An Open-label, Randomized Comparison of Levofloxacin and Amoxicillin/Clavulanate plus Clarithromycin for the Treatment of Hospitalized Patients with Community-acquired Pneumonia

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Background: Anti-pneumococcal fluoroquinolone has been used to treat community-acquired pneumonia (CAP) frequently because of its broad antimicrobial spectrum.

Methods: This randomized, open-label study was conducted in a tertiary teaching hospital. Eligible patients were randomized to levofloxacin 500 mg IV q24h followed by 500 mg orally q24h or a combination of amoxicillin/clavulanate 500 mg/100 mg IV q8h with oral clarithromycin 500 mg q12h and then oral amoxicillin/clavulanate 250 mg/125 mg q8h with oral clarithromycin 500 mg q12h for 7-14 days.

Results: From July 2004 to February 2006, 50 patients were enrolled (levofloxacin, n = 26; combination therapy, n = 24). The clinical response rate in the clinically evaluable population was similar for both groups (78.3% vs. 77.3%; p = 1.000). Levofloxacin had a higher microbiological response rate overall, and for Gram-negative and non-pseudomonas Gram-negative pathogens than the combination therapy but the difference was not statistically significant (60.0% vs. 38.9%, 55.0% vs. 21.0% and 75.0% vs. 25.0%, respectively). The length of hospital stay was similar for both groups (7.4 $\pm$3.1 vs. 6.8 $\pm$ 2.1 days; p = 1.000).

Conclusion: Patients who were admitted to our hospital for CAP were older and had more comorbidities with a much higher incidence of Gram-negative pathogens than in a previous study. Levofloxacin was at least as effective as amoxicillin/clavulanate plus clarithromycin in clinical and microbiological responses. Levofloxacin had a higher microbiological eradication rate than the combination therapy but the difference was not statistically significant. This deserves further study with a larer sample size.

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Key words: community-acquired pneumonia, clinical trial, elderly, fluoroquinolones, levofloxacin

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Worldwide, community-acquired pneumonia (CAP) remains a life-threatening infection of the lower respiratory tract despite the availability of many potent antimicrobial agents.[1] It accounts for 5.6 million cases and more than 1 million hospitalizations annually in the United States, and the cost burden is significantly high for patients aged over 65 years with comorbidity.[2] The overall mortality rate among patients hospitalized with CAP ranges from 5% to 25%.[3] The evidence-based guidelines published by the scientific societies[4-6] have recommended two regimes for hospitalized patients with CAP who do not need intensive care: combination therapy of intravenous β-lactam plus a macrolide or monotherapy of an antipneumococcal fluoroquinolone (FQ). Guidelines of the British Thoracic Society (BTS) give preference to combination therapy as initial therapy and FQ as an alternative choice if combination therapy is not tolerated.[4] Guidelines of the Infectious Diseases Society of America (IDSA)[5] and the American Thoracic Society (ATS)[6] recommend FQ as the primary or secondary consideration for patients with complicated CAP. Hospitalized patients with pneumonia receiving timely guideline-based empirical antibiotics have been considered to have better outcomes than those receiving non-guideline treatment.[7-10]

An FQ, such as levofloxacin, has the advantage of being able to cover Gram-positive pathogens, including penicillin-resistant Streptococcus pneumoniae, Gram-negative and atypical pathogens with a single agent, generally given once a day.[11-15] After levofloxacin was approved as a broad-spectrum antimicrobial agent by the United States Food and Drug Administration in 1997, prescribing levofloxacin as the first-line antibiotic for hospitalized CAP treatment became popular. A number of trials have been conducted to evaluate the efficacy of levofloxacin monotherapy compared to combination therapy of ceftriaxone plus macrolide for the treatment of CAP.[16-19] Most of these trials revealed that levofloxacin monotherapy is equivalent to or more effective than combination regimens in clinical and microbiological responses.

The combination therapy of amoxicillin/clavulanate plus clarithromycin is another choice that conforms to guidelines. Currently, amoxicillin/clavulanate plus clarithromycin is one of the standard regimens for the treatment of hospitalized patients with CAP in our hospital. However, the prevalence of β-lactam and macrolide resistance has increased dramatically during the past 2 decades.[20-22] Facing the challenge of elderly patients with more comorbidities and increasing antimicrobial drug resistance, we attempt to evaluate the efficiency of FQ monotherapy and combination therapy in our current practice.

The present study is designed to compare the clinical efficacy and safety of levofloxacin monotherapy with a combination of amoxicillin/clavulanate plus clarithromycin for the treatment of hospitalized patients with CAP who do not need intensive care.

METHODS

Study design

This study was conducted at Chang Gung Memorial Hospital, a 3,000-bed tertiary teaching medical center in northern Taiwan. The in-patient department of thoracic medicine includes a 170-bed ordinary ward. This is a randomized, open-label study comparing the clinical efficacy and safety of levofloxacin monotherapy with the combination therapy of amoxicillin/clavulanate plus clarithromycin for hospitalized patients with CAP. This project has been approved by the Chang Gung Memorial Hospital Ethics Committee. Informed consent was obtained from all subjects.

Inclusion criteria

Patients aged ≥ 18 years were eligible for the study if they had a diagnosis of pneumonia acquired in the community and had been admitted to hospital. The diagnosis criteria were as follows: (1) characteristic clinical signs, including ≥ 1 of the following: (a) fever (oral temperature ≥ 38°C) or hypothermia (≤ 35°C), (b) leukocytosis (>10,000 white blood cells/mm^3) or bands > 10%; (2) acute infiltrate consistent with pneumonia on chest radiography; (3) at least one respiratory symptom: (a) cough or increasing cough severity, (b) purulent sputum/acute change in the quality of sputum, (c) dyspnea.

Exclusion criteria

Patients meeting any of the following criteria were not eligible for admission into the study: (1) previous allergic or serious adverse reaction to levofloxacin, clarithromycin, amoxicillin/clavulanate or

any members of the FQ, β-lactam or macrolide classes of antimicrobials; (2) severe renal failure (creatinine clearance < 20 ml/min); (3) neutropenia (< 500 polymorphonuclear cells (PMNs)/mm^3); (4) unstable psychiatric conditions; (5) pregnancy or nursing; (6) use of study drugs within 30 days prior to entry into the study; (7) previous antimicrobial therapy, other than study drug, taken for more than 24 hours; (8) anticipated requirement for the initiation of systemic corticosteroids, unless such therapy was already being prescribed for an unrelated medical condition. Further exclusions included: those with healthcare-associated pneumonia (HCAP), including any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; anyone residing in a nursing home or long-term care facility; anyone receiving intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection; anyone attending a hemodialysis clinic.

Randomization procedures

Patients were assigned to one of two treatment regimens based on a computer-generated randomization schedule. The study drug was dispensed sequentially based on this randomization code, which provided for equal numbers of patients in the two regimens.

Dosage and administration

Patients randomly assigned to levofloxacin received 500 mg IV q24h transitioning to oral levofloxacin 500 mg q24h when the patients' conditions were compatible with criteria for shifting to oral medication (mentioned below). Levofloxacin was taken for a total of 7 to 14 days. Patients randomly assigned to the comparator group received amoxicillin/clavulanate 500 mg/100 mg IV q8h with oral clarithromycin 500 mg q12h and then switched to oral amoxicillin/clavulanate 250 mg/125 mg q8h with oral clarithromycin 500 mg q12h. Combination therapy was taken for total of 7 to 14 days. General guidelines for switching to the oral regimen of the study medication include: (1) cough and respiratory distress are improving; (2) patient has been afebrile for a minimum of 8 hours; (3) the white blood cell count is returning to normal; (4) there is no evidence of abnormal gastrointestinal absorption.

Study evaluation

At the admission visit, pertinent medical history, vital signs, and signs and symptoms, including cough, sputum production, purulent sputum and dyspnea, were recorded. The severity of pneumonia was accessed by a Fine Risk Score (FRS).[23] Scores between 71 and 130 indicate moderate to severe pneumonia. Posteroanterior view chest x-ray (CXR) was obtained. Within 24 hours prior to study entry, respiratory secretion was obtained for routine culture and Gram stain. Blood samples were collected, including alanine transaminase, blood urea nitrogen, glucose (non-fasting) and serum creatinine, hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count and differential white cell count, and analyzed to meet entry criteria and get baseline data.

On-Therapy Visit: between study day 2 to 4, all patients were seen after approximately 72 hours of therapy to evaluate vital signs, signs and symptoms, and to assess adverse events.

Post-Therapy Visit: between study day 5 to 7, patients' signs, symptoms, CXR, adverse events and overall clinical progress were compared to those observed on admission. Respiratory secretions were obtained, if possible, for routine culture and Gram stain. Blood samples were collected, including the same categories as those on admission.

One-month Post-Therapy Visit: between 21-28 days after completion of the study drug course, patients' vital signs, clinical response compared to the 5-7 day post-therapy visit and adverse events were assessed. CXR and respiratory secretion were obtained if the clinical condition was progressing.

Serology test

Serology test for *Mycoplasma pneumoniae* IgM was performed before treatment and 5-7 days after the first serology test to determine the disease pathogen.

Safety evaluations

All patients were questioned regarding possible adverse events during the course of the study. All adverse events were recorded. Safety was also assessed by the physical examinations and laboratory tests performed during the course of the study.

Clinical efficacy evaluations

Clinical response was determined by comparing patients' admission signs and symptoms to those observed at 5-7 days post-therapy. The following definitions were used to classify clinical response: (1) Clinical Cure: resolution of abnormal pretreatment clinical signs and symptoms, and no further antimicrobial therapy for CAP required; (2) Clinical Improvement: clinical findings subsiding significantly but with incomplete resolution of clinical evidence of infection at the follow-up evaluation in a subject who requires no further antimicrobial therapy for CAP; (3) Clinical Failure: no apparent response to therapy or an incomplete response requiring additional antimicrobial therapy for CAP; (4) Unable to Evaluate: clinical judgment of cure, improvement or failure cannot be made due to inadequate follow-up data.

A long-term evaluation was made based on the information obtained at the 1-month post-therapy visit of clinically successful patients in both groups. Long-term evaluation was determined as: (1) Long-term Clinical Cure: resolution of signs and symptoms associated with active infection, and no additional effective antimicrobial therapy for CAP; (2) Long-term Clinical Improvement: continued incomplete resolution of signs and symptoms, with no deterioration during the follow-up period and no requirement for additional effective antimicrobial therapy for CAP; (3) Clinical Relapse: resolution or improvement of signs and symptoms at the post-therapy evaluation, with reappearance or deterioration of signs and symptoms of infection; (4) Unable to Evaluate: due to patient being lost to follow-up and not returning for post-study evaluation.

Microbiological response

For each pathogen, microbiological response was based on evaluations at 5-7 days and was defined as follows for patients with bacteriological confirmation of the pathogen at admission: (1) Eradicated: absence of the identified admission pathogen in the post-therapy culture; (2) Presumed Eradicated: presumed absence of the identified admission pathogen(s) due to substantial improvement of infection so that no material for culture was available; (3) Persisted: continued presence of the identified admission pathogen; (4) Presumed persisted: presumed presence of the identified admission pathogen post-therapy for patients with clinical failure; (5) New infection: appearance of a pathogen other than the original pathogen(s) identified and isolated at admission, and signs and symptoms of pneumonia; (6) Unable to evaluate: inadequate follow-up etc.

Planned analyses

Three populations were identified for the purposes of analysis. The intent-to-treat population (ITT) consisted of all randomized patients. The modified intent-to-treatment population (MITT) consisted of all ITT patients who had a confirmed diagnosis of CAP and who had taken the study drug at least once. The clinically evaluable population consisted of all ITT patients who had a confirmed diagnosis of CAP and who had taken the study drug for at least 3 days without a clinical response of "unable to evaluate".

The clinical response was evaluated in the ITT, MITT and clinically evaluable population. The microbiologically evaluable population consisted of the clinically evaluable population who had appropriate bacteriological cultures and infection that had been bacteriologically proven.

The primary efficacy variables were the clinical responses and microbiological responses. The cured and improved clinical responses were combined and classified as clinical success. The eradicated and presumed eradicated microbiological responses were combined and classified as microbiological success. The classes of persistent, presumed persistent, new infection and unable to evaluate were defined as microbiological failure. Length of hospital stay and long-term evaluation were compared between the clinically successful patients of both groups. The long-term evaluation of the clinically cured and improved cases were combined and classified as clinical success.

Sample size determination

The minimum sample size needed to show that levofloxacin is at least as effective as combination therapy was determined as follows. The calculation is based on the following assumptions: (1) the null hypothesis is that the clinical success rate for amoxicillin/clavulanate plus clarithromycin minus the success rate for levofloxacin is greater than or equal to 15%; (2) the alternative hypothesis is that the success rate difference is less than 15%; (3) the alternative

for which the sample size is calculated is that 87% is the success rate for both treatment groups; (4) the test is conducted at the $\alpha = 0.025$ significance level and with power $1 - \beta = 0.80$. Under these assumptions, the required number of evaluable patients per treatment group is 79, which means there should be a least 158 clinically evaluable patients. However, according to the rate of progress in this trial and considering the possible prolonged time for recruiting 158 evaluable patients, we analyzed the available data.

Analysis methods

Data analysis was performed using Graphpad Prism 4 software. The categorical variables were analyzed by Fisher's exact test and the numerical variables were analyzed by paired or unpaired Student's t-test. For unpaired data with uneven variation, a Mann-Whitney U test was used. The primary inferential analysis was the construction of a two-sided 95% confidence interval (CI) for the difference in clinical success rates between the two treatment groups, with the goal of confirming that levofloxacin monotherapy is at least as effective as amoxicillin/clavulanate plus clarithromycin. This goal was considered to be confirmed if the upper confidence limit was less than 15% (i.e. the alternative hypothesis: the difference in clinical success rates of two groups is $< 15\%$, represents a better response in the levofloxacin group). A *p* value of less than 0.05 was considered to be statistically significant. The odds ratio (OR) was presented to assess the priority of the levofloxacin group.

RESULTS

From July 2004 to February 2006, 50 patients were randomized to treatment. These patients were composed of the ITT population (Table 1). In the levofloxacin group, one patient's sputum acid fast stain revealed 2+ and diagnosis of pulmonary tuberculosis was confirmed later. The MITT population consisted of 49 patients. Four patients did not receive the study drug for more than 3 days in each group. One patient received another antibiotic on the first day and three patients received the study drug for less than 3 days because of personal choice. The clinically evaluable population was composed of 23 patients in the levofloxacin group and 22 patients in the combination group. Thirty-three pathogens were identified from 23 patients (51.1%) in the clinically evaluable population. These pathogens were evaluated for microbiological response (Table 5).

Table 1. Enrolled Patients' Characteristics

	Levofloxacin	Combination
Intent-to-treat population	26	24
Modified intent-to-treat population	25	24
Clinically evaluable population	23	22
Microbiologically evaluable population	13	10
Identified pathogens	15	18

Abbreviation: Combination: combination therapy of amoxicillin/clavulanate with clarithromycin

Baseline demographic and disease characteristics were similar in the clinically evaluable population (Table 2). The mean age was 68.1 ± 12.5 years and 31 patients (68.9%) were older than 65 years. There was no significant difference in FRS between the two groups. There were 32 patients with scores of more than 71 (71.1%). We analyzed the distribution of scores above and below 71, and there was also no significant difference between the two study groups.

More than 90% of patients in the clinically evaluable population had a productive cough, dyspnea and radiological evidence of pneumonia on admission (Table 3). Other symptoms included leukocytosis or left shift (73.3%), purulent sputum production (68.9%), tachycardia (44.4%) and fever (42.2%).

Table 4 reveals the clinical responses on the 7th day of admission. The overall clinical success rate was 78.3% in the levofloxacin group and 77.3% in the combination group in the clinically evaluable population. The result was similar in the MITT and ITT populations. In the clinically evaluable population, patients with FRS above 71, which means moderate to severe pneumonia, the success rate was 66.7% in the levofloxacin group versus 76.5% in the combination group. In patients with FRS below 71, the success rate was 100% in the levofloxacin group versus 80.0% in the combination group. There was no significant statistical difference in the success rate between the two study groups.

Table 2. Baseline Demographics and Comorbidities of the Clinically Evaluable Population

	Levofloxacin n = 23 (%)	Combination n = 22 (%)	*p* value
Gender			
Male	15 (65.2%)	18 (81.8%)	0.314
Female	8 (34.8%)	4 (18.2%)	
Age (Mean ± SD)	65.3 ± 13.2	71.0 ± 11.4	0.132
Comorbidity	21 (91.3%)	20 (90.9%)	1.000
Chronic pulmonary disease	13 (56.5%)	8 (36.4%)	0.236
Asthma	8	2	
COPD	3	8	
Bronchiectasis	2	0	
Old TB	3	1	
Cerebrovascular diseases	1 (4.3%)	3 (13.6%)	0.346
Renal insufficiency	2 (8.7%)	2 (10%)	1.000
Liver disease	4 (17.4%)	2 (9.1%)	0.665
Cardiovascular diseases	3 (13.0%)	2 (9.1%)	1.000
DM	4 (17.4%)	10 (45.5%)	0.057
Malignancy	1 (4.3%)	5 (22.7%)	0.096
Alcoholism	3 (13.0%)	0	0.233
Smoker/ex-smoker	14 (60.9%)	13 (59.1%)	1.000
Corticosteroid history			
Oral	4	5	0.722
Inhaled	8	7	1.000
Fine Risk Score			
Median	78	81	0.642
Range	38～118	42～118	
Fine Risk Score < 71	n = 8	n = 5	
Median	65	53	0.622
Range	38～67	42～69	
Fine Risk Score ≥ 71	n = 15	n = 17	
Median	89	89	0.850
Range	77～118	71～118	

Abbreviations: Combination: combination therapy of amoxicillin/clavulanate with clarithromycin; SD: standard deviation; COPD: chronic obstructive pulmonary disease; TB: tuberculosis; DM: diabetes mellitus

Table 3. Signs and Symptoms of Pneumonia in the Clinically Evaluable Population

	Levofloxacin n = 23	Combination n = 22	Total
Fever*	10 (43.5%)	9 (40.9%)	19 (42.2%)
Tachycardia†	10 (43.5%)	10 (45.5%)	20 (44.4%)
Purulent sputum‡	18 (78.3%)	13 (59.1%)	31 (68.9%)
Leukocytosis or left shift§	17 (73.9%)	16 (72.7%)	33 (73.3%)
Dyspnea	22 (95.7%)	19 (86.4%)	41 (91.1%)
Sputum production	22 (95.7%)	22 (100%)	44 (97.8%)
Cough	23 (100%)	22 (100%)	45 (100%)
Radiological evidence of pneumonia	23 (100%)	22 (100%)	45 (100%)

Abbreviations: Combination: combination therapy of amoxicillin/clavulanate with clarithromycin; *: oral temperature ≥ 38°C; †: heart rate above 100 beats/minute; ‡: acute change in the quality of sputum; §: white blood cells > 10,000/mm^3 or bands > 10%

Table 4. Clinical Response on the Seventh Day of Hospitalization

	Levofloxacin	Combination	*p* value
ITT population	n = 26	n = 24	
Clinical success	18 (69.2%)	17 (70.8%)	1.000
Failure	8 (30.8%)	7 (29.2%)	
MITT population	n = 25	n = 24	1.000
Clinical success	18 (72.0%)	17 (70.8%)	
Failure	7 (28.0%)	7 (29.2%)	
Clinically evaluable population	n = 23	n = 22	1.000
Clinical success	18 (78.3%)	17 (77.3%)	
Failure	5 (21.7%)	5 (22.7%)	
Fine risk score ≥ 71	n = 15	n = 17	0.700
Clinical success	10 (66.7%)	13 (76.5%)	
Failure	5 (33.3%)	4 (23.5%)	
Fine risk score < 71	n = 8	n = 5	
Clinical success	8 (100%)	4 (80%)	0.385
Failure	0	1 (20%)	

Abbreviations: Combination: combination therapy of amoxicillin/clavulanate with clarithromycin; ITT: intent-to-treat; MITT: modified intent-to-treat

The overall microbiological success rate was 60.0% in the levofloxacin group and 35.3% in the combination group (Table 5). Although the success rate was higher in the levofloxacin group than in the combination group, there was no statistically significant difference (OR: 2.36, 95% CI: 0.79~3.65). Table 6 shows all the causative pathogens and microbiological responses in each group. The number of Gram-negative causative pathogens (75.8%) was significantly higher than the number of Gram-positive (21.2%) ones. One patient had a positive result for Mycoplasma IgM in the combination group but the microbiological response could not be evaluated based on a serology test. Two patients with Pseudomonas and Acinetobacter baumannii in the levofloxacin group and two patients with Haemophilus parainfluenza and Klebsiella pneumoniae in the combination therapy group continuously received original regimens because their clinical conditions were improving, although microbiological failure was noted.

Since Gram-negative pathogens contributed to more than 70% of the identified pathogens, we next evaluated the efficacy of the study drugs to eradicate Gram-negative pathogens by excluding the Gram-positive pathogens and mycoplasma, which were successfully eradicated in both groups. In the Gram-negative CAP population, the microbiological success rate was 54.4% in the levofloxacin group and 21.4% in the combination group. Although the success rate was higher in the levofloxacin group than in the combination group, there was no statistically significant difference (OR: 4.40, 95% CI: 0.77~25.16).

Among Gram-negative pathogens, Pseudomonas aeruginosa was revealed in both groups. Such a pathogen should be treated with a combination of anti-pseudomonas antibiotics, as suggested in published guidelines.[4-6] Therefore, we further evaluated the drug efficacy for the non-pseudomonas Gram-negative pathogens. The success rate was higher in the levofloxacin group than in the combination group (75.0% versus 25.0%), with marginal significance (OR: 9.00, 95% CI: 0.96~13.95).

Icrobiald ty-acquired pneumonia The overall mean length of hospital stay for CAP in the clinically successful population was 7.1 ± 2.6 days. The length of hospital stay was similar in both groups (7.4 ± 3.1 versus 6.8 ± 2.1 days; p = 1.000). We excluded one patient in the levofloxacin group who was continu-

Table 5. Microbiological Evaluation of Identified Pathogens

Identified pathogen	Levofloxacin	Combination	OR, 95% CI
	n = 15	n = 17	
Successful eradication	9 (60%)	6 (35.30%)	2.75, 0.791~3.653
Eradication	5	6	
Presumed eradication	4	0	
Failed eradication	6 (40%)	11 (64.70%)	
Persistent	4	2	
Presumed persistent	1	4	
New infection	1	5	

Abbreviations: Combination: combination therapy of amoxicillin/clavulanate with clarithromycin; OR: odds ratio; CI: confident interval

Table 6. Microbiological Efficacy for Identified Pathogens

	Levofloxacin n = 15		Combination n = 18	
Eradication	Success n = 9	Failure n = 6	Success n = 6	Failure n = 11
Gram-positive pathogens n = 7 (21.2%)				
Streptococcus pneumoniae	3	0	2	0
Staphylococcus aureus	0	1	1	0
Gram-negative pathogens n = 25 (75.8%)				
Haemophilus influenza	1	0	1	0
Haemophilus parainfluenza	1	0	1	1*
Moraxella catarrhalis	1	0	0	0
Klebsiella pneumoniae	1	0	0	4*
Escherichia coli	0	0	1	2
Pseudomonas	0	3*	0	2
Shewanella putrefaciens	1	0	0	0
Acinetobacter baumanniiq	1	2*	0	0
Stenotrophomonas maltophilia	0	0	0	1
Citrobacter freundii	0	0	0	1
Mycoplasma pneumoniae n = 1 (3.0%)	0	0	1†	

Abbreviations: Combination: combination therapy of amoxicillin/clavulanate with clarithromycin; *: One patient with clinical cure/improvement; †: One patient had a positive result for Mycoplasma IgM in the combination group but the microbiological response could not be evaluated from a serology test.

ously hospitalized for cervical and perineum inflammation and vaginal bleeding after recovery from CAP.

At the 1-month post-therapy follow-up of the clinically successful population, equivalent outcome was noted in both groups (clinical success rate: 89.5% versus 88.2%, $p = 1.000$). Two clinical relapses were contributed to by Mycobacterium tuberculosis and Klebsiella pneumoniae. During the 1-month follow-up period, no significant clinical or laboratory abnormalities induced by the study drugs were recorded for the enrolled population.

DISCUSSION

Our study showed that levofloxacin monotherapy was as effective as the combination regimen of amoxicillin/clavulanate plus clarithromycin for the treatment of CAP in hospitalized patients. To our knowledge, this study is the first randomized study comparing levofloxacin monotherapy with sequential intravenous and oral amoxicillin/clavulanate-based combination therapy. The results in our study were similar to other clinical trials comparing levofloxacin to other β-lactams (most of them being ceftriaxone) plus macrolide as CAP therapy.[16-18]

In the study of Fine et al.,[23] an FRS of 71 to 130 indicated moderate to severe disease and an associated need for hospitalization. The CAP mortality rate was less than 1% in patients with an FRS below 71, suggesting that patients with lower FRS do not need hospitalization. The clinical response was not statistically significant in subgroups of patients with FRS below or above 71. This means that levofloxacin monotherapy is as effective as combination therapy in the treatment of patients with different severities of CAP. In this study, patients with FRS below 71 made up 28.9% of the clinically evaluable population. However, disease severity was not the only criteria for administration. ATS guidelines describe such a decision as an "art of medicine". Social considerations, e.g. social insurance or home care support, should also be considered.[6] In addition to the severity index, IDSA guidelines also emphasize the importance of clinical judgment and safety of the initial site of treatment.[5]

Nearly 70% of our patients were older than 65 years. This could explain why there were lower percentages of fever and leukocytosis in our patients. Ninety-one percent of them had at least one comorbidity. These results are compatible with other studies that demonstrated that seniors with comorbid conditions have a higher risk of hospital admission and mortality.[23-28] Kaplan et al. revealed that advanced age and an increasing number of comorbidities were major independent risk factors for one-year post discharge mortality.[26] Efforts should be made to reduce preventable comorbidities, and provide effective influenza and pneumococcal vaccination.

Causative pathogens were identified in more than half of the clinically evaluable population. In previous reports, incidence of CAP due to Gram-negative pathogens was about 11%.[27,29] In our study, 75.8% of CAP was due to Gram-negative pathogens, which was significantly higher than previous reports. The significantly higher percentage of Gram-negative pathogens compared to previous reports is discussed below. Documented risk factors for CAP due to Gram-negative pathogens include aspiration, previous hospital admission, previous antibiotic use, medical comorbidity and residence in a nursing home.[29] Ruiz et al.[27] also showed that patients older than 60 years with any comorbidity have a higher risk of infection from Gram-negative bacteria, particularly Pseudomonas infection. It is possible that, as our hospital is a referral hospital for northern Taiwan, patients were older with many comorbidities and, therefore, were at high risk of Gram-negative infection. Further, the small number of cases is another important limitation. These data reflect the experience of one tertiary teaching hospital. It may not be extrapolated universally. However, such local data can remind us that it is important to ensure adequate empiric antibiotics to cover Gram-negative pathogens for older patients with many comorbidities.

The incidence of atypical pneumonia in this study was rare. IDSA guidelines (2000) for CAP in adults mentioned that *Mycoplasma pneumoniae* is a common cause of respiratory tract infections, primarily in those aged 5-9 years of age and in young adults. This organism causes a small percentage of cases of CAP requiring hospitalization. The impact of age on the etiology of CAP shows that patients aged < 60 years are at risk for an "atypical" bacterial etiology, especially Mycoplasma pneumoniae.[27] Nearly 70% of our patients were older than 65 years

of age. This could explain why there were lower percentages of atypical pneumonia and a low identifying rate of Mycoplasma pneumoniae in the older patient population of our study.

Levofloxacin had a higher microbiological eradication rate than the combination therapy in the overall, Gram-negative pathogens and non-pseudomonas Gram-negative pathogens, although there were no statistically significant differences. The better efficiency of levofloxacin in the eradication of Gram-negative pathogens was compatible with a large study conducted in the United States in 2000.[15] It is rational to predict that it will be statistically significant in a larger sample size.

The adverse effects of levofloxacin monotherapy and combination therapy in one 236-patient study[14] were reported as 4.5% and 4.4%, respectively. In our study, no adverse effects caused by the study drugs were recorded. Levofloxacin has other potential advantages for clinical practice. Its oral formulation is essentially 100% bioavailable[14] and parenteral levofloxacin may be switched to an oral formulation easily, achieving better compliance. Further, levofloxacin penetrates well into the lung epithelium and macrophage, achieving higher levels in the lung than in serum.[30] The once daily administration also lessens nurses' workload.

One of the limitations of our study was the small sample size. After 1 year and 7 months, we supposed that the time needed for recruiting patients to the estimated numbers would take another 3 years. Considering the limited resources of our department, we decided to analyze currently available data first. Of course, we knew that the sample size of the analysis was small and the power of the analysis would not be adequate but we hoped that this local preliminary finding would provide more discussion about this important issue. The power for microbiological response in Gram-negative non-pseudomonas pathogens was 0.48 and we estimate that if the pathogen sample size was increased to 62, the power would become 0.8. A larger patient pool would probably exhibit significant difference in microbiological response between the study groups. Another limitation is that we did not specifically identify viruses, Chlamydia and Legionella species. Such management conformed to the suggestion of published guidelines for usual clinical practice, except in enigmatic severe pneumonia, during outbreaks or for epidemiological reasons.[4-6] These data represent an endemic condition at a tertiary medical center that may not be able to be simply applied to every type of hospital. However, these results remind us of the importance of the increasing burden of elderly patients with comorbidity and the necessity of effective empiric antibiotics to cover Gram-negative pathogens in the management of CAP.

This hospital-based study revealed that, for hospitalized patients with CAP, levofloxacin monotherapy is at least as effective as a combination therapy of amoxicillin/clavulanate plus clarithromycin in clinical and microbiological efficacy, and long-term evaluation.

Patients who were admitted to our hospital for CAP were older and had more comorbidities, with a much higher incidence of Gram-negative pathogens than in a previous study. Levofloxacin had a higher microbiological response rate in overall, Gram-negative and non-pseudomonas Gram-negative pathogens but the difference was not statistically significant. This deserves further study with a larger sample size in the future.

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REFERENCES

1. Gant V, Parton S. Community-acquired pneumonia. Curr Opin Pulm Med 2000;6:226-33.
2. Niederman MS, McCombs JS, Unger AN, Kumar A, Popovian R. The cost of treating community-acquired pneumonia. Clin Ther 1998;20:820-37.
3. Ginesu F, Pirina P, Deiola G, Ostera S, Mele S, Fois AG. Etiology and therapy of community-acquired pneumonia. J Chemother 1997;9:285-92.
4. British Thoracic Society Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults. Thorax 2001;56:IV1-64.
5. Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C. Infectious Diseases Society of America. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003;37:1405-33.
6. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, Dean N, File T, Fine MJ, Gross PA, Martinez F, Marrie TJ, Plouffe JF, Ramirez J,

Sarosi GA, Torres A, Wilson R, Yu VL; American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730-54.
7. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 2004;164:637-44.
8. Leroy O, Santre C, Beuscart C, Georges H, Guery B, Jacquier JM, Beaucaire G. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. Intensive Care Med 1995;21:24-31.
9. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002;122:262-8.
10. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.
11. Hurst M, Lamb HM, Scott LJ, Figgitt DP. Levofloxacin: an updated review of its use in the treatment of bacterial infections. Drugs 2002;62:2127-67.
12. Mendes C, Kiffer CR, Blosser-Middleton RS, Jones ME, Karlowsky JA, Barth A, Rossi F, Andrade S, Sader HS, Thornsberry C, Sahm DF; GLOBAL Surveillance Initiative 2001-2002. Antimicrobial susceptibility to levofloxacin and other antibacterial agents among common respiratory pathogens-a Brazilian perspective from the GLOBAL Surveillance Initiative 2001-2002. Clin Microbiol Infect 2004;10:521-6.
13. Dunbar LM, Khashab MM, Kahn JB, Zadeikis N, Xiang JX, Tennenberg AM. Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. Curr Med Res Opin 2004;20:555-63.
14. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet 1997;32:101-19.
15. Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, Evangelista AT, Critchley IA, Sahm DF. Susceptibility to fluoroquinolones among commonly isolated Gram-negative bacilli in 2000: TRUST and TSN data for the United States. Tracking Resistance in the United States today. The Surveillance Network. Int J Antimicrob Agents 2002;19:21-31.
16. Frank E, Liu J, Kinasewitz G, Moran GJ, Oross MP, Olson WH, Reichl V, Freitag S, Bahal N, Wiesinger BA, Tennenberg A, Kahn JB. A multicenter, open-label, randomized comparison of levofloxacin and azithromycin plus ceftriaxone in hospitalized adults with moderate to severe community-acquired pneumonia. Clin Ther 2002;24:1292-308.
17. Zervos M, Mandell LA, Vrooman PS, Andrews CP, McIvor A, Abdulla RH, de Caprariis PJ, Knirsch CA, Amsden GW, Niederman MS, Lode H. Comparative efficacies and tolerabilities of intravenous azithromycin plus ceftriaxone and intravenous levofloxacin with step-down oral therapy for hospitalized patients with moderate to severe community-acquired pneumonia. Treat Respir Med 2004;3:329-36.
18. Querol-Ribelles JM, Tenias JM, Querol-Borras JM, Labrador T, Nieto A, Gonzalez-Granda D, Martinez I. Levofloxacin versus ceftriaxone plus clarithromycin in the treatment of adults with community-acquired pneumonia requiring hospitalization. Int J Antimicrob Agents 2005;25:75-83.
19. File TM Jr, Segreti J, Dunbar L, Player R, Kohler R, Williams RR, Kojak C, Rubin A. 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. Antimicrob Agents Chemother 1997;41:1965-72.
20. Song JH, Jung SI, Ko KS, Kim NY, Son JS, Chang HH, Ki HK, Oh WS, Suh JY, Peck KR, Lee NY, Yang Y, Lu Q, Chongthaleong A, Chiu CH, Lalitha MK, Perera J, Yee TT, Kumarasinghe G, Jamal F, Kamarulzaman A, Parasakthi N, Van PH, Carlos C, So T, Ng TK, Shibl A. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). Antimicrob Agents Chemother 2004;48:2101-7.
21. Felmingham D, Feldman C, Hryniewicz W, Klugman K, Kohno S, Low DE, Mendes C, Rodloff AC. Surveillance of resistance in bacteria causing community-acquired respiratory tract infections. Clin Microbiol Infect 2002;8 Suppl 2:12-42.
22. Oishi K, Yoshimine H, Watanabe H, Watanabe K, Tanimura S, Kawakami K, Iwagaki A, Nagai H, Goto H, Kudoh S, Kuriyama T, Fukuchi Y, Matsushima T, Shimada K, Matsumoto K, Nagatake T. Drug-resistant genes and serotypes of pneumococcal strains of community-acquired pneumonia among adults in Japan. Respirology 2006;11:429-36.
23. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243-50.
24. Kaplan V, Angus DC, Griffin MF, Clermont G, Scott Watson R, Linde-Zwirble WT. Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. Am J Respir Crit Care Med 2002;165:766-72.
25. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. JAMA 2005;294:2712-9.

26. Kaplan V, Clermont G, Griffin MF, Kasal J, Watson RS, Linde-Zwirble WT, Angus DC. Pneumonia: still the old man's friend? Arch Intern Med 2003;163:317-23.
27. Ruiz M, Ewig S, Marcos MA, Martinez JA, Arancibia F, Mensa J, Torres A. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med 1999;160:397-405.
28. Kobashi Y, Okimoto N, Matsushima T, Soejima R. Clinical analysis of community-acquired pneumonia in the elderly. Intern Med 2001;40:703-7.
29. Arancibia F, Bauer TT, Ewig S, Mensa J, Gonzalez J, Niederman MS, Torres A. Community-acquired pneumonia due to gram-negative bacteria and pseudomonas aeruginosa: incidence, risk, and prognosis. Arch Intern Med 2002;162:1849-58.
30. Boselli E, Breilh D, Rimmele T, Djabarouti S, Saux MC, Chassard D, Allaouchiche B. Pharmacokinetics and intrapulmonary diffusion of levofloxacin in critically ill patients with severe community-acquired pneumonia. Crit Care Med 2005;33:104-9.

開放性、隨機的方式比較評估可樂必妥 (Levofloxacin) 相較於安滅菌 (Amoxicillin/Clavulanate) 合併開羅理黴素 (Clarithromycin) 於治療需住院的社區性肺炎

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背 景：由於其廣泛的抗菌範圍，抗肺炎球菌的氟化奎林酮類抗生素已常用於治療社區感染的肺炎。

方 法：一項開放性、隨機的研究在一個第三級教學醫院進行。合適的病人隨機分成以可樂必妥針劑每日 500 毫克，接著換成口服每日 500 毫克，或每日每 8 小時以 500 毫克／125 毫克安滅菌針劑及 250 毫克／125 毫克膜衣錠合併每日每 12 小時 500 毫克開羅理黴素膜衣錠。整個治療時間至少爲七至十四天。

結 果：從西元 2004 年七月至西元 2006 年二月，五十位病人符合條件並加入研究 (可樂必妥，26 人；合併治療，24 人)。兩組的臨床反應率相似 (78.3% vs. 77.3%; $p = 1.000$)。可樂必妥在對所有的微生物，格蘭氏陰性菌以及非假單胞菌 (non-pseudomonas) 之格蘭氏陰性菌有較高的微生物學反應率 (60.0% vs. 38.9%; 55.0% vs. 21.0% and 75.0% vs. 25.0%) 但無統計學上的差異。兩組的住院天數是相似的 (7.4 ±3.1 vs. 6.8 ±2.1 days; $p = 1.000$)。

結 論：因社區感染肺炎至本院住院的病人，年齡較高，合併症較多，有較高的比率感染格藍氏陰性菌肺炎。可樂必妥至少和安滅菌加開羅理黴素的合併治療在臨床反應率和微生物學反應率一樣有效。可樂必妥有比合併治療較高的滅菌效果但無統計學上的差異，需要更多病人數的進一步試驗證實。

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關鍵詞：社區感染肺炎，臨床試驗，年長的，氟化奎林酮類抗生素，可樂必妥

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