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# A Multicenter, Randomized Study Comparing the Efficacy and Safety of Intravenous and/or Oral Levofloxacin versus Ceftriaxone and/or Cefuroxime Axetil in Treatment of Adults with Community-Acquired Pneumonia

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**Five hundred ninety patients were enrolled in a prospective, multicenter, randomized trial comparing the efficacy and safety of 7 to 14 days of levofloxacin treatment with that of ceftriaxone and/or cefuroxime axetil in the management of community-acquired pneumonia in adults. Patients received either intravenous and/or oral levofloxacin (500 mg once daily) or the comparative agents, parenteral ceftriaxone (1 to 2 g once to twice daily) and/or oral cefuroxime axetil (500 mg twice daily). Erythromycin or doxycycline could be added to the comparator arm at the investigator's discretion. The decision to use an intravenous or oral antimicrobial agent for initial therapy was made by the investigator. Clinical and microbiological evaluations were completed at the baseline, during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Four hundred fifty-six patients (226 given levofloxacin and 230 administered ceftriaxone and/or cefuroxime axetil) were evaluable for clinical efficacy. *Streptococcus pneumoniae* and *Haemophilus influenzae* were isolated in 15 and 12%, respectively, of clinically evaluable patients. One hundred fifty atypical pathogens were identified: 101 were *Chlamydia pneumoniae*, 41 were *Mycoplasma pneumoniae*, and 8 were *Legionella pneumophila*. Clinical success at 5 to 7 days posttherapy was superior for the levofloxacin group (96%) compared with the ceftriaxone and/or cefuroxime axetil group (90%) (95% confidence interval [CI] of −10.7 to −1.3). Among patients with typical respiratory pathogens who were evaluable for microbiological efficacy, the overall bacteriologic eradication rates were superior for levofloxacin (98%) compared with the ceftriaxone and/or cefuroxime axetil group (85%) (95% CI of −21.6 to −4.8). Levofloxacin eradicated 100% of the most frequently reported respiratory pathogens (i.e., *H. influenzae* and *S. pneumoniae*) and provided a >98% clinical success rate in patients with atypical pathogens. Both levofloxacin and ceftriaxone-cefuroxime axetil eradicated 100% of the *S. pneumoniae* cells detected in blood culture. Drug-related adverse events were reported in 5.8% of patients receiving levofloxacin and in 8.5% of patients administered ceftriaxone and/or cefuroxime axetil. Gastrointestinal and central and peripheral nervous system adverse events were the most common events reported in each treatment group. In conclusion, these results demonstrate that treatment with levofloxacin is superior to ceftriaxone and/or cefuroxime axetil therapy in the management of community-acquired pneumonia in adults.**

Respiratory illnesses are among the most frequently encountered by physicians in the United States in both their outpatient and hospital practices. In particular, community-acquired pneumonia has an estimated annual incidence of 4 million cases in ambulatory patients, or 12 cases per 1,000 persons (2). Pneumonia, in general, is the sixth leading cause of death in the United States and is responsible for more than 600,000 hospital admissions per year (2, 28). For cases of community-acquired pneumonia requiring hospital admission, mortality rates approximate 13.7% (9) and appear to be even higher in the elderly population (28).

The most common bacterial pathogens associated with community-acquired pneumonia are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae* (10). In the last decade, however, pathogens such as *Moraxella catarrhalis*, *Legionella pneumophila*, and *Chlamydia pneumoniae* (TWAR) have been identified more frequently (9). Accordingly, empirical therapy should predictably inhibit *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, and atypical pathogens.

Levofloxacin, the purified levorotatory isomer of the racemate ofloxacin, is the primary chemical component responsible for the antibacterial activity of ofloxacin (13). It has a broad spectrum of antibacterial activity and an effective in vitro profile against gram-negative and gram-positive aerobes, as well as atypical pathogens (12, 13, 17, 38). Levofloxacin has excellent in vitro activity against typical respiratory pathogens (*S. pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*) and atypical pathogens such as *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila* (12, 13, 17, 38). These data suggest that levofloxacin would be an appropriate therapeutic choice in the treatment of community-acquired bacterial pneumonia.

Ceftriaxone and cefuroxime axetil are both cephalosporins with stability to commonly encountered β-lactamases. In addi-

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tion, these agents have documented in vitro activity against many typical aerobic gram-positive cocci and gram-negative bacilli associated with community-acquired pneumonia (31, 35). Numerous clinical trials have led to reports of the effectiveness of ceftriaxone (1, 3, 15, 25, 34) and cefuroxime axetil (4, 7, 36) in the management of lower respiratory tract infections, including community-acquired pneumonia caused by susceptible pathogens. One important limitation, however, of all β-lactam agents is their lack of in vitro activity against atypical respiratory tract pathogens.

The initial management of community-acquired pneumonia requires a decision regarding the need for patient hospitalization. In select circumstances, the patient may be ill enough to require hospital admission and intravenous (i.v.) antibiotics. Subsequently, oral antibiotics may replace i.v. agents once the patient has improved and if an efficacious and safe oral agent with which to treat the infecting pathogen(s) is available. The two dosage forms (oral and i.v.) of levofloxacin are interchangeable based on the nearly 100% oral bioavailability and the similar serum concentration-versus-time profiles of oral and i.v. levofloxacin (6). In addition, levofloxacin can be given once daily, which may enhance patient compliance.

The primary objective of the present study was to compare the efficacy and safety of intravenous and/or oral levofloxacin therapy with those of ceftriaxone and/or cefuroxime axetil therapy (with or without erythromycin or doxycycline) in the management of adult patients with community-acquired pneumonia.

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## MATERIALS AND METHODS

**Patient selection.** Adult patients with a primary diagnosis of community-acquired pneumonia were eligible for enrollment, and patients could be treated either in the hospital or on an outpatient basis. Patients had to have a new pulmonary infiltrate, as revealed by chest roentgenogram, compatible with pneumonia and two or more signs and symptoms consistent with a lower respiratory tract infection (i.e., elevated temperature, new or increased cough, production of purulent sputum, rales or pleuritic chest pain, and shortness of breath). Excluded from the study were patients with infections due to organisms known to be resistant to a study drug prior to study entry; patients with a diagnosis of cystic fibrosis or fungal infection; patients with empyema; patients with human immunodeficiency virus infection and CD4 counts of $<200$ cells/mm$^3$; patients with neutropenia ($<500$ cells/mm$^3$); patients with hospital-acquired infections; patients requiring a second systemic antimicrobial agent; patients with a history of seizures or a major psychiatric disorder; patients with a history of allergy to a study drug(s) or to β-lactam or quinolone antimicrobial agents; women who were pregnant or nursing; patients with severe renal impairment (creatinine clearance of $<20$ ml/min); and patients who had received any investigational agent within 30 days of study entry. Patients who received previous antimicrobial therapy could be enrolled if their duration of therapy had been $\leq 24$ h or if they had failed to respond to such therapy. The study was approved by each center's institutional review board, and all patients provided written informed consent.

**Study design and antimicrobial therapy.** This was a multicenter, prospective, randomized, open-label, active-controlled study. Patients were randomly assigned to one of two treatment groups: those receiving levofloxacin (i.v. and/or orally) and those administered ceftriaxone (parenterally) and/or cefuroxime axetil (orally). The decision to initiate i.v. or oral antimicrobial agents therapy was at the discretion of the investigator. Levofloxacin (The R. W. Johnson Pharmaceutical Research Institute, Raritan, N.J.) was administered i.v., as a 1-h infusion, at a dosage of 500 mg once daily or orally at a dosage of 500 mg once daily for 7 to 14 days. Ceftriaxone (Rocephin; Hoffman LaRoche, Nutley, N.J.) was administered i.v. at a dosage of 1 or 2 g once or twice daily for 7 to 14 days. Cefuroxime axetil (Ceftin; Glaxo, Research Triangle Park, N.C.) was given orally at a dosage of 500 mg twice daily for 7 to 14 days. The investigator could switch a patient from i.v. to oral therapy at any time if such a change was clinically indicated. In addition, for those patients receiving ceftriaxone and/or cefuroxime axetil treatment, i.v. or oral erythromycin could be added to the regimen at a dosage of 500 mg to 1 g every 6 h if atypical respiratory pathogens were suspected or proven; doxycycline was allowed if the patient could not tolerate erythromycin.

**Microbiological investigations.** A sputum specimen for routine culture and Gram stain was obtained within 48 h prior to the start of treatment. Identification of causative organisms and testing for aerobic susceptibility to all study drugs by disk and MIC methods were performed according to National Committee for Clinical Laboratory Standards procedures (29, 30). When available, a direct fluorescent antibody test and culture for *L. pneumophila* were performed on sputum (21). A urine antigen assay for *Legionella* spp. was also performed at the time of admission. In addition, blood samples were obtained from inpatients for blood culture. Acute- and convalescent-phase (study days 21 to 28) serological studies for *M. pneumoniae* (enzyme-linked immunosorbent assay), *L. pneumophila* (enzyme-linked immunosorbent assay), and *C. pneumoniae* (microimmunofluorescence test) were performed on all patients. Identification of atypical pathogens was performed at standardized reference laboratories. *L. pneumophila* and *M. pneumoniae* identifications were conducted at Covance Central Laboratory Services (formerly Corning Scicor Laboratories), Indianapolis, Ind., and *C. pneumoniae* testing was done at Infectious Disease Laboratory (Robert B. Jones, director), Department of Medicine, Indiana University School of Medicine, Indianapolis, Ind.

Microbiological identification of atypical pathogens and classification of the diagnosis as definitive or probable were defined as follows:

**(i) Definitive identification.** A definitive identification of *L. pneumophila* required a positive culture, urinary antigen test, direct fluorescent antibody test, or a fourfold increase in the immunoglobulin G (IgG) or IgM titer compared to the admission titer. A definitive identification of *C. pneumoniae* or *M. pneumoniae* required a fourfold increase in the IgG or IgM titer compared to the admission titer.

**(ii) Probable identification.** A probable identification of *L. pneumophila* required a single elevated IgG or IgM titer of $\geq$1:256, while that of *C. pneumoniae* required a single elevated IgG titer of $>$1:512 or IgM titer of $\geq$1:32. A probable identification of *M. pneumoniae* required a single elevated IgG titer of $\geq$1:128 or IgM titer of $\geq$1:16.

**Clinical and microbiological evaluations.** Clinical response was the primary efficacy variable in this study. Patients were evaluated for clinical symptoms and physical signs of infection prior to therapy, 2 to 4 days after starting treatment, 5 to 7 days posttreatment, and 21 to 28 days posttreatment. Patients were considered to have severe infections if they met at least one of the following criteria: bacteremia, hypotension at time of baseline (diastolic blood pressure of $<$60 mm Hg), or a baseline respiratory rate of $\geq$30 breaths per min (5). The remainder of the patients were considered to have infections of mild to moderate severity.

Clinical assessment was made on the basis of changes in symptoms and signs from the initial (pretherapy) presentation, as well as by comparing the posttherapy chest roentgenograms, when available, with those obtained upon admission. The clinical response at the first posttherapy visit (5 to 7 days posttherapy) was categorized as cured (resolution of signs and symptoms associated with active infection along with improvement in chest roentgenogram findings), improved (incomplete resolution of signs, symptoms, and chest roentgenogram findings), failure (no response to therapy), or indeterminate (no evaluation possible). At the second posttherapy visit (21 to 28 days posttherapy), patients were categorized as cured (resolution of signs and symptoms associated with active infection along with improvement in chest roentgenogram findings), improved (continued incomplete resolution of signs and symptoms with no deterioration or relapse during the follow-up period), relapsed (resolution or improvement of signs and symptoms at the initial posttherapy evaluation with reappearance or deterioration of signs and symptoms of infection), or indeterminate (no evaluation possible). Patients were considered clinically unevaluable for the following reasons: concomitant administration of a nonstudy antimicrobial agent(s), an insufficient course of therapy ($<$5 days, or if the patient was a clinical failure and received $<$48 h of therapy), discontinuation of a study drug due to an adverse event, violation of entry criteria, failure to return for posttherapy evaluations, inappropriate timing of posttherapy clinical evaluation ($>$10 days posttherapy), or other protocol violations, such as patient noncompliance (received $<$70% of the study drug).

Bacterial response to treatment was a secondary efficacy variable in this study, and its evaluation included assessment of pathogens isolated from respiratory specimens and blood cultures. A culture was considered microbiologically evaluable if it was adequate and obtained at the appropriate time and if the patient was clinically evaluable. Microbiological responses after completion of therapy were defined as eradication or presumed eradication (admission pathogen[s] was absent, or there was no material available for culture because of a favorable clinical response), persistence (admission pathogen[s] was present at the end of therapy), persistence with acquisition of resistance (persistence of the admission pathogen at posttherapy with documented acquisition of resistance), or indeterminate (not evaluable for any reason; e.g., patient lost to follow-up or posttherapy culture not obtained). Superinfection was defined as a new infection-causing organism, found at any site during therapy, which required a change in antimicrobial therapy.

**Safety evaluations.** All patients who received at least one dose of the study drug were evaluated for drug safety. Adverse events were categorized by the investigator as to their intensity (mild, moderate, or marked) and their relationship to the study drug (none, remote, possible, probable, or definite). Laboratory

TABLE 1. Demographic and baseline characteristics of clinically and microbiologically evaluable patients

| Characteristic | Value for group treated with[a]: | | | |
|---|---|---|---|---|
| | Levofloxacin | | Ceftriaxone and/or cefuroxime axetil | |
| | Clinically evaluable patients ($n$ = 226) | Microbiologically evaluable patients ($n$ = 128) | Clinically evaluable patients ($n$ = 230) | Microbiologically evaluable patients ($n$ = 144) |
| Sex | | | | |
| Men | 125 (55) | 73 (57) | 124 (54) | 83 (58) |
| Women | 101 (45) | 55 (43) | 106 (46) | 61 (42) |
| Race | | | | |
| Caucasian | 147 (65) | 86 (67) | 151 (66) | 101 (70) |
| Black | 74 (33) | 41 (32) | 75 (33) | 42 (29) |
| Other | 5 (2) | 1 (1) | 4 (2) | 1 (1) |
| Age (yr) | | | | |
| Mean ± SD | 49.1 ± 17.6 | 50.0 ± 17.9 | 50.1 ± 18.5 | 50.6 ± 17.7 |
| Range | 19–87 | 19–87 | 18–93 | 18–88 |
| Infection severity | | | | |
| Severe | 36 (16) | 21 (16) | 37 (16) | 28 (19) |
| Mild to moderate | 190 (84) | 107 (84) | 193 (84) | 116 (81) |
| Patient status | | | | |
| Inpatient | 104 (46) | 60 (47) | 96 (42) | 60 (42) |
| Outpatient | 122 (54) | 68 (53) | 134 (58) | 84 (58) |

[a] Values represent numbers (percentages) of patients except where otherwise indicated.

tests were performed prior to therapy, 5 to 7 days posttherapy, and 21 to 28 days posttherapy, as well as when clinically indicated.

**Statistical analyses.** The primary objective of this study was to determine if levofloxacin therapy was statistically equivalent to treatment with ceftriaxone and/or cefuroxime axetil. Clinical response was considered the primary efficacy variable. The sample size estimate of 366 clinically evaluable patients assumed an 80% power to detect a 15% difference in clinical success (cure plus improved) rates between the two treatment groups, assuming 81 and 85% clinical success rates for the levofloxacin and ceftriaxone and/or cefuroxime axetil treatment groups and a 2.5% significance level. Two-sided 95% confidence intervals (95% CIs; normal approximation to the binomial with a continuity correction) were calculated for the differences in the clinical success and microbiological eradication rates of the two treatment groups (19). Study centers with fewer than 10 evaluable patients were pooled.

A two-sided $t$ test for two independent samples was used to compare the mean ages of males, females, and both sexes combined of the two treatment groups. A two-sided Fisher's exact test was used to compare differences in the proportions of males and of white patients in the treatment groups. A $P$ value of $\leq 0.05$ was considered to be statistically significant. Rates of occurrence of adverse events in the two groups were compared, using 95% CIs for their differences.

## RESULTS

The intent-to-treat population consisted of 590 patients enrolled at 40 centers: 295 were treated with levofloxacin, and 295 were treated with ceftriaxone and/or cefuroxime axetil. Six patients (four in the levofloxacin group and two in the ceftriaxone and/or cefuroxime axetil group) were lost to follow-up and therefore not evaluable for safety. The demographic and baseline characteristics of the intent-to-treat group were comparable for the levofloxacin and ceftriaxone and/or cefuroxime axetil treatment populations. Three hundred ten patients (53%) were enrolled as outpatients, and 280 patients (47%) were initially treated in the hospital. The majority of patients (84%) were categorized as having infections of mild to moderate severity. The demographic and baseline characteristics of the patients included in the groups evaluable for efficacy were found to be similar for the two treatment groups and were comparable to those of the intent-to-treat population (Table 1). The mortality rate in hospitalized patients was 3.6%; 1.4 and 5.6% of hospitalized patients in the levofloxacin and ceftriaxone and/or cefuroxime axetil groups, respectively, died.

Two hundred twenty-six patients in the levofloxacin group and 230 in the ceftriaxone and/or cefuroxime axetil group were clinically evaluable. The reasons that patients were considered clinically unevaluable included insufficient course of therapy (for 18 receiving levofloxacin and 15 receiving ceftriaxone and/or cefuroxime axetil), inappropriate timing of posttherapy clinical evaluation (for 17 receiving levofloxacin and 12 receiving ceftriaxone and/or cefuroxime axetil), no posttherapy evaluation (for 12 receiving levofloxacin and 16 receiving ceftriaxone and/or cefuroxime axetil), other protocol violations (for 10 receiving levofloxacin and 9 receiving ceftriaxone and/or cefuroxime axetil), unconfirmed clinical diagnosis (for 4 receiving levofloxacin and 4 receiving ceftriaxone and/or cefuroxime axetil), effective concomitant therapy (for 4 receiving levofloxacin and 7 receiving ceftriaxone and/or cefuroxime axetil), and unevaluable for safety (for 4 receiving levofloxacin and 2 receiving ceftriaxone and/or cefuroxime axetil).

The mean total duration of treatment for clinically evaluable patients for both treatment groups was 11.7 days. Five patients (2.2%) received only i.v. levofloxacin, and 138 (61%) received only the oral formulation. The mean durations of i.v. and oral levofloxacin therapy were 3.4 and 10.6 days, respectively. In the comparator group, 5 patients (2.2%) received only i.v. ceftriaxone and 116 patients (50.4%) received only oral cefuroxime axetil; the remainder received both ceftriaxone and cefuroxime axetil. The mean durations of i.v. ceftriaxone and oral cefuroxime axetil treatments were 3.4 and 10.3 days, respectively. Fifty clinically evaluable patients (22%) receiving ceftriaxone and/or cefuroxime axetil also received erythromycin or doxycycline therapy.

The most common typical bacterial pathogens among clinically evaluable patients were *S. pneumoniae* (isolated from 63 sputum specimens) and *H. influenzae* (isolated from 54 sputum specimens). One hundred fifty atypical pathogens were iden-

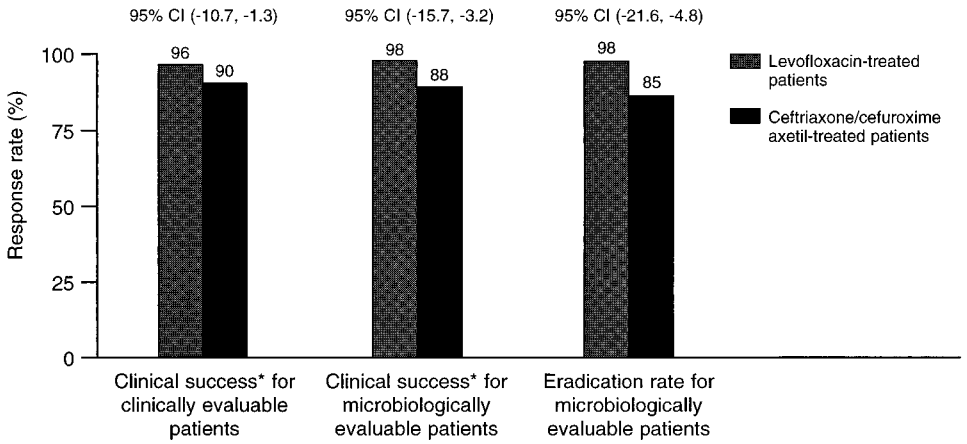


FIG. 1. Clinical and microbiological responses at 5 to 7 days posttherapy in clinically and microbiologically evaluable patients. Clinical success*, sum of cured and improved.

tified: 101 were *C. pneumoniae* (30 definitive and 71 probable), 41 were *M. pneumoniae* (10 definitive and 31 probable), and 8 were *Legionella* spp. (5 definitive and 3 probable).

The clinical success rates (cure or improvement) at 5 to 7 days posttherapy were 96% for the levofloxacin group and 90% for the ceftriaxone and/or cefuroxime axetil group (Fig. 1). The 95% CI of −10.7 to −1.3 suggests that levofloxacin was superior to ceftriaxone and/or cefuroxime axetil. Clinical failures occurred in 8 patients (3.5%) receiving levofloxacin and in 22 patients (9.6%) receiving ceftriaxone and/or cefuroxime axetil (Table 2). Of the 22 clinical failures in the cephalosporin group, 2 received i.v. ceftriaxone only, 12 received cefuroxime axetil only, and 8 received both i.v. ceftriaxone and oral cefuroxime axetil. Of the eight clinical failures in the levofloxacin group, two were associated with microbiological persistence, one involved eradication of the pathogen from the patient, and five were indeterminate with regard to the microbiological response (i.e., no pathogen was identified at admission). The corresponding numbers in the ceftriaxone-cefuroxime axetil group were as follows: 11 patients who clinically failed therapy had pathogens which persisted, in 3 patients the admission pathogen was eradicated, 3 patients had a single atypical pathogen, and in 5 patients no pathogen was identified at admission. Table 2 lists the admission pathogens (if available) associated with clinical failures in clinically evaluable patients.

The proportions of patients with evidence of clinical resolution of symptoms and signs of pneumonia are presented in Tables 3 and 4, respectively. Among clinically evaluable patients, resolution or improvement of abnormal pretherapy radiographic findings was observed at the posttherapy visit in 97% of patients treated with levofloxacin and in 91% of those treated with ceftriaxone and/or cefuroxime axetil.

One hundred ninety patients (84%) and 193 patients (84%) in the levofloxacin and ceftriaxone-cefuroxime axetil groups, respectively, had mild to moderate infections. Clinical success rates for those with mild to moderate infections and those with severe infections were similar in both treatment groups. The cure rates in both treatment groups decreased with advanced age.

Of those determined to be cured or improved at 5 to 7 days posttherapy and evaluated at 3 to 4 weeks posttherapy, relapse occurred in six patients in the levofloxacin group and in four patients in the ceftriaxone-cefuroxime axetil group.

Seventeen clinically evaluable patients (nine receiving levofloxacin and eight receiving ceftriaxone and/or cefuroxime axetil) had concurrent bacteremias caused by *S. pneumoniae*. The

TABLE 2. Pathogens associated with clinical failures in clinically evaluable patients

| Treatment group | Pathogen[a] | | | No. with no organism[b] |
|---|---|---|---|---|
| | Persisting | Eradicated | Atypical | |
| Levofloxacin[c] ($n$ = 8) | *H. parainfluenzae*<br>*S. pyogenes* | *H. haemolyticus* | *C. pneumoniae* | 5 |
| Ceftriaxone and/or cefuroxime axetil[d] ($n$ = 16) | *H. parainfluenzae* (5)<br>*H. influenzae* (4)<br>*P. aeruginosa* | *K. pneumoniae*<br>*S. pneumoniae* (2)<br>*H. influenzae* (2)<br>*E. cloacae*<br>*S. aureus*<br>*Streptococcus* group C | *C. pneumoniae* (2) | 3 |
| Ceftriaxone and/or cefuroxime axetil plus erythromycin or doxycycline[e] ($n$ = 6) | *H. parainfluenzae*<br>*K. pneumoniae* | | *C. pneumoniae* (2)<br>*L. pneumophila* | 2 |

[a] Numbers in parentheses indicate the number of patients with the particular pathogen.
[b] Number of patients from which no organism was isolated at the time of admission.
[c] One patient in this group had two pathogens isolated at admission.
[d] Three patients in this group had more than one pathogen. Two patients had two pathogens isolated at admission, and one patient had six. In the latter patient, *P. aeruginosa* persisted and *E. cloacae*, *H. influenzae*, *S. aureus*, *S. pneumoniae*, and *Streptococcus* group C were eradicated.
[e] One patient in this group had two pathogens isolated at admission.

TABLE 3. Proportions of clinically evaluable patients with resolution or improvement of clinical symptoms based on posttherapy clinical assessment

| Presenting symptom | Proportion of patients with resolution or improvement of symptoms in group treated with[a]: | |
|---|---|---|
| | Levofloxacin | Ceftriaxone and/or cefuroxime axetil |
| Chills | 147/153 (96) | 134/139 (96) |
| Pleuritic chest pain | 126/140 (90) | 109/128 (85) |
| Shortness of breath | 138/164 (84) | 120/177 (68) |
| Increase in cough | 128/219 (58) | 128/226 (57) |
| Increase in sputum | 151/203 (74) | 139/198 (70) |
| Purulent sputum | 165/172 (96) | 143/162 (88) |

[a] The numerator of each value represents the number of patients experiencing resolution or improvement as determined during a posttherapy test-of-cure visit. The denominator represents the number of patients with that symptom at admission. The values in parentheses are percentages.

clinical success rate for these 17 patients was 100%, with clinical cures being observed in 78% of the levofloxacin-treated patients and 50% of ceftriaxone- or cefuroxime axetil-treated patients; the remainder of the patients in both groups exhibited clinical improvement.

The clinical success rates in clinically evaluable patients of the two groups were also compared based on the pathogen isolated at admission (Table 5). Clinical success rates for the two most prevalent typical respiratory pathogens, *H. influenzae* and *S. pneumoniae*, were 100% for both pathogens in the levofloxacin group and 79 and 94%, respectively, in the ceftriaxone and/or cefuroxime axetil group. With the exception of one patient with *Haemophilus parainfluenzae*, patients in the levofloxacin group had a 100% clinical success rate for the common typical respiratory pathogens.

*C. pneumoniae* was identified in 47 levofloxacin-treated and 54 ceftriaxone and/or cefuroxime axetil-treated clinically evaluable patients. Clinical success was observed in 98% of levofloxacin-treated patients and in 93% of ceftriaxone- and/or cefuroxime axetil-treated patients with this pathogen. Clinical success rates for the atypical pathogens *M. pneumoniae* and *L. pneumophila* were 100% for both pathogens in the levofloxacin group and 100 and 66%, respectively, in the ceftriaxone and/or cefuroxime axetil group. For the three atypical pathogens, overall, clinical success was observed in 99% of cases in levofloxacin-treated patients and in 94% of cases in ceftriaxone- and/or cefuroxime axetil-treated patients. Twenty-eight percent of patients in the ceftriaxone and/or cefuroxime axetil group who subsequently were found to have atypical pathogens received erythromycin or doxycycline. The clinical response was similar for those patients in the comparator arm with atypical pathogens who received erythromycin or doxycycline and those who did not. Also, the clinical response rates for patients with atypical pathogens that met definitive diagnostic requirements were not different from the responses when all cases were included (definitive plus probable cases). Of the 101 clinically evaluable patients who were serologically positive for *C. pneumoniae*, 49 (49%) were coinfected with other pathogens. Eighteen of the 41 patients (44%) identified as being infected with *M. pneumoniae* were coinfected with another pathogen(s). Similarly, 63% (five of eight) of patients infected with *L. pneumophila* were coinfected with another pathogen(s).

TABLE 4. Proportion of clinically evaluable patients with resolution or improvement of clinical signs of pneumonia based on posttherapy clinical assessment[a]

| Presenting sign | Proportion of patients with resolution or improvement of signs in group treated with[b]: | | | |
|---|---|---|---|---|
| | Levofloxacin | | Ceftriaxone and/or cefuroxime axetil | |
| | No. resolved | No. improved | No. resolved | No. improved |
| Diminished breath sounds | 95/124 (77) | 9/124 (7) | 110/143 (77) | 12/143 (8) |
| Rales | 119/139 (86) | 11/139 (8) | 122/163 (75) | 27/163 (17) |
| Egophony | 50/51 (98) | 0/51 (0) | 50/53 (94) | 2/53 (4) |
| Rhonchi | 91/107 (85) | 7/107 (7) | 101/130 (78) | 11/130 (8) |
| Wheezing | 70/81 (86) | 6/81 (7) | 59/75 (78) | 7/75 (9) |

[a] Signs were graded as none, mild, moderate, or severe. Improvement was defined as a decrease in severity without complete resolution.

[b] The numerator of each value represents the number of patients experiencing resolution or improvement as determined during a posttherapy test-of-cure visit. The denominator represents the number of patients with that sign at admission. The values in parentheses are percentages.

**Microbiological outcome.** One hundred twenty-eight patients in the levofloxacin group and 144 patients in the ceftriaxone and/or cefuroxime axetil group were microbiologically evaluable. The major reason why patients were excluded from this analysis was lack of a pretherapy pathogen (for 125 receiving levofloxacin and 113 receiving ceftriaxone and/or cefuroxime axetil).

In patients with typical pathogens, the microbiological response revealed eradication rates of 98% for those in the levofloxacin treatment group and 85% for those receiving ceftriaxone and/or cefuroxime axetil (Fig. 1). The 95% CI of −21.6 to −4.8 indicates superiority of levofloxacin over ceftriaxone and/or cefuroxime axetil in eradicating respiratory tract pathogens in this study. In both treatment groups, *S. pneumoniae* and *H. influenzae* were the most frequent typical respiratory pathogens causing infection (Table 6). By organism, the overall microbiological eradication rates were 98 and 89% for the levofloxacin and ceftriaxone and/or cefuroxime axetil treatment groups, respectively. In the levofloxacin group, eradication rates for the most common bacterial pathogens isolated by culture at the time of admission ranged from 88 to 100%. In contrast, for the most common respiratory pathogens, eradication rates with ceftriaxone and/or cefuroxime axetil ranged from 71 to 100%. The greatest difference in eradication rates was seen with *H. influenzae* isolates; levofloxacin eradicated 100% of these pathogens, compared to the ceftriaxone and/or cefuroxime axetil group eradication rate of 79% (95% CI, −39.2 to −2.5). Of the five isolates of *H. influenzae* associated with microbiological failure in the cephalosporin group, three were from patients treated with oral cefuroxime axetil only, one was from a patient treated with i.v. ceftriaxone only, and one was from a patient treated with both i.v. ceftriaxone and oral cefuroxime axetil.

None of the admission pathogens isolated were resistant to levofloxacin, while 5 of these pathogens were resistant to ceftriaxone and 19 were resistant to cefuroxime axetil. The pathogens resistant to ceftriaxone were *S. pneumoniae*, *Alcaligenes* spp., *Pseudomonas maltophilia*, and *Pseudomonas putida*. Those resistant to cefuroxime included *S. pneumoniae*, *Pseudomonas aeruginosa*, *H. parainfluenzae*, *Enterobacter cloacae*, *H. influenzae*, *Pseudomonas fluorescens*, *P. maltophilia*, and *P. putida.*

For microbiologically evaluable patients, levofloxacin eradicated all *S. pneumoniae* from both respiratory ($n = 30$) and blood ($n = 9$) sites. Of these 39 isolates of *S. pneumoniae* in the

TABLE 5. Clinical response, by pathogen, 5 to 7 days posttherapy for the clinically evaluable population

| Method of evaluation and pathogen detected | No. (%) of patients cured, improved, or deemed treatment failures in group treated with[a]: | | | | | |
|---|---|---|---|---|---|---|
| | Levofloxacin | | | Ceftriaxone and/or cefuroxime axetil | | |
| | No. (%) cured | No. (%) improved | No. (%) failed | No. (%) cured | No. (%) improved | No. (%) failed |
| Respiratory culture | | | | | | |
| *H. influenzae* | 24 (80) | 6 (20) | 0 (0) | 17 (71) | 2 (8) | 5 (21) |
| *S. pneumoniae* | 23 (77) | 7 (23) | 0 (0) | 24 (73) | 7 (21) | 2 (6) |
| *Staphylococcus aureus* | 8 (80) | 2 (20) | 0 (0) | 6 (67) | 2 (22) | 1 (11) |
| *H. parainfluenzae* | 6 (75) | 1 (12.5) | 1 (12.5) | 10 (46) | 6 (27) | 6 (27) |
| *Moraxella catarrhalis* | 4 (57) | 3 (43) | 0 (0) | 3 (43) | 4 (57) | 0 (0) |
| *K. pneumoniae* | 2 (67) | 1 (33) | 0 (0) | 6 (75) | 0 (0) | 2 (25) |
| Blood culture | | | | | | |
| *S. pneumoniae* | 7 (78) | 2 (22) | 0 (0) | 4 (50) | 4 (50) | 0 (0) |
| Serology | | | | | | |
| *C. pneumoniae* | 34 (72) | 12 (26) | 1 (2) | 34 (63) | 16 (30) | 4 (7) |
| *M. pneumoniae* | 15 (79) | 4 (21) | 0 (0) | 17 (77) | 5 (23) | 0 (0) |
| *L. pneumophila* | 4 (80) | 1 (20) | 0 (0) | 2 (66) | 0 (0) | 1 (33) |

[a] Number (%) of patients who had a particular pathogen, alone or in combination with another pathogen(s).

levofloxacin group, the MIC of penicillin was available for 28 isolates (20 from sputum and 8 from blood). Twenty-two isolates were sensitive to penicillin (MIC, ≤0.06 μg/ml), and six were of intermediate penicillin susceptibility (MIC, 0.1 to 1.0 μg/ml). None of the *S. pneumoniae* isolates in either group were highly penicillin resistant (MIC, ≥2.0 μg/ml).

Superinfections were reported in three levofloxacin patients (two *H. parainfluenzae* and one methicillin-resistant *S. aureus*) and in four ceftriaxone and/or cefuroxime axetil patients (one *H. parainfluenzae* and *Moraxella catarrhalis*, one methicillin-resistant *S. aureus*, one *Enterococcus faecalis*, and one *P. aeruginosa*). Two of the three superinfecting organisms from the levofloxacin-treated patients were susceptible to levofloxacin, and the susceptibility of the third was unknown; for ceftriaxone and/or cefuroxime axetil, two organisms were susceptible to either ceftriaxone or cefuroxime, one was resistant, and two were unknown. With the exception of one organism isolated from urine (*E. faecalis*), all superinfecting organisms were isolated from the respiratory tract.

TABLE 6. Microbiological eradication rate 5 to 7 days posttherapy for microbiologically evaluable patients

| Method of evaluation and pathogen detected | No. eradicated/total no. of isolates (%) for group treated with: | | 95% CI[a] |
|---|---|---|---|
| | Levofloxacin | Ceftriaxone and/or cefuroxime axetil | |
| Respiratory culture | | | |
| *H. influenzae* | 30/30 (100) | 19/24 (79) | −39.2–−2.5 |
| *S. pneumoniae* | 30/30 (100) | 31/32 (97) | −10.8–4.6 |
| *Staphylococcus aureus* | 10/10 (100) | 9/9 (100) | |
| *H. parainfluenzae* | 7/8 (88) | 15/21 (71) | |
| *Moraxella catarrhalis* | 7/7 (100) | 6/7 (86) | |
| *K. pneumoniae* | 3/3 (100) | 8/8 (100) | |
| Other[b] | 19/20 (95) | 27/29 (93) | |
| Blood culture | | | |
| *S. pneumoniae* | 9/9 (100) | 8/8 (100) | |
| *H. influenzae* | 0 | 1/1 (100) | |
| *K. pneumoniae* | 0 | 0/1 (0) | |

[a] Confidence intervals were calculated for those pathogens with 10 or more admission isolates in each group.

[b] Pathogens that were isolated infrequently ($n < 5$) for either treatment group. Pathogens that were not eradicated included *S. pyogenes* in the levofloxacin group and *K. oxytoca* and *P. aeruginosa* in the ceftriaxone-cefuroxime axetil group.

**Safety evaluations.** Five hundred eighty-four of the 590 patients (99%) enrolled in the study were evaluable for safety. The majority of adverse events were assessed as mild in severity. Adverse events categorized by the investigator as possibly or definitely drug related were reported in 17 patients (5.8%) receiving levofloxacin and in 25 patients (8.5%) administered ceftriaxone and/or cefuroxime axetil. Nausea (1.7%), diarrhea (1.4%), and injection site pain (1.0%) were the most common drug-related events among levofloxacin recipients. In the ceftriaxone and/or cefuroxime axetil group, the most common drug-related events were diarrhea (3.8%), nausea (2.0%), dyspepsia (1.0%), and vomiting (1.0%).

Premature discontinuation from the trial due to an adverse event occurred in 25 patients (13 administered levofloxacin and 12 receiving ceftriaxone and/or cefuroxime axetil); 17 were judged by the investigator to be probably, possibly, or definitely drug related (8 receiving levofloxacin and 9 given ceftriaxone and/or cefuroxime axetil). For the levofloxacin group, all but one patient discontinued use of the drug within 5 days of starting therapy, mostly due to gastrointestinal complaints or peripheral nervous system-related symptoms (i.e., tremor, speech disorder, or dizziness). Gastrointestinal complaints were the primary cause of early withdrawal in the ceftriaxone-cefuroxime axetil group.

## DISCUSSION

This multicenter trial demonstrated that levofloxacin, given either orally or i.v., was effective in the management of patients with community-acquired pneumonia. Furthermore, among clinically evaluable patients at 5 to 7 days posttherapy, levofloxacin treatment resulted in a 96% clinical cure or improvement rate, which is superior to that achieved with ceftriaxone and/or cefuroxime axetil therapy (90% clinical success rate). The results were similar in microbiologically evaluable patients, for which, again, levofloxacin was superior to ceftriaxone and/or cefuroxime axetil (clinical success rates of 98 and 88%, respectively). The mortality rate of 3.6% among hospi-

talized patients was lower than those previously found in epidemiologic studies (9). This may be due to the exclusion of patients considered to have a high probability of dying during the study. This exclusion is commonly used in clinical trials of antimicrobial agent efficacy.

Treatment of patients with community-acquired pneumonia is often empirical. Therefore, selection of an appropriate antibacterial agent should be, in large part, based on its microbiological activity. In this study, the most frequently isolated pyogenic respiratory pathogens were *S. pneumoniae* and *H. influenzae*; *H. parainfluenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis* were less common. Infection with any of three atypical pathogens—*C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*—was found 150 times (based primarily on serological results): in 71 levofloxacin-treated participants and in 79 ceftriaxone and/or cefuroxime-treated patients.

This study demonstrated that levofloxacin has predictable activity on both typical and atypical respiratory tract pathogens. In microbiologically evaluable patients, levofloxacin therapy provided an overall eradication rate by pathogen of 98%, which is superior to that observed in the group of patients treated with ceftriaxone and/or cefuroxime axetil (89%). Levofloxacin was significantly better than ceftriaxone or cefuroxime axetil at eradicating *H. influenzae* from the respiratory tract. Rates of eradication of *S. pneumoniae* from the respiratory tract and blood were similar for both agents; levofloxacin was 100% successful.

Levofloxacin treatment resulted in a 99% satisfactory clinical response in all patients with atypical pneumonia. In this study, *C. pneumoniae* was frequently identified as an associated pathogen, reinforcing the importance of this pathogen as a cause of community-acquired pneumonia. In all cases, *C. pneumoniae* was identified by serologic means. For serologic diagnosis of *C. pneumoniae*, we have used previously established criteria which include a single positive elevated IgG titer (23). However, since a single positive titer as a criterion for acute disease has various limitations (23), we have distinguished cases identified on the basis of a fourfold rise in titer (definitive diagnosis) from those with static elevated antibody titers (probable cases). Similar criteria were used for *M. pneumoniae* and *L. pneumophila* cases. The percentage of cases of *C. pneumoniae* classified as definitive in our study is similar to that of another large study of community-acquired pneumonia (33).

Due to the lack of accessible means of rapidly diagnosing *C. pneumoniae* and *M. pneumoniae* in cases of community-acquired pneumonia, patients are often treated empirically. Macrolides or tetracyclines are frequently added to β-lactam antibiotic therapy in the treatment of community-acquired pneumonia because β-lactams lack in vitro activity against atypical pathogens. The apparently good response of patients with *C. pneumoniae* and *M. pneumoniae* (including those diagnosed by definitive criteria) in the ceftriaxone-cefuroxime axetil arm is somewhat surprising since most of these patients did not receive additional antimicrobial agent therapy (i.e., erythromycin or doxycycline) specific for these organisms. However, the observation of resolution of *C. pneumoniae* disease by β-lactam treatment has been previously reported (16, 20, 27). It is possible that such cases represent self-limited disease or that patients who appear to respond to β-lactam therapy are actually responding to treatment of an undiagnosed bacterial copathogen. While the newer macrolides, azithromycin and clarithromycin, have reasonable activity against atypical pathogens, their abilities to eradicate *H. influenzae* and other aerobic gram-negative pathogens differ (18). The broad-spectrum coverage of levofloxacin offers a potential advantage over both β-lactam and newer macrolide therapies.

Because some currently marketed fluoroquinolones have marginal in vitro activity against *S. pneumoniae* (24), levofloxacin's performance in this trial is noteworthy. All isolates from nine microbiologically evaluable patients with *S. pneumoniae* bacteremia and 100% of the 30 respiratory isolates were successfully eradicated with levofloxacin therapy. Furthermore, there were no superinfections or relapses due to *S. pneumoniae* in the levofloxacin treatment group. In areas with high rates of pneumococcal resistance, however, local sensitivity patterns need to be considered. The good in vitro activity of levofloxacin against the pneumococcus, including penicillin-resistant isolates (22, 26), and its success in curing pneumococcal infections in this and other respiratory trials suggest that the prevailing concern over fluoroquinolone efficacy against this organism may not apply to this new agent (8, 11, 37).

In selecting an antimicrobial agent(s) for the treatment of community-acquired pneumonia, the practitioner must consider not only documented efficacy but also the adverse-events profile of the agent and the cost of therapy. In this multicenter study, levofloxacin was well tolerated and had a rate of drug-related adverse events similar to that of patients treated with ceftriaxone and/or cefuroxime axetil. Mild gastrointestinal events (e.g., nausea and diarrhea) were the most commonly reported adverse events in both treatment groups, and no patient in the levofloxacin group had a serious drug-related adverse event. Levofloxacin also provided the advantage of once-daily dosing, in both i.v. and oral dosage formulations, and offered the option of sequential therapy (i.v. to oral switch) without a change in drug. Other fluoroquinolones have been shown to have economic advantages for sequential therapy in the management of mild to moderate lower respiratory tract infections (14, 32).

This pivotal trial is the first to provide data demonstrating that i.v. or oral levofloxacin therapy is an effective and safe monotherapy for the empirical treatment of adult patients with community-acquired pneumonia. Levofloxacin has documented clinical efficacy against all common typical and atypical respiratory pathogens, including *S. pneumoniae.*

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