A Cost-Effectiveness Study of Sequential Therapy Using Levofloxacin Versus Cefuroxime in the Treatment of Moderate Risk Community-Acquired Pneumonia (ATS III) in Adults

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ABSTRACT

Objective: This study was undertaken to investigate the clinical effectiveness and cost-effectiveness of sequential therapy in adults with moderate-risk community-acquired pneumonia. To our knowledge, this is the first such study to be undertaken in a country where healthcare was paid for out-of-pocket.

Methods: This randomized open-label intention-to-treat cost-effectiveness study was taken from the society's viewpoint comparing patients randomized to sequential therapy of either levofloxacin alone or cefuroxime with or without erythromycin. Generally accepted guidelines on Good Clinical Practice were observed throughout the study period.

Results: Protocol-guided sequential therapy using levofloxacin as monotherapy demonstrated a total cost advantage over cefuroxime axetil with or without erythromycin. Drug acquisition costs were also statistically significantly lower ($p < 0.05$) in the levofloxacin group than in the cefuroxime axetil group for both inpatient and outpatient use.

Conclusions: Employment of sequential therapy by the protocol employed supplied physicians with unambiguous determinants of response of their patients and provided clearer foundations for discharge. While sequential therapy using either of the study treatment regimens did not differ in efficacy at the end of treatment, study results suggest that sequential therapy using a respiratory fluoroquinolone for these patients may afford a shorter duration of hospital stay, less adverse events and, ultimately, a reduction of out-of-pocket expenses that would have gone to hospital expenses (room and board, visits by healthcare personnel) had patients remained confined.

Key Words: community-acquired pneumonia, cost-effectiveness, sequential therapy, pharmacoeconomic, protocol-guided

Introduction

Despite an array of potent antimicrobials from which to choose, community-acquired pneumonia (CAP) remains a serious illness worldwide. Philippine health statistics show progressively increasing prevalences of 632,930 (829/100,000 population) in 2000, 652,585 (837.4/100,000 population) in 2001, and 734,581 (734,581/100,000) in 2002. The Philippine Health Statistics of 1998 reported pneumonia as the leading cause of death overall while in 2001, pneumonias ranked third in both morbidity and mortality. For the more serious forms of pneumonia, mortality rates are higher, especially for the elderly and for patients with chronic diseases. Among those hospitalized with CAP in the Philippines, mortality approached 25%, especially if the patient required admission to an ICU.[1]

Although efforts have been made to standardize and monitor the implementation of criteria for admission of patients with community-acquired pneumonia based on risk stratification, there remains a wide variety of local physician practices concerning the time that patients are switched from their IV antimicrobials to oral forms and the time of their hospital discharge.[2,3,4] In the Philippines, healthcare costs are mostly borne out-of-pocket by the patient. Generally, the largest slice of hospitalization cost is spent on medications, with diagnostic examinations and procedures coming in second and hospital stay third.[5] In light of the high prevalence of pneumonia in a predominantly low- to middle-class income population, decisions involving when to shift the patient from IV to oral therapy and when to send the patient home have a predictably greater impact on the lives of families who have to pay out-of-pocket for their health needs.

A pharmacoeconomic analysis, in contrast to a simple price comparison of the cost per dose or cost per day of medications in general (in the case of pneumonia, the cost of an antibiotic), provides a more accurate and complete description of the true cost of healthcare. Since pharmacoeconomics is an outcomes-based science, determining an economic outcome requires a clinical outcome. This economic study was conducted to compare the cost-effectiveness of sequential or switch therapy using levofloxacin vs. cefuroxime with or without erythromycin for the treatment of adult patients hospitalized with CAP. In measuring the cost-effectiveness of sequential therapy, the analysis was taken from the societal perspective.

Study objectives

This multicenter, parallel group, randomized, open-label, comparative clinical study aims to compare the clinical effectiveness and cost-effectiveness of sequential therapy using levofloxacin 500 mg IV OD for three to five days followed by 500 mg oral levofloxacin for a total treatment duration of seven to 10 days versus cefuroxime IV 1.5 g every 12 hours for three to five days followed by cefuroxime

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axetil 500 mg oral twice a day for a total of seven to 10 days treatment of adults with moderate-risk community-acquired pneumonia (ATS CAP III). Specific aims are three-fold: 1) to compare the clinical effectiveness of levofloxacin versus cefuroxime in the treatment of moderate-risk community-acquired pneumonia; 2) to compare the costs of treatment of adults admitted for non-severe community-acquired pneumonia (CAP III); and 3) using results obtained, to evaluate the cost-effectiveness of sequential therapy using the two treatment arms.

The primary measures of clinical effectiveness include changes from baseline clinical condition (signs and symptoms) at end of therapy and after a test of cure using a prescribed program of sequential therapy while secondary measures include the duration of hospital stay and the development of complications and adverse events.

The cost-effectiveness arm measured the total resource costs for direct medical costs, both inpatient and outpatient, and for lost productivity (indirect costs). These costs are evaluated in relation to the clinical outcome.

Materials and Methods

Severity classifications and management decisions incorporated in the protocol were based on the recommendations of the American Thoracic Society (2001),[6] the Infectious Disease Society of America (2003)[7] and the Philippine Practice Guidelines for the Diagnosis and Management of Community Acquired Pneumonia (2003)[8].

Ten local or national medical institutions located in the Metro Manila area (a majority with accredited residency training programs in internal medicine) were identified for this study. Adult patients with a clinical diagnosis of community-acquired pneumonia, moderate risk according to definitions of the American Thoracic Society and Philippine Practice Guidelines were eligible for enrollment. The protocol was submitted for review and approval to the Committee for Institutional Research and Development of the Philippine General Hospital, site of protocol development as well as data collation and analysis, and to the administrators and staff of the other participating hospitals.

All clinically evaluable adult patients who fulfilled the inclusion criteria for community-acquired pneumonia and gave consent for inclusion were enrolled in this pharmacoeconomic analysis. Patients were excluded if more than one dose of systemic antibiotic (or a combination of systemic antimicrobials) was administered within seven days of enrollment, if concomitant systemic antimicrobial therapy (except erythromycin) was necessary during the study period, if the investigator believed that more than 14 days of therapy would be required, or if expected survival was less than 72 hours.

Key exclusion criteria were: known or suspected aspiration pneumonia or obstructive pneumonia; active tuberculosis (with clinical signs and symptoms and a positive sputum AFB smear), empyema or active pulmonary malignancies; metastatic tumor; significant renal, hepatic, cardiovascular, or hematologic disease; serious, unstable underlying conditions; and female patients who were pregnant or nursing. Informed consent was obtained prior to study commencement.

Investigators from ten centers enrolled 420 patients between October 2003 and September 2005. The sample size was based on the anticipated evaluability rate and clinical response. Patients were randomized 1:1 to receive levofloxacin or cefuroxime (control). Patients in the levofloxacin group received 500 mg IV qd for two to five days, followed by 500 mg po qd for a total of five to 10 days of therapy. Patients in the control group received cefuroxime, 1.5 gm IV q 12h, for two to five days, followed by cefuroxime axetil 500 mg po bid, for a total of five to 10 days of therapy. For patients in the control group suspected by the site investigator to have atypical pathogens (Mycoplasma, Legionella, or Chlamydophilia), erythromycin, 500 to 1,000 mg IV q6h/500 mg po qid, for up to 21 days, could be added. The decision to switch from IV to oral therapy was initiated after two to three days of IV medication once ALL of the following criteria were met: marked resolution of respiratory distress (normalization of RR) and improvement of respiratory signs and symptoms present on admission, resolution of abnormal vital signs or return to the patient's usual baseline, ability to eat, drink and take oral medications and the stabilization of co-morbid condition or life-threatening complication, if initially present.

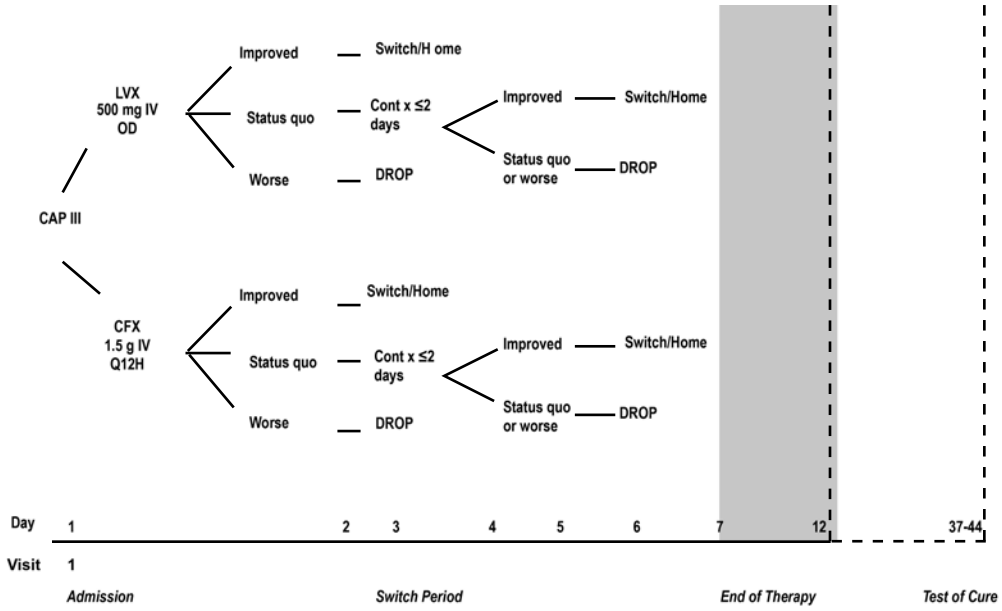
A patient was discharged once the conditions for switch therapy were fulfilled, he/she was able to tolerate the first dose of oral antibiotic (given in the hospital) without adverse reactions, mental status was returned to the patient's usual baseline and no other medical condition warranting continued hospitalization was present.

Maximal attempts to follow-up the clinical condition of discharged patients were done within two days of the end of their treatment and an assessment of treatment outcome was made at the test of cure visit (day 37 to day 44).

Generally accepted guidelines on Good Clinical Practice were observed throughout the study period. (Fig. 1)

The following clinical end points were used: ***success*** (all acute signs and symptoms of pneumonia were resolved or improved to a level such that no further antimicrobial therapy was required); or ***failure*** (signs or symptoms relevant to the original infection persisted or progressed after at least three days of therapy, change in antimicrobial therapy was necessary, or patient died due to pneumonia). In this intention-to-treat study, patients who, in the course of the study, were lost to follow-up or those who, after having been randomized to one or the other of the study drugs withdrew their consent to participate in the remainder of the study were classified as clinical failures.

Detailed information on the conduct of the trial, demographic descriptions of the study population, and clinical, bacteriological, and radiologic results were also



LVX- levofloxacin; CFX – cefuroxime; Day – day of study treatment/observation; Visit – number of study data recording/monitoring

Figure 1. Conduct of Study

analyzed. Safety, clinical, microbiological, and radiographic assessments were performed and recorded during therapy, days 8 to 11 of therapy (end-of-therapy visit), and at long-term follow-up 37 to 44 days since the start of therapy (test-of-cure visit). In this study, usual clinical practice was observed; since performing cultures for atypical pathogens is an infrequent practice in the Philippines, no studies for atypical pathogens were done. Retrospective evaluation of the progress or resolution of clinical symptoms to reflect response to treatment was conducted using a symptom score adapted from the CPIS and PORT[9] scoring.

Data for economic analysis was collected upon admission and continued for the duration of the patients' participation in the study.

Methods of the Economic Analysis

In the Philippines, hospitalization is an out-of pocket expense for the patient and his/her family; therefore, a cost-effectiveness analysis from the societal perspective was taken. Two types of costs were considered: medical costs and costs due to lost productivity of the patient and his/her caregiver. Medical costs included both inpatient and outpatient costs of study drugs, other medications, diagnostic tests, physician, nursing, and respiratory therapist visits, and room and board.

Clinical outcome was categorized as success (cure or improvement) or failure, as determined by the original clinical investigators. All adverse drug reactions were noted and followed-up until final outcome.

The times of initiation of switch therapy as well as the time/date of discharge were the clinical decisions most pertinent to cost. Since co-morbidities and adverse events both affect and are affected by the pneumonia and its treatment, costs attributable to these conditions were also added to the pneumonia-related costs.

Resource Utilization

Information collected by the clinical investigators on the case report form included comprehensive data for each patient. Length of stay, procedures performed, medications administered, adverse drug reactions, clinical response, and other factors were extracted and used to construct the pharmacoeconomic database.

Data was collected from the time of entry into the study until the required post-study visit and at 38 to 44 days after start of therapy. Resource utilization data were collected in a database to accumulate the information necessary for the economic analysis even after a patient was classified as a "failure" (defined as no response to therapy or relapse within the defined observation period).

Resource Costs

Utilization data for each resource were converted into resource costs by multiplying unit cost estimates by units of resource utilization observed in the trial. The costs of the study drugs were supplied by the protocol; all other costs were out-of-pocket. The per dose and per day costs of the drugs used are shown in Table 1. Costs for both study and non-study medications were obtained from the hospital pharmacy of East Avenue Medical Center, one of the study hospitals.

Statistical Analysis: Statistical analysis was performed using EpiInfo v. 3.3.2 on a personal computer. The probability of a type 1 error of 0.05 was used to determine statistical

Table 1. Per dose and per day costs of study drugs

	IV		IV	
	Per dose	**Per day**	**Per dose**	**Per day**
Levofloxacin	1,121.00	1,121.00	177.00	177.00
Cefuroxime	(Levox@ 500 mg)	1,804.00	(Levox@ 500	289.00
Erythromycin	451.00	1,028.80	mg)	158.00
	(Zinacef@ 750		144.50	
	mg)		39.50	
	257.50		(Erythrocin@	
	(500 mg vial)		500 mg vial)	

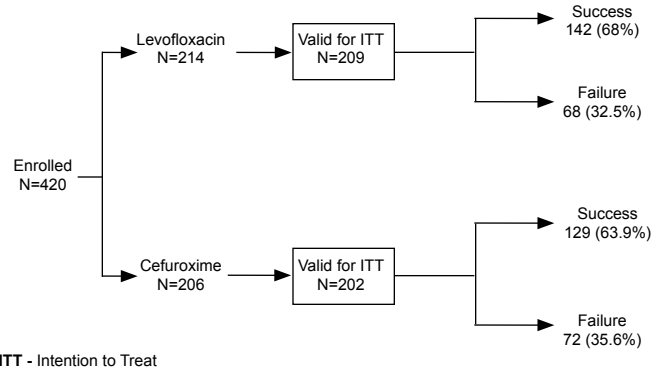


Figure 2. General Schema

significance. Discrete variables (sex, race, age category, infection severity, and efficacy) were compared across these groups, using chi-square tests. Two-sided t-tests were used for analyses of continuous variables (mean costs and mean age). P values of significance levels of estimates are reported for all comparisons.

This was a study of equivalence, or a clinical trial with a positive control. The objective of the trial was to test whether employing a protocol for switch therapy using levofloxacin is as good as employing the same protocol using the established or standard treatment for CAP III, cefuroxime. The effectiveness of cefuroxime has been proven in several studies.[10,11] The present trial is similar in population, concomitant therapy, and dosage to the above studies.

The sample size for the clinical study was based on power calculations for detecting a statistically significant difference at conventional levels ($P < 0.05$) in the primary clinical end point (clinical treatment success). This trial's sample size was computed on the basis of a dichotomous response: success or failure and with the objective of establishing equivalency.

From previous studies, the cure rates of levofloxacin and cefuroxime are 96% and 90%, respectively.[10,11] Thus, we used the average of 93%. Level of confidence used is 95% ($\alpha = 0.05$); power for detecting a difference was 90% ($Z_\beta = 1.282$). We assumed that a clinically important difference between the two drugs should be at least 10%. Thus, a minimum of 137 subjects in each arm was computed to be necessary to demonstrate significance.

Results

The initial study included 420 patients admitted to ten (10) medical institutions; 214 patients were treated with levofloxacin and 206 patients were treated with cefuroxime. Patient demographics were similar between groups as was the distribution of prognostic factors (e.g., age, co-morbidities; Table 2). All patients randomized to the levofloxacin arm received 500 mg IV with switch to levofloxacin, 500 mg po qd. In the cefuroxime treatment group, patients were administered 1.5 mg IV q 12h with switch to oral 500 mg BID. The Philippine Practice Guidelines for the Management of Community-Acquired Pneumonia in Immunocompetent Adults[8] recommends the addition of a macrolide should the attending physician consider that the likelihood of an atypical pathogen affecting the patient exists. In this study, such a situation occurred in 44 (21.8%) of the cefuroxime-randomized patients; thus, IV erythromycin was prescribed concomitantly for them.

There was no difference between the groups in terms of the baseline frequency of occurrence of signs and symptoms (dyspnea, cough, respiratory rate, fever, and rales) that helped determine the pneumonia severity. Patients most frequently presented with productive cough (or acute worsening in severity or productivity of a chronic cough) and dyspnea.

Of the concurrent medical illnesses found to have a bearing on the severity and prognoses of the pneumonia, COPD was the most common followed by asthma, hypertension, diabetes mellitus and congestive heart failure. Again, there were no significant differences between the two study groups in the distribution of these co-morbidities. Patients received intravenous antimicrobials for an average of three days and remained hospitalized for the same length of time with no differences in either group. The overall in-hospital mortality rate was 4.1%.

Despite very specific inclusion and exclusion criteria which identified those patients who would be randomized, six patients had to be withdrawn due to protocol violations. One patient was noted to have a positive skin test to levofloxacin (it was a policy in the institution to do a skin test for all parenterally administered antibiotics), another two had positive AFB smears; a patient also had to be withdrawn because WBC was normal on admission but the results only came after the patient had been randomized and already received the first few doses of the drug. Eleven patients (two in the levofloxacin arm, nine in the cefuroxime arm) withdrew their consent to join the study and thus, by the nature of the study, had to be classified as failures; the two patients randomized to levofloxacin and three of the nine in the cefuroxime arm refused further treatment once they experienced clinical improvement.

Four hundred eleven patients (411; 209 or 50.5% on levofloxacin and 202 or 49.2% on cefuroxime) received study drugs by intention-to-treat. A little over a fifth (21.8%) of the patients randomized to the cefuroxime arm also received erythromycin for an average of 9.4 days. The mean

Table 2. Patient demographics by study arm

Variables	Levofloxacin (n=209)	Cefuroxime (n = 202)
Gender		
Male	110 (51.6%)	115 (55.8%)
Mean (SEM*) age, years	46.1 (1.32)	45.2 (1.32)
Employment		
Unemployed	132 (62.3%)	139 (67.8%)
Self-employed	80 (37.7%)	66 (32.2%)
Signs and Symptoms at Baseline		
Dyspnea	207 (97.6%)	201 (98.5%)
Cough with sputum	204 (95.3%)	198 (96.1%)
Pleuritic chest pain	130 (61.3%)	131 (63.9%)
Rales	202 (96.2%)	193 (95.1%)
Fever	164 (76.6%)	166 (80.6%)
Chills	59 (27.8%)	60 (29.6%)
RR > 30/min	156 (72.9%)	158 (76.7%)
Significant Concurrent Diseases at Baseline		
COPD	120 (57.4%)	108 (53.2%)
Hypertension	13 (6.1%)	7 (3.4%)
Diabetes	11 (5.1%)	6 (2.95)
Congestive Heart Failure	2 (0.9%)	2 (1.0%)
Asthma	17 (7.9%)	22 (10.7%)

total duration of treatment was 8.1 days in the levofloxacin arm and 8.8 days in the cefuroxime axetil arm. Patients were hospitalized for a mean duration of three days (day of switch in therapy); there was no significant difference in mean day of switch and of hospital discharge between study drugs. (Table 3) Sequential therapy using either of the study treatment regimens did not differ in efficacy at end of treatment (78.4% vs. 78.5% for levofloxacin and cefuroxime, respectively) or at test of cure, i.e., 69.3% for levofloxacin and 64.2% for cefuroxime ($p > 0.331$). The low success rates may be accounted for by the high number of individuals who failed to follow-up in this intention-to-treat study.

There were 71 reported sputum culture growths (Table 4). The most frequent isolate in both arms was α-hemolytic Streptococcus; along with this, gram negative organisms (Enterobacter in the levofloxacin arm and Enterobacter and Moraxella in the cefuroxime/erythromycin arm) accounted for more than 50% of isolates in both groups. This finding is in concordance with the patient population, over 50% in each group of which had chronic lung disease or other co-morbidities which predispose the individual to gram negative and/or mixed infections.

Table 3. Per dose and per day costs of study drugs

Clinical Outcome	Levofloxacin	Cefuroxime	P value
Mean (SEM) days of treatment with study drug, days	8.12 (0.154)	8.76 (0.172)	0.006
		3.1 (0.804)	0.203
		3.1 (0.816)	0.208
Mean (SEM) day of switch	3.0 (0.0819)		
Mean (SEM) day of discharge	3.0 (0.808)		
End of therapy overall clinical response			
Success, n (%)	167 (78.4%)	161 (78.5%)	1.000
Test of cure overall clinical response			
Success, n (%)	142 (69.3%)	129 (64.2%)	0.331

Table 4. Organisms cultured by randomized drug

Sputum culture organism	Levofloxacin		Cefuroxime		Total	
α hemolytic Strep	10	38.5%	12	26.7%	22	31.0%
Enterobacter sp.	5	19.2%	10	22.2%	15	21.1%
Moraxella cattaralis			8	17.8%	8	11.3%
S. aureus	3	11.5%	4	8.9%	7	9.9%
Pseudomonas sp	2	7.7%	2	4.4%	4	5.6%
Klebsiella sp.			3	6.7%	3	4.2%
Acinetobacter sp	1	3.8%	1	2.2%	2	2.8%
Pseudomonas aeruginosa	2	7.7%			2	2.8%
β hemolytic Strep			1	2.2%	1	1.4%
Citrobacter freundii	1	3.8%			1	1.4%
Enterobacter aerogenes			1	2.2%	1	1.4%
Enterobacter cloacae			1	2.2%	1	1.4%
Klebsiella pneumoniae			1	2.2%	1	1.4%
Moraxella sp			1	2.2%	1	1.4%
Strep agalactiae	1	3.8%			1	1.4%
Strep viridans	1	3.8%			1	1.4%
T O T A L	**26**	**100.0%**	**45**	**100.0%**	**71**	**100.0%**

There were a total of 44 adverse events (18 or 40.9% in the levofloxacin group and 26 or 59.1% in the cefuroxime group) reported by 31 patients. Patient complaints such as easy fatigue and hemoptysis were noted but assessed to be likely related more to the underlying or co-morbid condition and not to the study drug(s).

Twenty seven were deemed by investigators to be possibly related to the study drugs (Table 5). Most of the adverse events were evaluated as mild and did not necessitate discontinuation of the study drugs. In three patients, the drugs were discontinued. One patient in the levofloxacin arm, an 81 year old male, developed hypotension and went into respiratory failure a little more than 18 hours after his first dose of the drug. The assessment was a worsening of his underlying conditions (congestive heart failure, COPD) and he was transferred into the ICU. Another patient developed wheals and pruritus after the first dose of the drug. A patient randomized to the cefuroxime arm was also given erythromycin; this patient developed upper gastrointestinal bleeding on the third day of hospitalization

Table 5. Drug-related adverse events by study arm

Adverse event	Levofloxacin	Cefuroxime	Total
Abdominal pain	3	7	10
Diarrhea	1	2	3
Nausea and vomiting	1	2	3
Upper GI bleeding	0	2	2
Flatulence	1	0	1
Hypotension	1	0	1
Dizziness	0	1	1
Headache	1	0	1
Joint pains	0	2	2
Rashes	1	1	2
Pruritus	0	1	1
Phlebitis	0	1	1
T O T A L	**9**	**19**	**28**

Table 6. Reason for failure by study arm

Reason for withdrawal	Levofloxacin		Cefuroxime		Total	
	No.	%	No.	%	No.	%
Failure to return for follow-up	39	57.4%	36	50%	75	53.6%
Insufficient therapeutic response	6	8.8%	15	20.8%	21	15.7%
Died during study	8	11.6%	6	8.3%	14	10%
Adverse experience	2	2.9%	1	1.4%	3	21.4%
Refused treatment	2	2.9%	9	12.5%	11	7.8%
Inter-current illness	4	5.8%	2	2.7%	6	4.3%
Protocol violation	4	5.8%	2	2.7%	5	3.6%
Missing	3	4.4%	1	1.4%	4	2.8%
Total	**68**		**72**		**140**	**100.0**

and the site investigators opted to withdraw the patient from the study.

Adverse drug reactions in the cefuroxime arm occurred at a little over twice the rate of those in the levofloxacin arm with a majority of these events related to GI problems after oral administration.

Sixty eight (48.6%) clinical failures occurred with levofloxacin and 72 (51.4%) with cefuroxime (Table 6). Approximately half (53.6%) of the 140 treatment failures were due to a failure to return for follow-up. A large number of those who failed to follow-up in both arms were seen on visit 3 (end of therapy), less than a week after their discharge from the hospital. During this visit (visit 3), based on the physician's judgment and the patient's own perception, there was noted clinical improvement in eight of 10 patients (Table 3). Despite efforts to contact them, these patients, however, could not be located for their test of cure visit, i.e., approximately three weeks after end of therapy; thus, in the intention-to-treat analysis, they were regarded as failures.

Response to therapy was deemed by site investigators to be insufficient in twenty-three patients (six or 8.8% for levofloxacin and 15 or 20.8% for the cefuroxime/erythromycin group, $p<0.05$). Clinical condition and/or radiologic findings worsened within the first five days of hospitalization in all six of the levofloxacin patients and in 11 of 15 patients on cefuroxime. Of the remaining four patients randomized to the cefuroxime/erythromycin arm, one developed a gluteal abscess on his second day of hospitalization; blood cultures yielded *S. aureus*. A second antibiotic had to be added to the regimen of another patient who developed pleural effusion on his third day of confinement; blood cultures in this patient showed Enterobacter. Two patients were switched to oral antibiotics and discharged within the first five days of confinement; within a week after discharge, they consulted with other physicians (one was subsequently admitted) and started on other antibiotics.

Table 7 details the mean total cost estimates, by treatment, as well as those for the other component cost categories. The levofloxacin treatment group demonstrated a total cost advantage over cefuroxime axetil (savings from using

Table 7. Mean (per-patient) costs of medical resource use and lost productivity days, by study arm

	Levofloxacin (Pesos)	Cefuroxime (Pesos)	Difference (L – C)	P
Direct costs				
Inpatient costs	20,154.53	21,958.45	-1,803.92	0.075
Physician's visits	11,448.11	11,080.88	367.23	
Study drugs	3,745.89	5,944.45	-2,198.56	
Diagnostic tests	1,932.48	1,804.71	127.77	
Room and board	1,688.78	1,752.43	-63.65	
Nurses' visits	151.84	154.60	-2.76	
Other drugs	63.35	51.77	11.58	
Respiratory therapist visits				
Outpatient	8.55	6.28	2.27	0.822
Study drugs	2,038.79	2,485.91	-447.12	
Physician consultations	725.80	1,183.71	-457.91	
Diagnostic tests	299.06	348.30	-49.24	
Other drugs	221.56	267.74	-46.18	
Indirect Costs•	21.34	19.16	2.18	
In-hospital patient resources*	963.90	1,172.39	-208.49	0.031
All direct and indirect costs	**22,512.52**	**24,345.11**	**-1,832.59**	**0.095**

•In-hospital patient resources refer to resources expended by the patient while hospitalized. These include lost wages of the patient and his caretaker and food and transportation of the patient's caretaker during the patient's hospitalization.
*reflecting lost productivity

levofloxacin = Php 1,832.59); the total cost for cefuroxime axetil treatment was 8.1% higher than that for levofloxacin ($p = 0.095$). Acquisition costs of study medications were lower for the levofloxacin group versus the cefuroxime axetil group for both inpatient and outpatient use (savings of Php 2,198.56 and Php 447.12, respectively); the result achieved statistical significance ($p = 0.000$ for both in- and outpatient use). The indirect costs of hospital stay were also significantly different between the two groups. Since most of the patients in this study were unemployed, lost productivity was computed as amounts expended for additional food and transportation of family members or companions who acted as the patients' caretakers. Mean cost estimates for the other resource categories did not reach statistical significance.

Overall, statistically significant differences between treatments of hospitalized patients with community-acquired pneumonia utilizing either levofloxacin or cefuroxime with or without erythromycin were found in the following areas: duration of stay (levofloxacin < cefuroxime ± erythromycin), treatment response (levofloxacin > ± erythromycin ± erythromycin) and indirect costs of treatment which was reflective of lost productivity (levofloxacin < cefuroxime ± erythromycin). Patients randomized to the levofloxacin arm stayed for a shorter period of time while experiencing better clinical success and less adverse events than those randomized to the cefuroxime/cefuroxime-erythromycin arm. These findings are in addition to the significantly smaller amount spent procuring levofloxacin than that spent procuring cefuroxime with or without erythromycin.

Discussion

The Word Health Organization reported that in 2002, pneumonia was the leading cause of morbidity and the fourth leading cause of mortality in the Philippines, where poverty has severely undermined the health status of Filipinos. It is also a country where healthcare is still mainly financed through out-of-pocket payments. Efforts to ease this financial burden of paying for services include the promotion of effective health interventions to reduce the burden of disease and improve and maintain population health. In case of pneumonia, these measures can be translated to include the accurate diagnosis of the condition, the precise assessment of disease severity and the appropriateness of therapeutic management.

It is therefore imperative that the decision-making of healthcare givers be guided by judicious application of medical concepts applied to their patients' specific socioeconomic settings.

The American Thoracic Society, the Infectious Disease Society of America, The Canadian Medical Society and the British Thoracic Society have all published widely circulated guidelines for the treatment of CAP.[14,15,16,17] In 1998, the Philippines published our guidelines for the diagnosis and management of community-acquired pneumonia; these have since been updated (2004). All guidelines aimed to facilitate decision-making of healthcare givers as these best suited their country's health settings. As part of the efforts to maintain clinical outcome without inflating healthcare costs, a majority of guidelines include a sequential or step-down strategy for antibiotic therapy.

Despite the existence of these guidelines and extensive efforts to disseminate them, admission and discharge practices of patients with community-acquired pneumonia still vary among physicians who, though aware of the guidelines, attempt to apply them to patients who must shoulder the costs of applying these recommendations.[2,3] Perhaps partly or wholly because of this, admission criteria, diagnostic and antibiotic prescription practices, although far from capricious, are also not standardized. Further, differences in practice are also seen with reference to the length of hospital stay when related to the initiation (or not) of any form of antimicrobial streamlining.

The true cost of healthcare in a system such as that which exists in the Philippines cannot be reflected in a simple comparison of the cost per dose or cost per day of medications in general or, in the case of pneumonia, the cost of an antibiotic. A pharmacoeconomic analysis, in contrast to a simple price comparison, can provide a more accurate and complete description of the true cost of healthcare. Since pharmacoeconomics is an outcomes-based science, determining an economic outcome requires a clinical outcome.

Fine et al.[18] found that hospitalization costs for CAP costs are greatest in the first three days after admission and remained stable throughout the hospital stay; his findings suggested that substantial savings would result from even a single (1) day decrease in the length of stay. Esguerra's evaluation of the quality of care of patients with CAP admitted to a tertiary care training center in Metro Manila found that the mean duration of hospital stay of these patients was 7.3 days.[13]

In this study, investigators had the option to add erythromycin to the antimicrobial regimen of patients randomized to the cefuroxime arm whenever they suspected that an atypical etiology for the pneumonia might be present. This occurred in 44 of 202 patients (21.8%) on cefuroxime. While successful therapy was achieved with monotherapy (levofloxacin alone or cefuroxime alone) equally in both treatment arms, there were significantly more therapeutic failures in the group that was randomized to cefuroxime $\pm$ erythromycin. The average length of stay for this subgroup of patients was found to be 9.4 days, a finding that may, in part, explain the significant difference in the length of stay of randomized patients with those in the cefuroxime arm staying for a longer period than those in the levofloxacin arm.

Several studies have been published studying the cost-effectiveness of sequential therapy in the management of CAP. Ramirez[19] reported that switch therapy can reduce costs associated with drug administration and length of hospital stay. Rittenhouse et al.[20] studied the cost-effectiveness of the strategy in both in- and outpatients with CAP; Castro-Gardiola[21] in patients with severe and non-severe pneumonia.

This study found that in patients hospitalized for community-acquired pneumonia, clinical stability can be seen after an average of two to three days of parenteral therapy after which they can then be switched to oral therapy. It further showed that the day of switch can also be the day of discharge as taking the oral therapy at home not only resulted in good clinical outcome at test of cure but also a reduction of out-of-pocket expenses that would have gone to hospital expenses (room and board, visits by healthcare personnel) had they remained confined.

Niederman and colleagues[12] found that for hospitalized patients in the United States, room and board charges were the chief contributor to the total cost of care (26%) followed by pharmacy (20%), laboratory (13%), respiratory services (11%), and medical/surgical supplies (9%). A different scenario is seen in the Philippines where medicine is the leading expenditure in total costs (38%), second was examinations (27%), third was beds (22%) and the last was doctors' fees (13%).[5] As if to emphasize the import of out-of-pocket payment, the private hospitals were more expensive than the government hospitals, but also more efficient in the length of hospitalization. A disturbing but all too frequent finding is that of Esguerra et al.[13] from a tertiary care government hospital, i.e., many patients with severe pneumonia request to go home or be discharged against medical advice because they can no longer afford to pay their hospital expenses.

In the Philippines, while a large portion of the

patient's out-of-pocket expenses include antimicrobials for pneumonia, hospitalization adds other factors that impact on cost such as room and board charges, respiratory services, lost wages of the patient and/or his caretaker as well as food and transportation of the patient's caretaker during the patient's hospitalization. Therefore, attempts to reduce the patient's expenditures—while focusing on abbreviating morbidity—should also look at shortening the duration of hospital stay.

Despite the implementation of a protocol for the use or initiation of sequential therapy, however, our study showed that, in the Philippines, out of pocket health costs, along with or perhaps more than the patient's early response to treatment determine patient adherence to therapy and, ultimately, treatment success or failure.

Aside from a lower per-dose purchase price, overall costs of sequential therapy with levofloxacin tended to be less than those of sequential therapy using cefuroxime. This resulted largely from both a lower drug acquisition cost and a lower cost per day coverage of once-daily dosing compared with twice-daily dosing of cefuroxime axetil. Further, covering for suspected atypical pathogens by employing a second drug—erythromycin—resulted in prolongation of hospital stay; this, in turn, resulted in additional costs for room and board, lost wages for the patient and his caretaker as well as food and transportation for the patient's caretaker during the patient's hospitalization.

The findings in this study suggest that implementation of clinical guidelines particularly those related to switch therapy using levofloxacin for the treatment of hospitalized patients with community-acquired pneumonia is as clinically effective as using cefuroxime; it is, however, the more cost-effective option for the patient who pays for his or her hospitalization costs from out of pocket. To the authors' knowledge, this is the first cost-effectiveness study for hospitalized non-severe CAP to be conducted in Asia and with a sample population whose healthcare and hospitalization costs were being paid for out-of-pocket.

Conclusion

In patients hospitalized community-acquired pneumonia (ATS IIII) it is possible to switch treatment from intravenous (IV) to oral (levofloxacin or cefuroxime) therapy early and achieve successful cure. Though findings did not reach statistical significance, there is a suggestion that opting to switch from IV to oral levofloxacin may be a more cost-effective option since we found that patients treated with levofloxacin used fewer healthcare resources and had less adverse drug reactions than cefuroxime (with or without erythromycin). In addition to shorter hospital stay, the lower drug acquisition costs related to levofloxacin versus cefuroxime translate to greater savings for the patients.

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