrast, all seizures in the imipenem treatment group occurred during therapy with imipenem. Myocardial infarction occurred in 2%

TABLE 6. Superinfection and development of bacterial resistance

| Organism(s) | No. of organisms/total (%) | | | |
|---|---|---|---|---|
| | Efficacy-evaluable population | | Intent-to-treat population | |
| | Ciprofloxacin | Imipenem | Ciprofloxacin | Imipenem |
| Resistance developed[a] | | | | |
| *P. aeruginosa* | 12/36 (33) | 17/32 (53) | 13/47 (28) | 22/44 (50) |
| Methicillin-susceptible *S. aureus* | 5/20 (25) | 3/19 (16) | 6/33 (18) | 3/27 (11) |
| Other[b] | 2/7 (29) | 1/3 (33) | 4/45 (9) | 2/72 (3) |
| Superinfection[c] | | | | |
| *K. pneumoniae* | 4/21 (19) | 4/37 (11) | 5/32 (16) | 6/53 (11) |
| *P. aeruginosa* | 1/21 (5) | 7/37 (19) | 2/32 (6) | 9/53 (17) |
| *X. maltophilia* | 1/21 (5) | 5/37 (13) | 1/32 (3) | 7/53 (13) |
| Methicillin-susceptible *S. aureus* | 3/21 (14) | 2/37 (5) | 5/32 (16) | 2/53 (4) |
| *E. cloacae* | 0/21 (0) | 4/37 (11) | 1/32 (3) | 4/53 (8) |
| *Acinetobacter calcoaceticus* | 3/21 (14) | 1/37 (3) | 3/32 (9) | 1/53 (2) |
| Other[d] | 9/21 (43) | 14/37 (38) | 15/32 (47) | 24/53 (45) |

[a] Number of organisms that developed resistance/number of organisms present at entry.
[b] *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, group C streptococci, *Citrobacter diversus*, and *Enterobacter aerogenes*.
[c] Number of organisms responsible for superinfection/total cases of superinfection for the treatment group.
[d] *Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Pseudomonas cepacia*, group B streptococci, *Pseudomonas fluorescens*, *Haemophilus influenzae*, methicillin-resistant *Staphylococcus aureus*, coagulase-positive staphylococci, *Achromobacter xylosoxidans*, *Acinetobacter baumanni* (*anitratus*), *Chromobacterium violaceum*, *Serratia* species, *Streptococcus pneumoniae*, coagulase-negative staphylococci, *Bacteroides fragilis*, *Haemophilus parainfluenzae*, *Candida* species, *Serratia marcescens*, *Streptococcus viridans*, *Enterococcus* species, *Flavobacterium meningosepticum*, and *Aerococcus viridans*.

of imipenem patients but not at all in the ciprofloxacin treatment group ($P = 0.030$). Other adverse events occurred with similar frequencies in both treatment groups.

Changes in laboratory values of possible clinical significance that occurred with significantly different frequencies in the two treatment groups included hematocrit decreases (55% of ciprofloxacin-treated patients versus 65% of imipenem-treated patients), uric acid decreases (36 versus 49%), and blood urea nitrogen elevations (24 versus 13%). In addition, 38 and 39% of the ciprofloxacin- and imipenem-treated patients, respectively, who were receiving concomitant theophylline had increases in levels of theophylline in serum of ≥25% from the baseline at some time during the study. However, toxicity was not ascribed to theophylline by any investigator.

**Mortality.** There were 81 (20%) deaths in the intent-to-treat population while patients received the study drug or within the 30-day posttherapy period.

During the first 48 h after study entry, 11 patients (4 imipenem- and 7 ciprofloxacin-treated patients) died. *P. aeruginosa* was isolated from one of the ciprofloxacin-treated patients and one of the imipenem-treated patients who died within the first 48 h of therapy. *P. aeruginosa* was isolated on initial culture from 19 (23%) of the 81 patients who died, and only 2 (3%) of these patients died within the first 48 h of the study.

Of the 81 deaths that occurred, 43 were in the ciprofloxacin treatment group and 38 were in the imipenem treatment group ($P = 0.619$). Eighteen of the 43 deaths in the ciprofloxacin treatment group were attributed to the patients' underlying disease(s), 23 were attributed to bacterial infection, and 2 were considered indeterminate. In the imipenem treatment group, 21 deaths were attributed to an accompanying disease(s), 15 were attributed to bacterial infection, and 2 were considered indeterminate. As stated previously, these assignments were made by the investigators prior to unblinding of the study. The difference in the number of deaths attributed to bacterial infection in the ciprofloxacin versus the imipenem treatment group was not statistically significant ($P = 0.199$).

## DISCUSSION

Parenterally administered antimicrobial agents remain the cornerstone of therapy for severe pneumonia. Although numerous clinical studies have compared various antimicrobial regimens for the treatment of pneumonia, the ability to draw meaningful conclusions regarding the relative efficacy or safety of the agents being evaluated has often been compromised by aspects of trial design or the way results were analyzed and reported. Previous trials often excluded critically ill patients, especially those requiring mechanical ventilation or with severe renal or hepatic dysfunction (16, 17, 43). Most previous trials have employed nonblind study designs (15, 16, 23, 27, 48, 49), lacked an intent-to-treat analysis (16, 27), suffered from small patient sample sizes (39–41, 44), or enrolled patients with other infections in addition to pneumonia (21, 23, 27, 48, 49). This is the first large, randomized, double-blind comparative antimicrobial clinical trial utilizing a rigorous prospective study design with patients with severe pneumonia of which we are aware. Among the strengths of this study were the use of double-blind treatment assignment, analysis of predetermined endpoints before unblinding of the treatment allocation code, and enrollment of patients on the basis of severity of illness. This yielded a large, well-characterized, relatively homogeneous population of seriously ill patients, as evidenced by the large proportion requiring mechanical ventilation and the high initial APACHE II scores. Efficacy analyses of the data were performed for both the efficacy-evaluable and the intent-to-treat populations of patients.

The primary endpoint of this study was eradication of the pretreatment respiratory pathogen(s). Although the difference is not quite statistically significant by univariate analysis, treatment with ciprofloxacin resulted in a 10% higher bacteriological eradication rate than that observed in the imipenem-treated patients. The difference in bacteriological outcome was due mainly to the significantly higher eradication rate among members of the family *Enterobacteriaceae* in the ciprofloxacin treatment group. By using multivariate analysis to control for the presence of *P. aeruginosa* at initiation of therapy, patient

weight, and APACHE II score, ciprofloxacin therapy resulted in a bacteriological eradication rate significantly superior to that achieved with imipenem.

In this large, multicenter study, we have also shown that monotherapy with i.v. ciprofloxacin was superior to imipenem with respect to clinical efficacy in the efficacy-evaluable patient population. Furthermore, even after adjustment for potentially confounding factors highly associated with clinical failures, such as ventilator dependence, APACHE II score, and the presence of *P. aeruginosa* in the pretreatment sputum culture, ciprofloxacin treatment was significantly superior to imipenem in clinical efficacy, according to stepwise logistic regression analysis. In the intent-to-treat analysis, the difference in efficacy between the two treatment regimens did not quite reach significance.

A major clinical question is whether the use of a single antibiotic is sufficient for treatment of severe bacterial pneumonia in seriously ill patients, especially if the infection is with a nosocomially acquired gram-negative bacillus. The results presented here suggest that monotherapy is adequate for treatment of most cases of serious community- and hospital-acquired pneumonia, even in ventilator-dependent patients, unless the causative organism is *P. aeruginosa*. If cases with *P. aeruginosa* are excluded, the bacteriological eradication rates for the ciprofloxacin and imipenem treatment groups are 86 and 66%, respectively. Although some patients did receive concomitant antimicrobial agents, these agents did not generally overlap the spectrum of either study drug.

The importance of *P. aeruginosa* as a respiratory pathogen associated with severe illness and poor outcome is underscored by our stepwise logistic regression analysis, which indicates that the risk of clinical failure with either study drug was approximately double when this organism was cultured prior to institution of therapy. Of the *P. aeruginosa* strains which were susceptible to ciprofloxacin and imipenem prior to therapy, 33 and 53%, respectively, developed resistance during the trial in the efficacy-evaluable population. Even combination therapy with two appropriate antipseudomonal antibiotics may not result in clinical cure, lead to eradication of the organism, or prevent development of resistance (3, 36). In our study, for two-thirds of patients for whom study drug therapy failed, the failure was still evident at the 14- to 28-day posttherapy evaluation, despite the use of subsequent nonstudy antimicrobial agents. Nevertheless, in view of the overall increased likelihood of treatment failure or development of resistance reported in the literature and confirmed by this study, monotherapy with either imipenem or ciprofloxacin cannot be recommended for the treatment of pneumonia when *P. aeruginosa* is isolated. Although there are data that support the use of more than one antipseudomonal agent for the treatment of *P. aeruginosa* bacteremia (22), it is noteworthy that in no patient in this study with *P. aeruginosa* did resistance to either treatment regimen develop earlier than 3 days after initiation of treatment. Furthermore, the proportion of early deaths associated with pretherapy isolation of *P. aeruginosa* was not different from that associated with other organisms. Therefore, when a patient develops severe pneumonia, initial empiric antibiotic therapy with a single potent, broad-spectrum agent is reasonable until culture results are obtained. If *P. aeruginosa* is isolated, then the use of combination therapy appears to be prudent to avoid the emergence of resistance, although routine use of combination antibiotics for severe pneumonia may increase the risk of toxicity or superinfection (24).

There are some limits to this study. Recent data suggest that the clinical criteria used to diagnose pneumonia lack specificity (2, 13, 42, 45, 46). Although strict diagnostic criteria were employed, newer invasive diagnostic methods, such as use of a protected specimen brush or bronchoalveolar lavage, were not routinely employed in this study. However, our entry criteria were those which most clinicians would still employ to make a diagnosis of pneumonia and are consistent with recently published guidelines for the conduct of clinical studies for anti-infective agents (4, 8). While some invasive diagnostic procedures may eventually gain wider acceptance, they are not routinely used to make a bacteriological or clinical diagnosis in most institutions. Furthermore, few data that demonstrate a clear diagnostic or prognostic benefit for these procedures are available (9, 35).

In addition, it must be emphasized that our study population was not necessarily representative of all patients with severe pneumonia. This was primarily because many of the investigators who participated in the study were intensivists or pulmonologists in charge of intensive care units. Nevertheless, the results described here are probably generalizable to most patients with severe pneumonia, especially those receiving mechanical ventilation.

The only two adverse events of statistical significance were seizures and myocardial infarction. Both ciprofloxacin and imipenem have been associated with central nervous system side effects, such as seizures (1, 25). In the present study, seizures occurred significantly more frequently among patients treated with imipenem than among those treated with ciprofloxacin, despite an equal distribution of predisposing conditions. The occurrence of myocardial infarction, although not explainable, was limited to the imipenem treatment group.

In summary, this multicenter, prospective, randomized, blinded, controlled trial demonstrated that ciprofloxacin is superior to imipenem with respect to the clinical response of patients and equivalent to imipenem with respect to eradication of pulmonary pathogens in patients with severe pneumonia. The major risk factors for failure of bacteriological eradication were presence of *P. aeruginosa*, a low body weight, and a high APACHE II score. Risk factors for clinical failure with either regimen also included a high APACHE II score and the presence of *P. aeruginosa* in the pretreatment culture, as well as ventilator dependence. Antibiotic monotherapy can be used successfully to treat severe pneumonia; however, this study clearly demonstrates that additional strategies are necessary to treat pneumonia associated with *P. aeruginosa*, although initial monotherapy appears to be safe for 48 h, until culture results are obtained.

## ACKNOWLEDGMENTS

This work was supported by a research grant from Miles Inc. Pharmaceutical Division, West Haven, Conn.

We thank Adrienne L. Block for editorial contributions and Lisa S. Bednarik for preparation of the manuscript.

## REFERENCES

1. **Arcieri, G. M., N. Becker, B. Esposito, E. Griffith, and A. Heyd.** 1987. Safety of intravenous ciprofloxacin: a review. Am. J. Med. **87**(Suppl. 5A):92S–97S.
2. **Baselski, V. S., M. El-Torky, J. J. Coalson, and J. P. Griffin.** 1992. The standardization of criteria for processing and interpreting laboratory specimens in patients with suspected ventilator-associated pneumonia. Infect. Control Hosp. Epidemiol. **13**:657–666.
3. **Bayer, A. S.** 1989. Clinical utility of new quinolones in treatment of osteomyelitis and lower respiratory tract infections. Eur. J. Clin. Microbiol. Infect. Dis. **8**:1102–1110.
4. **Beam, T. R., Jr., D. N. Gilbert, and C. M. Kunin.** 1992. General guidelines for the clinical evaluation of anti-infective drug products. Clin. Infect. Dis. **15**(Suppl. 1):S5–S32.
5. **Berre, J., J.-P. Thys, M. Husson, D. Gangji, and J. Klastersky.**

1988. Penetration of ciprofloxacin in bronchial secretions after intravenous administration. J. Antimicrob. Chemother. **22**:499–504.

6. **Celis, R., A. Torres, J. M. Gatell, M. Almela, R. Rodriguez-Roisin, and A. Agusti-Vidal.** 1988. Nosocomial pneumonia: a multivariate analysis of risk and prognosis. Chest **93**:318–324.
7. **Chastre, J., F. Viau, P. Brun, et al.** 1984. Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. Am. Rev. Respir. Dis. **130**:924–929.
8. **Chow, A. W., C. B. Hall, J. O. Klein, R. B. Kammer, R. D. Meyer, and J. S. Remington.** 1992. General guidelines for the evaluation of new anti-infective drugs for the treatment of respiratory tract infections. Clin. Infect. Dis. **15**(Suppl. 1):S62–S88.
9. **Cook, D. J., J. M. Fitzgerald, G. H. Guyatt, and S. Walter.** Evaluation of the protected brush catheter and bronchoalveolar lavage in the diagnosis of nosocomial pneumonia. J. Intensive Care Med. **6**:196–205.
10. **Craig, C. P., and S. Connelly.** 1984. Effect of intensive care unit nosocomial pneumonia on duration of stay and mortality. Am. J. Infect. Control **12**:233–238.
11. **Craven, D. E., L. M. Kunches, V. Kilinsky, D. A. Lichtenberg, B. J. Make, and W. R. McCabe.** 1986. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. Am. Rev. Respir. Dis. **133**:792–796.
12. **Fagon, J.-Y., J. Chastre, Y. Domart, J.-L. Trouillet, J. Pierre, C. Darne, and C. Gibert.** 1989. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Am. Rev. Respir. Dis. **139**:877–884.
13. **Fagon, J.-Y., J. Chastre, A. J. Hance, M. Guiget, J.-L. Trouillet, Y. Domart, J. Pierre, and C. Gibert.** 1988. Detection of nosocomial lung infection in ventilated patients: use of a protected specimen brush and quantitative culture techniques in 147 patients. Am. Rev. Respir. Dis. **138**:110–116.
14. **Faling, L. J.** 1988. New advances in diagnosing nosocomial pneumonia in intubated patients. Part I. Am. Rev. Respir. Dis. **137**:253–255.
15. **Fernandez-Guerrero, M., F. Gudiol, A. Rodriguez-Torres, C. Arnau, L. Valdes, and C. Vallve.** 1991. Nosocomial pneumonia: comparative multicentre trial between monotherapy with cefotaxime and treatment with antibiotic combinations. Infection **19**(Suppl. 6):S320–S325.
16. **Garber, G. E., P. Auger, R. M. T. Chan, J. M. Conly, S. D. Shafran, and M. Gerson.** 1992. A multicenter, open comparative study of parenteral cefotaxime and ceftriaxone in the treatment of nosocomial lower respiratory tract infections. Diagn. Microbiol. Infect. Dis. **15**:85–88.
17. **Gentry, L. O., G. Rodriguez-Gomez, R. B. Kohler, F. A. Khan, and M. W. Rytel.** 1992. Parenteral followed by oral ofloxacin for nosocomial pneumonia and community-acquired pneumonia requiring hospitalization. Am. Rev. Respir. Dis. **145**:31–35.
18. **Gleeson, K., and H. Y. Reynolds.** 1992. Pneumonia in the intensive care unit setting. J. Intensive Care Med. **7**:24–35.
19. **Gudiol, F., C. Cabellos, R. Pallares, J. Linares, and J. Ariza.** 1989. Intravenous ciprofloxacin therapy in severe infections. Am. J. Med. **87**(Suppl. 5A):221S–224S.
20. **Haley, R. W., D. H. Culver, J. W. White, W. M. Morgan, and T. G. Emori.** 1985. The nationwide nosocomial infection rate. Am. J. Epidemiol. **121**:159–167.
21. **Hartenauer, U., L. S. Weilemann, K. F. Bodmann, W. W. Ritzerfeld, S. Asmus, and E. M. W. Koch.** 1990. Comparative clinical trial of ceftazidime and imipenem/cilastatin in patients with severe nosocomial pneumonias and septicaemias. J. Hosp. Infect. **15**(Suppl. A):61–64.
22. **Hilf, M., V. L. Yu, J. Sharp, J. J. Zuraleff, J. A. Korvick, and R. R. Muder.** 1989. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. Am. J. Med. **87**:540–546.
23. **Hirata-Dulas, C. A., D. J. Stein, D. R. Guay, R. P. Gruninger, and P. K. Peterson.** 1991. A randomized study of ciprofloxacin versus ceftriaxone in the treatment of nursing home-acquired lower respiratory tract infections. J. Am. Geriatr. Soc. **39**:979–985.

23a. **Knaus, W. A., E. A. Draper, D. P. Wagner, and J. E. Zimmerman.** 1985. APACHE II: a severity of disease classification system. Crit. Care Med. **13**:818–829.

24. **LaForce, F. M.** 1989. Systemic antimicrobial therapy of nosocomial pneumonia: monotherapy versus combination therapy. Eur. J. Clin. Microbiol. Infect. Dis. **8**:61–68.
25. **Leo, R. J., and C. H. Ballow.** 1991. Seizure activity associated with imipenem use: clinical case reports and review of the literature. DICP Ann. Pharmacother. **25**:351–354.
26. **Leu, H.-S., D. L. Kaiser, M. Mori, R. F. Woolson, and R. P. Wenzel.** 1989. Hospital acquired pneumonia: attributable mortality and morbidity. Am. J. Epidemiol. **129**:1258–1267.
27. **Lode, H., R. Wiley, G. Hoffken, J. Wagner, and K. Borner.** 1987. Prospective randomized controlled study of ciprofloxacin versus imipenem-cilastatin in severe clinical infections. Antimicrob. Agents Chemother. **31**:1491–1496.
28. **Mangi, R. J., K. M. Peccerillo, J. Ryan, C. Berenson, T. Greco, G. Thornton, and V. T. Andriole.** 1992. Cefoperazone versus ceftriaxone monotherapy of nosocomial pneumonia. Diagn. Microbiol. Infect. Dis. **15**:441–447.
29. **Mangi, R. J., J. Ryan, C. Berenson, T. Greco, M. Simms III, G. Thornton, and V. T. Andriole.** 1988. Cefoperazone versus ceftazidime monotherapy of nosocomial pneumonia. Am. J. Med. **85**(Suppl. 1A):44–48.
30. **Mantel, N., and W. Haenszel.** 1959. Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. **22**:719–748.
31. **Martin, C., F. Gouin, F. Fourier, W. Junginger, and B. L. Prieur.** 1988. Pefloxacin in the treatment of nosocomial lower respiratory tract infections in intensive care patients. J. Antimicrob. Chemother. **21**:795–799.
32. **National Committee for Clinical Laboratory Standards.** 1990. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically: 2nd ed. M7-A2. National Committee for Clinical Laboratory Standards, Villanova, Pa.
33. **National Committee for Clinical Laboratory Standards.** 1990. Performance standards for antimicrobial disk susceptibility tests: 4th ed. M2-A4. National Committee for Clinical Laboratory Standards, Villanova, Pa.
34. **Neu, H. C., and P. Labthavikul.** 1982. Comparative in vitro activity of *N*-formimidoyl thienamycin against gram-positive and gram-negative aerobic and anaerobic species and its β-lactamase stability. Antimicrob. Agents Chemother. **21**:180–187.
35. **Niederman, M. S.** 1991. Diagnosing nosocomial pneumonia: to brush or not to brush. J. Intensive Care Med. **6**:151–152. (Editorial.)
36. **Niederman, M. S., R. D. Ferranti, A. Zeigler, W. W. Merrill, and H. Y. Reynolds.** 1984. Respiratory infection complicating long-term tracheostomy: the implication of persistent gram-negative tracheobronchial colonization. Chest **85**:39–44.
37. **Pachon, J., M. D. Prados, F. Capote, J. A. Cuello, J. Garnacho, and A. Verano.** 1990. Severe community-acquired pneumonia: etiology, prognosis, and treatment. Am. Rev. Respir. Dis. **142**:369–373.
38. **Peloquin, C. A., T. J. Cumbo, D. E. Nix, M. F. Sands, and J. J. Schentag.** 1989. Intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections: impact of plasma concentrations, organism MIC, and clinical condition on bacterial eradication. Arch. Intern. Med. **149**:2269–2273.
39. **Potgieter, P. D., D. M. Linton, A. A. Forder, and H. Plumb.** 1988. Imipenem/cilastatin in the treatment of severe nosocomial pneumonia. S. Afr. Med. J. **74**:390–392.
40. **Rapp, R. P., M. Billeter, J. Hatton, A. B. Young, P. A. Tibbs, and R. J. Dempsey.** 1991. Intravenous ciprofloxacin versus ceftazidime for treatment of nosocomial pneumonia and urinary tract infection. Clin. Pharm. **10**:49–55.
41. **Rapp, R. P., B. Young, K. Bertch, P. Tibbs, and T. S. Foster.** 1987. Clinical outcome of nosocomial pneumonia following imipenem/cilastatin therapy. Drug Intell. Clin. Pharm. **21**:272–276.
42. **Richard, C., M. Pezzano, B. Bouhaja, E. Rottman, A. Rimailho, B. Riou, and P. Auzepy.** 1988. Comparison of non-protected lower respiratory tract secretions and protected specimen brush samples in the diagnosis of pneumonia. Intensive Care Med. **14**:30–33.
43. **Rivera-Vazquez, C. R., C. H. Ramirez-Ronda, J. R. Rodriguez, and**

**S. Saavedra.** 1989. A comparative analysis of aztreonam + clindamycin versus tobramycin + clindamycin or amikacin + mezlocillin in the treatment of gram-negative lower respiratory tract infections. Chemotherapy **35**(Suppl. 1):89–100.

44. **Salata, R. A., R. L. Gebhart, D. L. Palmer, B. H. Wade, W. M. Scheld, D. H. M. Groschel, R. P. Wenzel, G. L. Mandell, and R. J. Duma.** 1985. Pneumonia treated with imipenem. Am. J. Med. **78**(Suppl. 6A):104–109.
45. **Torres, A., J. Puig de la Bellacasa, J. Rodriguez-Roisin, M. T. Jimenez de Anta, and A. Agusti-Vidal.** 1988. Diagnostic value of telescoping plugged catheters in mechanically ventilated patients with bacterial pneumonia using the Metras catheter. Am. Rev. Respir. Dis. **138**:117–120.
46. **Torres, A., J. Puig de la Bellacasa, A. Xaubert, J. Gonzalez, J. Rodriguez-Roisin, M. T. Jimenez de Anta, and A. Agusti-Vidal.** 1989. Diagnostic value of quantitative cultures of bronchoalveolar lavage and telescoping plugged catheters in mechanically ventilated patients with bacterial pneumonia. Am. Rev. Respir. Dis. **140**:306–310.
47. **Torres, A., J. Serra-Batlles, A. Ferrer, P. Jimenez, R. Celis, E. Cobo, and R. Rodriguez-Roisin.** 1991. Severe community-acquired pneumonia. Am. Rev. Respir. Dis. **144**:312–318.
48. **Trenholme, G. M., J. C. Pottage, Jr., and P. H. Karakusis.** 1985. Use of ceftazidime in the treatment of nosocomial lower respiratory infections. Am. J. Med. **79**(Suppl. 2A):32–36.
49. **Trenholme, G. M., B. A. Schmitt, J. Spear, L. C. Gvazdinskas, and S. Levin.** 1989. Randomized study of intravenous/oral ciprofloxacin versus ceftazidime in the treatment of hospital and nursing home patients with lower respiratory tract infections. Am. J. Med. **87**(Suppl. 5A):116S–118S.
50. **Unertl, K., G. Ruckdeschel, H. Forst, and F. P. Lehnert.** 1986. Imipenem/cilastatin for the treatment of respiratory tract infections in patients with ventilatory support. Infection **14**(Suppl. 2):176–180.
51. **van Caekenberghe, D. L., and S. R. Pattyn.** 1984. In vitro activity of ciprofloxacin compared with those of other new fluorinated piperazinyl-substituted quinolone derivatives. Antimicrob. Agents Chemother. **25**:518–521.
52. **Wolfson, J. S., and D. C. Hooper.** 1989. Fluoroquinolone antimicrobial agents. Clin. Microbiol. Rev. **2**:378–424.
53. **Wunderink, R. G., L. S. Woldenberg, J. Zeiss, C. M. Day, J. Ciemins, and D. A. Lacher.** 1992. The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. Chest **101**:458–463.
54. **Zelen, M.** 1971. The analysis of several 2 × 2 contingency tables. Biometrika **58**:129–137.