Clinical Outcomes for Hospitalized Patients with *Legionella* Pneumonia in the Antigenuria Era: The Influence of Levofloxacin Therapy

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**Background.** Although the reduction in case-fatality rate recently observed among patients with *Legionella* pneumonia has been largely attributed to the progressive utilization of urine antigen testing, other factors, such as changes in empirical antibiotic therapy, may also have contributed. We have analyzed more-recent outcomes of *Legionella* pneumonia in an institution where urine antigen testing was reflexly performed in cases of community-acquired pneumonia without an etiological diagnosis.

**Methods.** From a prospective series of 1934 consecutive cases of community-acquired pneumonia in non-immunocompromised adults, 139 cases of *Legionella pneumophila* pneumonia were selected for observational review. *Legionella* cases were analyzed for outcome with respect to antibiotic treatment, mortality, complications, length of stay, time to defervescence, and stability.

**Results.** The early case-fatality rate was 2.9% (4 of 139 patients), and the overall case-fatality rate was 5% (7 of 139 patients). One hundred twenty patients (86.3%) received an appropriate initial therapy, which included macrolides (i.e., erythromycin or clarithromycin) in 80 patients and levofloxacin in 40. Levofloxacin progressively replaced macrolides as the initial therapy during the study period. Compared with patients who received macrolides, patients who received levofloxacin had a faster time to defervescence (2.0 vs. 4.5 days; \(P < .001\)) and to clinical stability (3 vs. 5 days; \(P = .002\)). No differences were found regarding the development of complications (25% vs. 25%; \(P = .002\)) and case-fatality rate (2.5% vs. 5%; \(P = .518\)). The median length of hospital stay was 8 days in patients treated with levofloxacin and 10 days in those who received macrolides (\(P = .014\)).

**Conclusions.** *Legionella* pneumonia is still associated with significant complications in hospitalized patients, but recent mortality is substantially lower than that found in earlier series. Levofloxacin may produce a faster clinical response than older macrolides, allowing for shorter hospital stay.
ment of in-hospital complications, length of stay, and mortality in an institution where urine antigen testing was consistently performed during the study period.

METHODS

Setting and study design. The study was conducted at a 900-bed university hospital for adults in Barcelona, Spain (Hospital Universitari de Bellvitge). The hospital serves an urban area of 1,100,000 inhabitants and has ∼24,000 admissions annually. All 1934 non–severely immunosuppressed patients with community-acquired pneumonia admitted to the hospital between 13 February 1995 and 31 December 2003 were prospectively recruited and followed up. Patients with neutropenia (i.e., those with a granulocyte count of <1.0 × 10⁹ cells/L), those with AIDS, and transplant recipients were not included. The definition of pneumonia and hospitalization criteria have been described elsewhere [5].

For the purposes of the present observational study, we analyzed data on 139 cases of Legionella pneumonia, diagnosed with use of ≥1 of the following methods: urine antigen test; isolation of Legionella in sputum, transthoracic needle aspiration specimen, or pleural fluid; and/or a 4-fold increase in the antibody titer. We compared clinical outcomes for patients treated with levofloxacin with outcomes for those who received macrolides.

Clinical evaluation, antibiotic therapy, and follow-up. At the initial visit to the emergency department, patients gave a complete clinical history, underwent physical examination, and underwent chemical and hematological testing. Microbiological studies included blood cultures and sputum Gram stain and culture, when available. A urine antigen test for Legionella species was performed at hospital admission, if indicated by the attending physician, but was performed 48 h after admission for all patients for whom nonetiological diagnosis had been made (reflex testing). Paired serum samples were obtained during the acute and convalescent phases of infection (separated by a 3–8 week interval) for serological studies.

Antibiotic therapy was initiated in the emergency department in accordance with hospital guidelines, which recommended the administration of a β-lactam (either ceftriaxone or amoxicillin-clavulanate, administered intravenously) with or without a macrolide (either erythromycin 1000 mg iv q.i.d. or clarithromycin 500 mg iv b.i.d.); from 1998 onward, levofloxacin (500 mg iv q.d.) was also allowed. Patients with a urine antigen test result positive for Legionella at admission were treated with a macrolide (with or without rifampin, on the basis of physician preference) or levofloxacin. Those patients initially treated with other antibiotics were switched to appropriate therapy. Recommended duration of therapy was 10–14 days.

Patients were seen daily during their hospital stay by ≥1 of the investigators, who provided medical advice when requested and stored clinical data in a computer-assisted protocol. All patients were evaluated for adverse events. Assessments included evaluation of changes in vital signs, clinical laboratory results, and physical examination findings. A long-term follow-up visit took place ~1 month after discharge.

Definitions. To stratify patients into risk classes, we used the validated prediction rule, calculated according to the pneumonia severity index (PSI) [15]. The time to overall clinical stability was defined as the time required for 5 vital signs to become stable (temperature, ≤37.2°C; heart rate, ≤100 beats/min; respiratory rate, ≤24 breaths/min; systolic blood pressure, ≥90 mm Hg; oxygen saturation on room air, >90%) with normalization of mental status and the ability to eat [16]. A variable was considered stable if all measurements in a 24-h period met stability criteria.

Complications were defined as any untoward circumstance occurring during hospitalization, with the exception of the side effects of the treatment. Length of hospital stay was calculated as the time from the admission date to the date of discharge from the hospital. Early case-fatality rate was defined as death (as proportion of cases) due to any cause ≤48 h after hospitalization. Overall case-fatality rate was defined as death (as proportion of cases) due to any cause ≤30 days after hospitalization.

Microbiologic studies. Investigation of pathogens in blood, normally sterile fluids, sputum, and other samples was performed using standard microbiological procedures. L. pneumophila serogroup 1 antigen in urine was detected by an immunoenzymetric commercial method (Legionella Urinary Antigen; Binax). Isolation of Legionella species was attempted in sputum samples and other respiratory samples by the selective medium buffered charcoal yeast extract-α. EIA was used to detect antibodies against L. pneumophila serogroups 1–6.

Statistical analysis. To detect significant differences between antibiotic treatment groups, we used the χ² test with continuity correction for categorical variables and the Student’s t test or the Mann-Whitney U test for continuous variables, when appropriate. In all analyses, P values <.05 were considered to be statistically significant.

RESULTS

During the study period, 1934 non–severely immunosuppressed adults with community-acquired pneumonia were admitted to our institution. L. pneumophila was the causative organism in 139 (7.2%) of the cases. The diagnosis was established with use of ≥1 of the following methods: urine antigen test (in 120 cases), seroconversion (in 80), and/or positive culture (in 43). Culture results were positive for 32 of 59 cases in which sputum samples were available, in 9 of 14 cases in which transthoracic needle aspiration specimens were available, and in 2 of 10 cases in which pleural fluid
samples were available. All cases identified by culture corresponded to *L. pneumophila* serogroup 1. Only 19 cases were diagnosed by serological methods alone. Two cases of mixed infection were detected (1 case of *Chlamydia pneumoniae* infection and 1 case of *Chlamydia psittaci* infection).

Cases were uniformly distributed during the study period. Figure 1 shows the total number of cases distributed every 3 years and the number of patients who underwent urine antigen testing in that period, which was also constant.

One hundred twenty (86.3%) of the 139 patients with *Legionella* pneumonia were men, with a mean age (± SD) of 56.6 ± 13.5 years. Seventy-one (51.1%) of the patients were smokers, and 59 (42.4%) had a history of alcohol abuse. Twenty-five patients (17.9%) had been immunized with influenza vaccine for the influenza season, and 8 (5.8%) had received 23-valent pneumococcal capsular polysaccharide vaccine in the 5 years before admission to the hospital. Seventy-four patients (53.2%) had underlying diseases, mainly chronic heart disease (in 25 patients), diabetes mellitus (in 20), chronic obstructive pulmonary disease (in 15), chronic liver disease (in 6), and cancer (in 5). Five patients (3.6%) had a history of long-term steroid use. Sixty-three patients (45.3%) had received antibiotic therapy before hospitalization (mainly β-lactam antibiotics [in 56 cases]).

Sixty-four patients (46%) were classified into high-risk pneumonia classes (risk classes IV–V) according to PSI score. One hundred twenty (86.3%) of the patients received an appropriate initial therapy, which included levofloxacin for 40 patients and macrolides for the remaining 80 patients (erythromycin for 53 patients and clarithromycin for 27 patients). Forty-eight patients who were treated with macrolides were also given rifampin. Ten (25%) of the patients in the levofloxacin group and 21 (26.2%) in the macrolide group received steroids for the current episode of pneumonia (*P* = .883). Levofloxacin progressively replaced macrolides as the initial therapy during the study (figure 1). Eighteen patients (13%) received an inappropriate empirical therapy with β-lactam antibiotics, which was promptly modified to cover *Legionella* when the result of the urine antigen test was available; all of these patients remained febrile at the time they were switched to macrolides (13 patients) or levofloxacin (5 patients). One additional patient received initial therapy with both levofloxacin and clarithromycin. As shown in table 1, demographic and clinical characteristics were similar when comparing patients treated initially with levofloxacin or macrolides. There were no differences between treatment groups regarding the presence at baseline of significant prognostic factors, such as age >70 years, presence of comorbid conditions, hypoalbuminemia, renal insufficiency, and multilobar pneumonia. The mean partial pressure of oxygen breathing room air at admission to the hospital was similar in the 2 groups (59.72 mm Hg vs. 59.57 mm Hg; *P* = .950). The percentage of patients classified into high-risk pneumonia classes according to PSI score (i.e., those with >90 points) did not differ between treatment groups (42.5% vs. 47.5%; *P* = .688).

The mean duration of intravenous therapy (± SD) was 3.74 ± 2.57 days for patients treated with levofloxacin and 3.42 ± 4.51 days for those treated with macrolides (*P* = .043). Complete duration of antibiotic therapy (± SD) was 11.10 ± 6.39 days and 15.44 ± 7.83 days, respectively (*P* = .004). Table 2 shows the main clinical outcomes for patients treated with either levofloxacin or macrolides. As can be seen, patients receiving levofloxacin had a faster time to defervescence and to resolution of cough. No difference was observed in time to resolution of chest pain between the 2 groups. Patients treated with levofloxacin achieved overall clinical stability significantly earlier than did patients treated with macrolides (3.0 vs. 5.0 days).

![Figure 1](https://academic.oup.com/cid/article-abstract/40/6/796/346029/1)

**Figure 1.** Data for patients hospitalized with *Legionella* pneumonia in Spain, 1995–2003. Levofloxacin, cases treated with levofloxacin; LP, cases of *Legionella* pneumonia; macrolides, cases treated with macrolides; mortality, mortality associated with *Legionella* pneumonia; urinary antigen test, cases of *Legionella* pneumonia confirmed with use of urine antigen testing.
As shown in table 2, there were no significant differences between treatment groups regarding the development of complications, which occurred in 25% of both antibiotic treatment groups. The most frequent complications were respiratory failure and a worsening of comorbid conditions. The median length of hospital stay was significantly shorter for patients treated with levofloxacin. The length of stay for other patients with pneumonia did not change significantly over the study period, ranging from a mean of 10.95 days in 1995 to a mean of 10.52 in 2003. No differences in outcome between patients who received either erythromycin or clarithromycin or patients who received regimens that included rifampin were observed.

The incidence of treatment-related adverse events was similar for the 2 groups, occurring in 8 (20%) of 40 patients in the levofloxacin treatment group, compared with 24 (30%) of 80 patients in the macrolide group ($P = .243$). All of the drug-related adverse events were minor, the most common events being phlebitis (occurring in 12.5% of patients in the levofloxacin group, compared with 10% of patients in the macrolide group), gastrointestinal disorders (5% vs. 5%), liver function test abnormalities (2.5% vs. 3.7%), and rash (2.5% vs. 3.7%).

When considering the total number of patients with Legionella pneumonia, the early case-fatality rate was 2.9% (4 of 139 patients), and the overall case-fatality rate was 5% (7 of 139 patients). No patients died during the last 3 years of the study (0 of 46 patients). As shown in table 2, early and overall case-fatality rates did not differ significantly between patients receiving levofloxacin and those receiving macrolides. Although there was a trend towards a lower case-fatality rate in the levofloxacin group, small numbers of fatal cases of pneumonia may produce type II error. Among patients who received an initial inappropriate empirical therapy, the early case-fatality rate was 5.5% (1 of 18 patients), and the overall case-fatality rate was 11.1% (2 of 18 patients).

**DISCUSSION**

The present study offers a detailed analysis of clinical outcomes for a large series of patients with community-acquired Legionella pneumonia documented in recent years in a single institution. Clinical management and diagnostic evaluation of patients with community-acquired pneumonia, including urine antigen testing, did not undergo substantial changes during the study period, although levofloxacin has progressively replaced...
Table 2. Clinical outcomes for 120 patients with community-acquired *Legionella* pneumonia treated with either levofloxacin or macrolides.

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Lvfx treatment group (n = 40)</th>
<th>Macrolide treatment group (n = 80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to defervescence, days (^{b})</td>
<td>2.50 ± 1.90</td>
<td>6.10 ± 6.49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time to resolution of cough, days</td>
<td>3.11 ± 1.41</td>
<td>5.20 ± 2.75</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time to resolution of chest pain, days</td>
<td>3.75 ± 2.31</td>
<td>3.89 ± 3.07</td>
<td>.993</td>
</tr>
<tr>
<td>Time to achieve clinical stability, days</td>
<td>3.55 ± 2.54</td>
<td>6.62 ± 6.68</td>
<td>.002</td>
</tr>
<tr>
<td>In-hospital complications (^{c})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>10 (25)</td>
<td>20 (25)</td>
<td>.906</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>4 (10)</td>
<td>12 (15)</td>
<td>.507</td>
</tr>
<tr>
<td>Worsening of comorbid conditions</td>
<td>5 (12.5)</td>
<td>6 (7.5)</td>
<td>.371</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3 (7.5)</td>
<td>6 (7.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>9.73 ± 5.7</td>
<td>14.48 ± 13.1</td>
<td>.014</td>
</tr>
<tr>
<td>Early case-fatality rate (^{d})</td>
<td>0</td>
<td>3 (3.7)</td>
<td>.550</td>
</tr>
<tr>
<td>Overall case-fatality rate (^{e})</td>
<td>1 (2.5)</td>
<td>4 (5)</td>
<td>.518</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; Lvfx, levofloxacin.

\(^{a}\) Forty-eight patients who were treated with macrolides also received rifampin.

\(^{b}\) Temperature, <37.0°C.

\(^{c}\) Some patients had >1 complication.

\(^{d}\) Death <48 h after admission.

\(^{e}\) Death <30 days after admission.

macrolides as the initial therapy for *Legionella* pneumonia since 1998.

Benin et al. [13] recently reported data from a large-scale study by the Centers for Disease Control and Prevention showing a decrease in the case-fatality rate for community-acquired *Legionella* pneumonia from 26% to 10% for the period 1980–1998. These investigators observed a relationship between the increasing use of urine antigen testing as a useful diagnostic tool for *Legionella* pneumonia and the sustained decrease in mortality. However, they stated that improvement in empirical antibiotic treatments, promoted by the implementation of community-acquired pneumonia guidelines, could be another reason for the reduction in mortality. We observed a low case-fatality rate throughout the entire study period; this low rate was more evident during the last 3 years of the study period, when levofloxacin accounted for most initial treatments (figure 1). This finding is in accordance with some recent case studies of patients with *Legionella* pneumonia who received diagnoses by means of urine antigen testing; these case studies have reported case-fatality rates of 0%–5% [9, 17, 18].

Although there have been no prospective controlled trials addressing the subject, some authorities have recommended therapy with fluoroquinolones or azithromycin, rather than with older macrolides, for the treatment of *Legionella* pneumonia [1]. Indeed, these agents have been shown to be better than erythromycin in inhibiting the intracellular growth of *L. pneumophila*, both in vitro and in animal models [19–22].

In this regard, Yu et al. [18] have reported a successful experience with levofloxacin therapy in 75 hospitalized and ambulatory patients with *Legionella* pneumonia who were identified through a database of patients enrolled in 6 trials involving community-acquired pneumonia. Similarly, Plouffe et al. [17] reported similar results using azithromycin in an open, noncomparative trial involving 25 hospitalized patients with *Legionella* pneumonia who had significant comorbidities. Both studies indicate that use of these highly active agents may
shorten the duration of antibiotic treatment, although neither study analyzed outcomes other than clinical response (i.e., cure, improvement, or failure) and safety. In our study, we observed a nonsignificant trend toward a lower case-fatality rate in patients who received levofloxacin therapy. However, there were significant differences favoring levofloxacin in important outcomes other than mortality, such as time to defervescence, time to overall clinical stability, duration of antibiotic treatment, and length of hospital stay. These data provide evidence about the safety of an early switch from intravenous to oral levofloxacin for treatment of *Legionella* pneumonia and suggest that the use of agents with enhanced activity against *Legionella* species may result in a faster resolution of clinical signs and symptoms. Moreover, they provide valuable information in terms of better understanding the continuous improvement in *Legionella* pneumonia outcomes following the generalized use of urine antigen testing. Because our study is not randomized, the possible superiority of levofloxacin therapy over therapy with the older macrolides should be interpreted with caution. It is possible that concomitant early recognition of *Legionella* and a trend toward levofloxacin treatment in the past few years coincided to produce less morbidity and fewer fatalities and that levofloxacin is not a better treatment than macrolides. A prospective, randomized trial comparing therapy with the more effective macrolide, azithromycin, with levofloxacin therapy is warranted. However, it seems unlikely that any randomized trials involving the antibiotic treatment of *Legionella* pneumonia will be possible in the near future [23, 24].

In summary, our data show that, although *Legionella* pneumonia continues to be associated with significant morbidity in hospitalized patients, the current mortality rate is substantially lower than that traditionally reported. Furthermore, our findings suggest that levofloxacin therapy produces a faster clinical response than does therapy with the older macrolides, allowing a shorter length of hospital stay.

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