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V. Erard · O. Lamy · P.-Y. Bochud · J. Bille · A. Cometta · T. Calandra

Full-Course Oral Levofloxacin for Treatment of Hospitalized Patients with Community-Acquired Pneumonia

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Abstract Most guidelines for the management of hospitalized patients with community-acquired pneumonia (CAP) recommend commencing therapy with intravenous antibiotics, primarily because of concern about absorption of oral antibiotics in acutely ill patients. However, patients who respond are rapidly switched to oral therapy, which has been shown to reduce costs and to shorten the length of stay. The aim of the present study was to determine whether a full course of oral antibiotics is as efficacious and as safe as intravenous-to-oral sequential antibiotic therapy for the treatment of hospitalized, non-ICU patients with CAP. In an open-labelled, controlled study, 129 hospitalized patients with CAP were randomly assigned in a 2:1 ratio to receive either a full course of oral levofloxacin (500 mg q12 h) or an intravenous-to-oral sequential therapy consisting of intravenous ceftriaxone (2 g q24 h) with or without clarithromycin (500 mg q12 h) followed by an oral antibiotic (a beta-lactam agent in the majority of patients). The primary study endpoint was the resolution of CAP; secondary endpoints included length of stay and overall mortality. CAP resolved in 72 of 79 (91.1%) patients in the levofloxacin group and in 34 of 37 (91.9%) patients in the intravenous-to-oral sequential therapy group (difference, −0.8%, 95%CI, −11.6–10.0). Median length of stay was 8 days (range, 2–74 days) in the levofloxacin group and 10 days (range, 3–29 days) in the intravenous-to-oral sequential therapy group (P=0.28). Day 30 mortality rates were 1.3% (1 of 79) and 8.1% (3 of 37), respectively (difference, −6.8%, 95%CI, −16.0–2.3). Full-course oral levofloxacin is as efficacious and as safe as standard intravenous-to-oral sequential antibiotic therapy for the treatment of hospitalized patients with CAP.

V. Erard · P.-Y. Bochud · A. Cometta · T. Calandra (✉)
Division of Infectious Diseases,
Centre Hospitalier Universitaire Vaudois,
1011 Lausanne, Switzerland
e-mail: Thierry.Calandra@chuv.hospvd.ch
Tel.: +41-21-314-1037
Fax: +41-21-314-1036

O. Lamy
Department of Internal Medicine (Service A),
Centre Hospitalier Universitaire Vaudois,
1011 Lausanne, Switzerland

J. Bille
Institute of Microbiology,
Centre Hospitalier Universitaire Vaudois,
1011 Lausanne, Switzerland

A. Cometta
Service of Medicine,
Centre Hospitalier Yverdon-Chamblon,
1400 Yverdon-les-Bains, Switzerland

Introduction

With the exception of the guidelines of the British Thoracic Society, which encourage oral therapy for nonsevere cases [1], most guidelines for the management of hospitalized patients with community-acquired pneumonia (CAP) generally recommend commencing therapy with intravenous antibiotics [2, 3, 4]. However, the choice of parenteral over oral therapy is guided by prudence rather than by clinical evidence of superiority, primarily because of concern about absorption of oral antibiotics in critically ill patients. Moreover, patients who improve clinically are rapidly switched to oral therapy, usually within 3 days, since intravenous-to-oral sequential or step-down therapy has been shown to be safe, to reduce treatment costs and to shorten the length of stay [5, 6, 7, 8, 9, 10, 11, 12, 13]. We therefore evaluated the efficacy and safety of a full course of oral antibiotics for the treatment of patients hospitalized with CAP.

Fluoroquinolones with enhanced activity against pneumococci (such as levofloxacin, gatifloxacin and moxifloxacin) have become important agents in the management of patients with CAP due to their excellent bioavailability, their broad-spectrum antimicrobial activity against gram-positive, gram-negative and atypical intracellular bacteria, and their favourable safety profile, [2, 3, 4]. Amongst the fluoroquinolones, levofloxacin has been shown to be highly efficacious when given orally to

outpatients or as intravenous-to-oral sequential therapy to inpatients with CAP [12, 14, 15]. The efficacy and safety of a full course of oral levofloxacin was thus compared with that of a standard intravenous-to-oral sequential therapy, which consisted of intravenous ceftriaxone (2 g q24 h) with or without clarithromycin (500 mg q12 h) followed by an oral antibiotic (a beta-lactam agent in the majority of patients) for the treatment of hospitalized, non-ICU adult patients with CAP. The study was designed as an open-labelled, randomized, controlled pilot observational study to assess the feasibility and safety of oral antibiotic therapy in these patients.

Materials and Methods

Patients

All consecutive adult patients (age $\geq$18 years) admitted for the treatment of CAP were eligible for enrolment if they met the following criteria: presence of a newly acquired pulmonary infiltrate on a chest radiograph compatible with pneumonia and at least one of the following symptoms or signs that developed within 48 h of admission: fever (>38°C), chills, dyspnoea, cough, sputum production, pleuritic chest pain, altered breath sounds, dull percussion sounds, bronchial rales or pleural rub. Exclusion criteria included admission to an ICU; high likelihood of being discharged from hospital within 24 h of admission; previous hospitalization or stay in a nursing home within 10 days and 4 weeks of admission, respectively; inability to take oral medication; and presence of any of the following conditions or diseases: pregnancy, cystic fibrosis, epilepsy, neutropenia defined as a neutrophil count of less than 500 cells/mm^3, organ transplantation, treatment with cytotoxic or immunosuppressive agents other than corticosteroids for the treatment of chronic obstructive pulmonary disease, infection with the human immunodeficiency virus, treatment with a fluoroquinolone within 1 week of admission and history of allergy to beta-lactam or fluoroquinolone antibiotics.

Study Design and Setting

The study was designed as a prospective, randomized, open-labelled, controlled pilot observational study conducted in two Swiss medical centres: a 900-bed teaching hospital that serves as both as city hospital and a tertiary reference centre providing services to an area populated with more than 500,000 inhabitants (Centre Hospitalier Universitaire Vaudois, Lausanne) and a 160-bed community hospital (Centre Hospitalier Yverdon-Chamblon, Yverdon-les-Bains). The study was approved by the ethics committees of both institutions, and written informed consent was obtained from each patient or legal guardian.

Patients were randomized in a 2:1 ratio to receive a full course of oral levofloxacin (500 mg q12 h) or an intravenous-to-oral sequential therapy regimen consisting of intravenous ceftriaxone (2 g q24 h) with or without concomitant intravenous or oral clarithromycin (500 mg q12 h) followed by an oral antibiotic therapy chosen by the physician-in-charge according to CAP treatment guidelines in use at the participating institutions [16]. The choice of a 2:1 ratio was guided by the desire to expose more patients to oral than conventional intravenous-to-oral sequential therapy in this pilot feasibility study. The addition of clarithromycin was recommended in patients who presented with hyponatremia, elevated liver enzymes, unexplained diarrhoea, elevation of creatine phosphokinase, altered mental status, oligoanuria, elevated respiratory rate (>30/min) and/or hypotension (systolic or diastolic blood pressure of less than 90 or 60 mmHg, respectively).

Intravenous-to-oral switch was recommended after 2–3 days of therapy in patients with clinical evidence of improvement (such as temperature of <38°C and respiratory rate <24/min) who were able to tolerate oral medication and had intact gastrointestinal motility. Recommended duration of antibiotic therapy was 7–10 days. Patients with suspected or proven *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or *Legionella pneumophila* pneumonia or necrotizing pneumonia such as that due to *Staphylococcus aureus*, enteric gram-negative bacteria or *Pseudomonas aeruginosa* were treated for 2–3 weeks with appropriate antibiotics on the basis of the results of in vitro susceptibility tests. In patients with renal failure, daily doses of levofloxacin were adapted on the basis of creatinine clearance as calculated according to Cockcroft and Gault [17].

Clinical and Laboratory Evaluation

The study protocol required that, whenever possible, the following be performed prior to the initiation of antibiotic therapy: a complete medical history; physical examination; chest radiograph; oxygen saturation test; haematological investigations (determination of haemoglobin, haematocrit, leucocyte and platelet counts); biochemistry tests (determination of electrolytes, urea, creatinine, bilirubin, serum transaminase, alkaline phosphatase and C-reactive protein); two sets of blood cultures; and Gram stain and cultures of expectorated sputum, pleural fluid or any other infected sites. Except in cases of suspected *Legionella* pneumonia, Gram stain of sputum was considered to be evaluable and was accepted for culture if it contained fewer than 25 epithelial cells per low-power field [18]. Identification of the microorganisms and antibiotic susceptibility testing were performed according to standard procedures [19, 20]. Urinary antigen detection tests for *Streptococcus pneumoniae* (Binax NOW ICT *Streptococcus pneumoniae*) and *Legionella pneumophila* serogroup 1 (Binax NOW ICT *Legionella*) were performed in every patient (*Streptococcus pneumoniae*) or whenever Legionnaire's disease was suspected. Serological analyses for respiratory pathogens were not performed on a routine basis. Follow-up studies were performed as clinically indicated and until resolution of laboratory test abnormalities or discharge of the patient from hospital. Symptoms and clinical signs were evaluated by a research nurse and by the infectious diseases fellow in charge of the study, daily during the first week and thereafter every other day. Severity of CAP was assessed by the Prognostic Score Index proposed by Fine et al. [21].

Definitions

The etiological diagnosis of CAP was considered definitive when *Streptococcus pneumoniae* or a likely respiratory pathogen (such as *Haemophilus influenzae* or *Moraxella catarrhalis*) was isolated from blood cultures, an uncontaminated specimen (i.e. pleural fluid or transthoracic aspirate) or expectorated sputum; when the urinary *Legionella pneumophila* antigen test was positive; or when there was a greater than or equal to fourfold increase in antibody titres to *Legionella pneumophila*, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. The etiological diagnosis of CAP was considered probable when a urinary *Streptococcus pneumoniae* capsular antigen test was positive or when the expectorated sputum was positive for uncommon respiratory pathogens (such as enteric gram-negative bacteria or *Staphylococcus aureus*) that were predominant on Gram stain.

Evaluation of Response and Adverse Events

The primary study endpoint was the resolution of CAP, evaluated on day 30. Secondary endpoints included overall and infection-related day 30-mortality (checked by a phone call for patients who had been discharged) and length of hospital stay. Clinical response was evaluated as a success if clinical signs and symptoms of

infection and laboratory test abnormalities resolved and the infecting microorganism was eradicated (for patients with a microbiologically documented infection). Clinical response was evaluated as a failure in the event of the following: (i) the patient died of pneumonia, (ii) pneumonia did not improve or worsened under antibiotic therapy, (iii) pneumonia relapsed within 7 days after discontinuation of antibiotics or (iv) an adverse event occurred that required discontinuation of therapy. All patients who received at least one dose of the study drug were evaluated for adverse events, which were classified as possibly, probably or definitely related to antibiotic therapy. Relapse was assessed by phone call on day 30.

Statistical Analysis

Categorical variables were compared using the chi-square test. In two-by-two situations, Yate's correction for continuity was used, whereas Fisher's exact test was used when any cell size was less than five. For continuous variables, the nonparametric Mann-Whitney test was used to compare the distribution between the two treatment groups. All reported significance levels are two-sided. The SPSS program was used for statistical computations (SPSS for Windows, 1999).

Results

From April 2000 to April 2001, 201 patients admitted with CAP were screened, 144 were eligible for the study, 15 refused to participate and 129 were randomized. Thirteen patients were withdrawn from the study for the following reasons: primary diagnosis other than CAP (10 patients), lost to follow-up (2 patients) or discharge from hospital within 24 h of admission (1 patient). Thus, 116 patients (oral levofloxacin, 79; intravenous-to-oral sequential therapy, 37) were evaluable for response to antibiotic in a per-protocol analysis. Characteristics of the patients (Table 1) were comparable in the two treatment groups except for the higher median baseline serum creatinine level in the levofloxacin group (102 vs. 94 mmol/l, P=0.02). In both treatment groups, more than 60% of the patients had a Prognostic Score Index of IV or V, and more than 70% of the patients had comorbidities, mostly cardiopulmonary diseases. Sixteen (14%) patients had received antibiotics (median duration of therapy, 1.5 days) prior to admission.

Table 1 Characteristics of the patients included in the study

Characteristic	Oral levofloxacin group	lntravenous-to-oral sequential therapy group
Total no. of patients	79	37
No. of males/females	46/33	25/12
Median age in years (range)	77 (24–92)	77 (26–95)
Prognostic Score Index, no. (%)		
I	0 (0%)	1 (3%)
II	14 (18%)	8 (22%)
III	14 (18%)	5 (14%)
IV	47 (59%)	20 (54%)
V	4 (5%)	3 (8%)
Previous antibiotics, no. (%)	12 (15%)	4 (5%)
Comorbidities[a], no. (%)	57 (72%)	27 (73%)
Heart failure	36 (46%)	12 (32%)
COPD	24 (30%)	11 (30%)
Asthma	5 (6%)	2 (5%)
Diabetes	4 (5%)	3 (8%)
Renal failure	12 (15%)	2 (5%)
Cancer	5 (6%)	1 (3%)
Cerebrovascular diseases	3 (3%)	5 (13%)
Liver disease	2 (3%)	0 (0%)
Neuromuscular disease	1 (1%)	1 (3%)
Median clinical parameters (range)		
Temperature, °C	38 (36–40)	38 (35–40)
Heart rate, min^{-1}	97 (54–160)	103 (67–140)
Systolic pressure, mmHg	130 (98–190)	134 (113–192)
Diastolic pressure, mmHg	80 (60–135)	80 (58–110)
Respiratory rate, min^{-1}	22 (9–36)	24 (12–52)
Median laboratory parameters (range)		
Leucocyte count, $10^3/mm^3$	12.4 (5.1–35.5)	13.8 (4.8–30)
C-reactive protein, mg/l	143 (1–450)	171 (10–513)
Creatinine, mmol/l[b]	102 (61–320)	94 (65–167)
Sodium, mmol/l	136 (125–143)	135 (116–140)
Abnormal chest radiograph, no. (%)	79 (100%)	37 (100%)
Bilateral infiltrate	9 (11%)	3 (8%)
More than 1 lobe involved	13 (16%)	3 (8%)

COPD, chronic obstructive pulmonary disease
[a] Some patients had more than one comorbidity
[b] P=0.04

Table 2 Etiology of pneumonia in the study patients

Etiological characteristic	Oral levofloxacin group	lntravenous-to-oral sequential therapy group
No. of patients	79	37
No. (%) with microbiologically documented pneumonia	18 (23%)	11 (30%)
No. of microorganisms isolated[a]	22	12
Gram-positive bacteria		
Streptococcus pneumoniae	11	8
Staphylococcus aureus	2	0
Group G streptococci	1	0
Gram-negative bacteria		
Haemophilus influenzae	3	1
Escherichia coli	1	1
Moraxella catarrhalis	2	0
Klebsiella pneumoniae	0	1
Legionella pneumophila	1	0
Pasteurella multocida	1	0
Other	0	1

[a] More than 1 microorganism was isolated in 5 patients (*Streptococcus pneumoniae* and *Haemophilus influenzae* in 3, *Streptococcus pneumoniae* and *Moraxella catarrhalis* in 1 and *Staphylococcus aureus* and group G streptococci in 1)

Table 3 Outcome of the patients included in the study

Outcome	Oral levofloxacin group	lntravenous-to-oral sequential therapy group
No. of patients	79	37
Cure, no. (%)	72 (91.1%)	34 (91.9%)
Failure, no. (%)	7 (8.9%)	3 (8.1%)
Nonresponse, no. (%)	2 (2.5%)	1 (2.7%)
Relapse/reinfection, no. (%)	2 (2.5%)	1 (2.7%)
Death due to infection, no. (%)	0 (0%)	1 (2.7%)
Adverse event(s), no. (%)	3 (3.8%)	0 (0%)
Median length of stay in days (range)	8 (2–74)	10 (3–29)
Overall mortality at day 30, no. (%)	1 (1.3%)	3 (8.1%)

Blood cultures were performed in 76 (66%) patients and were positive in 4. Bacteraemia was due to *Streptococcus pneumoniae* (2 episodes) and to *Staphylococcus aureus* and group G streptococci (1 episode) in the levofloxacin group and to *Streptococcus pneumoniae* (1 episode) in the intravenous-to-oral sequential therapy group. Cultures of expectorated sputum were performed in 46 (40%) patients, and *Streptococcus pneumoniae* and *Legionella* urinary antigens were measured in 79 (68%) patients and 26 (22%) patients, respectively. Pneumonia was microbiologically documented in 29 (25%) patients (Table 2). The aetiology of pneumonia was considered definitive in 15 patients and probable in 14. *Streptococcus pneumoniae* was the most common pathogen (66%), followed by *Haemophilus influenzae* (14%), *Staphylococcus aureus* (7%), *Moraxella catarrhalis* (7%) and *Escherichia coli* (7%). Five patients had mixed infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* in three, *Streptococcus pneumoniae* and *Moraxella catarrhalis* in one and *Staphylococcus aureus* and group G streptococci in one. All isolates of *Streptococcus pneumoniae* were susceptible to levofloxacin and to ceftriaxone, 71% were susceptible to penicillin G and 57% were susceptible to clarithromycin.

The median duration of antibiotic therapy was 11 days (range, 5–22 days) in the levofloxacin group and 13 days (range, 9–28 days) in the intravenous-to-oral sequential therapy group (P=0.01). In the levofloxacin group, two patients received the first dose of antibiotic intravenously. In the intravenous-to-oral sequential therapy group, 20 (54%) patients were treated with ceftriaxone plus oral clarithromycin and 17 (46%) patients with ceftriaxone monotherapy. The median duration of intravenous ceftriaxone was 4 days (range, 2–11 days). Five patients received a full course of intravenous therapy, given in combination with clarithromycin in two, whereas 32 patients were switched to oral therapy consisting of amoxicillin/clavulanate (17 patients), cefuroxime (7 patients), clarithromycin (4 patients) or levofloxacin (4 patients). Clinical response rates were similar in both treatment groups (levofloxacin, 91.1%; intravenous-to-oral sequential therapy, 91.9%; difference, –0.8%; 95%CI, −11.6–10.0) (Table 3). Treatment failures were due to nonresponse, reinfection or adverse events, each occurring in three patients. Antibiotics had to be changed after 3, 5 and 7 days, respectively, due to lack of clinical improvement in 3 patients (levofloxacin group, 2; intravenous-to-oral sequential therapy group, 1) with CAP of undetermined aetiology. All patients improved after

modification of antibiotic therapy. One patient in the levafloxacin group was readmitted because of relapsing CAP due to a penicillin- and macrolide-susceptible strain of *Streptococcus pneumoniae*; relapse occurred 7 days after discontinuation of levofloxacin for the first of episode of CAP, for which no microorganism had been isolated. Unfortunately, the susceptibility of the *Streptococcus pneumoniae* isolate to levofloxacin was not tested. Pneumococcal pneumonia was cured with intravenous ceftriaxone followed by oral cefuroxime. The other two patients (levofloxacin group, 1; intravenous-to-oral sequential therapy group, 1) presented with acute bronchitis 7 and 10 days after discontinuation of antibiotic therapy. These upper respiratory tract infections were not present when the patients were enrolled into the study.

The median length of stay was 8 days (range, 2–74 days) in the levofloxacin group and 10 days (range, 3–29 days) in the intravenous-to-oral sequential therapy group (P=0.28). Four patients died (overall mortality, 3.4%) (levofloxacin group, 1 [1.3%]; intravenous-to-oral sequential therapy, 3 [8.1%]; difference, −6.8%; 95%CI,−16.0–2.3), all of whom had a Prognostic Score Index of IV and were 79–87 years of age. Pneumonia was considered the cause of death in only one patient (intravenous-to-oral sequential therapy group), who had severe chronic obstructive pulmonary disease and died on day 12 despite treatment with broad-spectrum intravenous antibiotics. Blood and expectorated sputum cultures remained negative, and no autopsy was performed. In the other three patients, death was attributed to cardiac (2 patients) or digestive (1 patient) events. Antibiotic-associated adverse events occurred in five (6%) patients in the levofloxacin group and two (5%) patients in the intravenous-to-oral sequential therapy group. The adverse events reported in the levofloxacin group were nausea (2 patients), diarrhoea (2 patients) and seizure (1 patient). Treatment was discontinued in three patients, but the relationship between the adverse event and the study drug was not established definitively. In the intravenous-to-oral sequential therapy group, one patient developed nausea that was possibly related to the study drug(s), and one had *Clostridium difficile* colitis, considered definitely related to antibiotic therapy.

Discussion

Until recently, administration of parenteral antibiotics was considered the standard of care for the treatment of infections in acutely ill hospitalized patients, including patients with CAP. However, the advent of potent, broad-spectrum, bactericidal antibiotics with excellent bioavailability, such as beta-lactam agents and fluoroquinolones, has offered clinicians the option to safely treat moderately ill patients with oral antibiotics. Recent studies have indeed shown that fluoroquinolones with enhanced activity against pneumococci, given either orally to outpatients or as intravenous-to-oral sequential or step-down therapy to inpatients, are highly efficacious and safe for the treatment of patients with CAP [14, 22, 23, 24, 25, 26, 27, 28, 29].

The results of the present study show that a full oral course of levofloxacin is as efficacious (response rate, 91% in levafloxacin group vs. 92% in intravenous-to-to oral therapy group) and as safe (rate of adverse events, 6% vs. 5%; mortality, 1% vs. 8%) as standard intravenous-to-oral step-down therapy for the treatment of hospitalized patients with CAP. As a safeguard against the risk of underdosing due to a less-than-optimal absorption of oral antibiotic in these severely ill patients, levofloxacin (500 mg) was given twice daily instead of once daily as usually prescribed in patients with CAP. The high proportion of patients with a Prognostic Score Index of IV or V (>60%), the high rate of patients with comorbidities (>70%) and the elevated median age (77 years) indicate that most of the patients enrolled were critically ill [2, 3, 4, 21]. The high response rate (91%) and the low mortality rate (1.3%) in the levofloxacin group are comparable with those observed in numerous intravenous-to-oral sequential studies and demonstrate the efficacy and safety of a fully oral antibiotic treatment for inpatients with CAP. Given their favourable antimicrobial, clinical and safety profiles, fluoroquinolones with enhanced activity against *Streptococcus pneumoniae* are now widely used for the treatment of CAP, especially in areas with high rates of resistance to penicillin and macrolides. However, as a word of caution against the indiscriminate use of this class of antibiotics, especially in the context of low resistance to other commonly used antibiotics or for the treatment of outpatients with uncomplicated CAP, physicians should be aware that resistance is emerging [30], as might have occurred in one of our patients, and that treatment failures have been reported [31].

Treatment with oral antibiotics helps minimize the use of intravenous catheters, thereby reducing nursing time and improving the patient's comfort and mobility and thus preventing complications of intravenous therapy such as phlebitis, catheter-related infections, bedsores and thromboembolic events. Moreover, previous studies have demonstrated that an early switch from intravenous to oral antibiotics in patients with CAP reduces treatment costs and shortens the length of hospital stay [5, 6, 7, 8, 9, 10, 11, 12, 13]. The median length of stay was numerically lower (8 vs. 10 days) in the oral therapy group than in the intravenous therapy group, but this difference was not statistically significant. This was not unexpected. Indeed, in a mostly elderly patient population with frequent comorbidities, the management of the underlying diseases rather than the treatment of CAP and the time needed to find an appropriate social environment compatible with a safe return to home usually are the main determinants of the length of stay [4]. Administration of a full oral course of antibiotics may help to further shorten the patient's hospital stay without comorbidities.

Few studies have examined the feasibility of an exclusively oral therapy for inpatients with CAP. The first studies were conducted with penicillin V, cefpo-

doxime, ofloxacin or azithromycin [32, 33, 34, 35], which are either no longer appropriate or could only be used in a minority of hospitalized patients with CAP [2, 3, 4]. More recently, oral cefuroxime therapy and amoxicillin/clavulanate given with or without a macrolide were observed to be as efficacious as intravenous-to-oral step-down therapy in 85 hospitalized patients with nonsevere CAP [36]. Only two studies have compared the efficacy of fluoroquinolone monotherapy with that of standard oral or intravenous antibiotics [15, 37]. Once-daily oral sparfloxacin was shown to be as efficacious as oral amoxicillin in a prospective, randomized trial of mostly young inpatients with CAP and no comorbidities [37]. In the other study, conducted in a sicker patient population, intravenous-to-oral sequential levofloxaxin was found to be as effective as intravenous ceftriaxone followed by various oral antibiotics or cefpodoxime for inpatients with CAP [15]. Therefore, the present observational and feasibility study strongly suggests that a full course of oral fluoroquinolone therapy is as efficacious as standard intravenous-to-oral step-down therapy for the treatment of hospitalized non-ICU adult patients with CAP.

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