

Cost-effectiveness of full-course oral levofloxacin in severe community-acquired pneumonia

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Cost-effectiveness of full-course oral levofloxacin in severe community-acquired pneumonia. J-B. Wasserfallen, V. Erard, A. Cometta, T. Calandra, O. Lamy. ©ERS Journals Ltd 2004.

ABSTRACT: Oral levofloxacin is as efficient as sequential antibiotic treatment in community-acquired pneumonia (CAP). The current authors assessed whether oral levofloxacin treatment of patients with severe CAP, followed-up for 30 days, would save money.

Over a 12-month period, 129 hospitalised patients with severe non-intensive care unit CAP were randomly assigned to receive either oral levofloxacin or sequential antibiotic treatment. Direct and indirect costs were compared over a 30-day period from several perspectives.

CAP resolved in 71 out of 77 oral levofloxacin (92%) and in 34 out of 37 sequential antibiotic treatment patients (92%). Patients' characteristics, treatment duration, hospital length of stay and mortality were similar in both groups. Drug acquisition costs were 1.7-times smaller in oral levofloxacin patients, who were less often transferred to rehabilitation centres, but they used more physicians' visits during follow-up and their total costs were lower. As only a minority of patients was still active, inability to work and, hence, indirect costs were similar in both groups.

In this study, oral levofloxacin for severe non-intensive care unit community-acquired pneumonia was equally effective as sequential antibiotic treatment, but did not lead to major costs savings except for drug acquisition costs. External factors linked with patients' characteristics and/or medical practice are likely to play a role and should be addressed.

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Community-acquired pneumonia (CAP) is a common condition especially in elderly patients [1], with a significant mortality ranging from 1% in ambulatory patients to 36.5% in intensive care patients [2]. As hospitalisations are frequent and account for 90% of total costs of treatment, costs for healthcare services are important [3, 4].

It is, therefore, no surprise that different measures have been studied to decrease practice variation in CAP treatment. Prediction rules have been developed to identify low-risk patients [5] who could be treated as outpatients. Different guidelines were issued about the assessment and treatment of such patients and were recently updated [6]. The duration of *i.v.* antibiotic treatment has been evaluated and an early switch to oral therapy has been advocated [7]. Both measures were shown to decrease the length of stay and, hence, the costs of hospitalisation [1, 7]. Furthermore, in-hospital observation of low-risk pneumonia patients after conversion from parenteral to oral antimicrobial therapy did not provide clinical benefit [8].

Fluoroquinolones have an excellent intestinal absorption, which makes *i.v.* administration no longer absolutely necessary. A recent review of 10 studies [9] showed that they were as effective and safe as traditional regimens. As the price of fluoroquinolones is intermediate between *i.v.* and oral formulations of currently used antibiotics, their use could save money [10, 11].

For hospitals, adoption of a global payment system according to all-patient diagnoses-related groups is an

important incentive factor for the optimal use of fixed resources. In this setting, fluoroquinolones can be a very interesting kind of drug. From a societal perspective, however, the additional cost of the oral formulation can increase the whole cost of treatment. The effectiveness and safety of a full course of oral levofloxacin *versus* conventional sequential antibiotic therapy in patients with severe CAP requiring hospitalisation and follow-up for 30 days have been previously assessed in a clinical prospective trial [12]. However, this paper assesses whether oral levofloxacin treatment leads to direct and indirect costs savings from the perspective of a provider, payer and society.

Patients and methods

Study population

Patient selection criteria have been described in detail elsewhere [12]. In short, all consecutive adult patients requiring hospitalisation for a primary diagnosis of CAP were eligible for enrolment. Exclusion criteria included admission to an intensive care unit (ICU), high likelihood to be discharged from hospital within 24 h of admission, previous hospitalisation or stay in a nursing home within 10 days and 4 weeks of admission, respectively, and inability to take oral medication.

Study design and antimicrobial therapy

The study was a prospective, randomised, controlled trial conducted in two Swiss medical centres: 1) a 900-bed teaching hospital serving both as a city hospital and as a tertiary reference centre providing services to an area of >500,000 inhabitants (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland); and 2) a 160-bed community hospital (Centre Hospitalier Yverdon-Chablons, Yverdon-les-Bains, Switzerland). 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 randomised in a 2:1 ratio to a full course of oral levofloxacin (500 mg *b.i.d.*) or an *i.v.*-to-oral sequential therapy regimen consisting of *i.v.* ceftriaxone (2 g *q.d.*) with or without concomitant *i.v.* or oral clarithromycin (500 mg *b.i.d.*), followed by an oral antibiotic therapy chosen by the physician in charge according to treatment guidelines for patients with CAP in use at the participating institutions. The detailed study protocol has been published elsewhere [12].

Economic data

Only patients with complete cost data were included in this economic study. Cost data used specific hospital data from 2000, as displayed in table 1. From a hospital perspective, marginal costs were computed from the running costs of the different wards divided by the observed number of patient-days in each specific unit in the year 2000. The medical, nursing, administrative and logistic cost components were singled out. Specific nursing workload, such as the insertion of an *i.v.* line, the administration of *i.v.* drugs and respiratory therapy, was computed according to Patient Research Nursing scores [13]. Respiratory therapist treatment was computed according to the same method as described previously. Drug acquisition costs were retrieved from the "Compendium Suisse des Médicaments", 2000 edition [14]. Rehabilitation costs were computed according to the same method as described for the hospital.

From a health insurance company perspective, hospital and rehabilitation daily charges and outpatient charges were computed from the official tariff used in Switzerland (table 1). In Switzerland's healthcare system, insurance companies pay only about half the real cost of the hospital stay (the rest being paid by the state), but the whole cost for outpatient care. The current authors did not try to compute whole costs, as overheads are difficult to single out in this healthcare system.

Finally, indirect cost linked with work inability was computed according to the Swiss standard wages of the European profession classification [15]. Both outpatient treatment and work inability were censored at day 30 after study entry.

Statistical analysis

Results were reported as mean±SD or SEM for normally distributed variables and as median (range) otherwise. Comparison for categorical data was performed by Chi-squared 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 U-test was used to compare the distribution between the two treatment groups. All reported significance levels are two-sided. Statistical significance was assumed at $p < 0.05$.

Table 1.—Costs and prices used for the economic assessment

Type of resource	Unit cost €	Daily cost €
Provider's perspective (marginal costs)		
Hospitalisation		
Medical care	43.33	6.84
Respiratory therapist	8×3.19	51.12
Nursing care		
Emergency dept		244.73
Ordinary ward		147.60
Intermediate care		333.55
Intensive care		519.49
Administrative tasks		
Emergency dept		17.89
Ordinary ward		7.67
Intermediate care		13.42
Intensive care		19.17
Logistics		
Linen		24.28
Food		21.73
Pneumonia treatment		
Levofloxacin 2×500 mg·day ⁻¹ <i>p.o.</i>	6.04	12.08
Ceftriaxone 2 g·day ⁻¹ <i>i.v.</i>	49.44	49.44
Clarithromycin 2×500 mg·day ⁻¹ <i>p.o.</i>	4.01	8.02
Clarithromycin 2×500 mg·day ⁻¹ <i>i.v.</i>	32.62	65.24
Infusion line insertion	4×3.39	13.55
Infusion administration	2×3.39	6.77
Inhalation therapy	9×3.39	30.48
Rehabilitation centre		
Medical care	38.00	4.60
Nursing care		97.76
Administration		8.95
Logistics		
Linen		24.28
Food		21.73
Payer's perspective (charges)		
Hospital day		
Ordinary ward		266.67
Intermediate care		500.00
Intensive care		1000.00
Rehabilitation day		
Outpatient care		
Medical visit	40.26	
Respiratory therapy	27.92	
Chest radiograph	58.50	
Society's perspective (indirect costs)		
Hourly wages for working patients		
Healthcare worker	22.88	
Administrative worker	19.17	
Market worker	14.76	
Craft worker	19.17	

Data are presented as n.

Results

From April 2000–April 2001, 201 patients admitted with CAP were screened, 144 were eligible for the study, 15 refused to participate and 129 were randomised. A total of 15 patients were withdrawn from the study after randomisation because of incorrect entry diagnosis (n=10), loss to follow-up (n=2), missing cost data (n=2) or discharge from hospital within 24 h of admission (n=1). All of the 114 remaining patients were available for analysis (77 in the levofloxacin group and 37 in the sequential therapy group).

Patients' characteristics (table 2) were comparable in the two treatment groups. In both treatment groups, >60% of the

Table 2. – Patients' social and clinical characteristics

Characteristics	Oral levofloxacin	Sequential treatment
Patients n	77	37
Mean age yrs	70.7±17.1	69.8±19.2
Sex		
Female	32 (42)	12 (32)
Male	45 (58)	25 (68)
Profession		
Active	15 (19)	6 (16)
Housekeeping	7 (9)	2 (5)
Retiree	55 (72)	29 (79)
Pneumonia Severity Index		
I	0 (0)	1 (3)
II	14 (18)	8 (22)
III	14 (18)	5 (14)
IV	45 (59)	20 (54)
V	4 (5)	3 (8)
Co-morbidities	57 (72)	27 (73)

Data are expressed as n, mean±SD and n (%).

patients (72 out of 114) had a pneumonia severity index (PSI) of IV or V and >70% of the patients (84 out of 114) had co-morbidities, mostly cardiopulmonary diseases.

Outcome characteristics are displayed in table 3. Treatment duration was similar in both groups (levofloxacin mean 12.1±8.7 days *versus* sequential treatment mean 13.5±3.6 days). In the *i.v.*-to-oral sequential therapy group, 20 patients (54%) were treated with ceftriaxone plus oral clarithromycin and 17 patients (46%) with ceftriaxone monotherapy. Ceftriaxone was administered for a median (range) duration of 4.5 days (2–28).

The cure rate was similar (71 out of 77, 92%) in the levofloxacin group and in the sequential therapy group (34 out of 37, 92%). Four patients died (overall mortality 3.4%) (levofloxacin n=1, 1.3%; *i.v.*-to-oral sequential therapy n=3, 8.1%; difference -6.8% (95% CI -16.0–2.3)); all had a PSI of IV and were aged 79–87 yrs. Three of these deaths occurred during the hospital stay and only one (from the sequential therapy group) during the follow-up period.

The hospital length of stay was similar in both groups, but more variable in the levofloxacin group. Two patients in the levofloxacin group were clearly outliers with a length of stay of 69 and 72 days, respectively. There was no difference in the number of *i.v.* lines inserted, inhalation therapy or treatments by the respiratory therapist between the two groups.

Table 3. – Distribution of hospital resources use and post-hospital orientation and outcome

Treatment characteristics	Oral levofloxacin	Sequential treatment	p-value
Patients n	77	37	
Hospital length of stay days	9.8±11.0	9.8±6.3	0.181
Antibiotics treatment duration days	12.1±8.7	13.5±3.6	0.230
Rehabilitation			
Number of patients	17(22)	11(30)	
Length of stay days	25.5±14.8	17.3±7.1	0.074
Outpatient care			
Number of patients	76(100)	35(100)	
Physician visits	1.2±1.1	0.8±0.8	0.078
Respiratory therapist visits	0.1±0.8	0.2±0.8	0.459
Chest radiographs	0.2±0.4	0.2±0.5	0.931
Inability to work			
Number of patients	15(19.5)	5(13.5)	
Days off work	21.0±7.9	21.6±10.2	0.752

Data are presented as n, mean±SD and n (%) unless otherwise stated.

Corresponding cost data are displayed in table 4. As usual, the cost distribution was not normally distributed and the two outliers in the levofloxacin group had a significant impact, so that, from a hospital perspective, total hospital costs were higher in the levofloxacin group. Excluding these two patients inverted the trend and the median difference between the two groups reached statistical significance (median difference €650, p=0.05). In all analyses, a highly significant difference was observed in drug-acquisition costs: sequential treatment was 1.7 times more expensive than oral levofloxacin (95% CI 22.6–307.0, p=0.023). Nurses' work time with drug administration was also reduced in the levofloxacin group. The proportion of patients sent to rehabilitation was slightly smaller in the oral levofloxacin group (n=17, 22% *versus* n=11, 30%), and the mean length of stay was similar. As a consequence, the total of hospital and rehabilitation marginal costs was not different between the two groups.

The same was true when the analysis was carried out with tariffs from a health insurance perspective. However, given the smaller proportion of patients sent to rehabilitation in the levofloxacin group, the number of patients requiring physicians' visits in the 30-day follow-up was higher in the oral levofloxacin group, but this difference did not reach statistical significance. There was no difference in the number of treatments by physical therapists and chest radiographs performed during the 1-month outpatient follow-up.

As far as indirect costs were concerned, all active patients in the levofloxacin group (n=14) and five out of six in the sequential treatment group were temporarily unable to work. There was no difference in the duration of work leave (table 3) and the indirect costs incurred by the two groups were not different (table 4).

Discussion

While a full course of oral levofloxacin, the latest advocated step in improving practice patterns in the treatment of CAP, brought the same benefit to the patients as standard *i.v.*-to-oral sequential therapy, it did not result in obvious savings for the healthcare system in the specific setting studied, either from a provider's or a payer's perspective. In particular, the statistically significant savings in drug acquisition cost were offset by other charges linked with treating these patients. However, excluding the two patients with especially long hospital stays in the levofloxacin group lowered average hospital and rehabilitation costs in the levofloxacin group

Table 4. – Distribution of the different costs of community-acquired pneumonia treatment

Type of costs	Oral levofloxacin costs €	Sequential treatment costs €	p-value
Patients n	77	37	
Provider's perspective (marginal costs)			
Hospitalisation			
Physician attending	69.6±78.9	70.3±45.1	0.959
Nurses work with drugs	205.5±158.7	239.8±148.8	0.273
Physical therapist	250.7±499.5	217.7±287.6	0.709
Drug acquisition cost	243.4±527.5	415.4±271.4	<0.001
<i>i.v.</i>	87.1±515.0	332.6±278.3	0.008
Oral	156.3±107.5	82.8±43.9	<0.001
Hotel cost	2717.2±5255.5	2275.6±1545.8	0.618
Total hospital	3486.4±6199.4	3218.7±1948.3	0.798
Rehabilitation	853.6±1914.7	777.7±1337.1	0.829
Total marginal costs	4404.1±7097.3	4044.5±2551.6	0.766
Payer's perspective (charges)			
Hospital care	3644.7±8212.3	2779.4±2155.4	0.529
Rehabilitation care	1033.3±2317.8	941.4±1618.7	0.829
Outpatient care			
Physician visits	49.4±48.0	31.8±34.9	0.027
Respiratory therapist	3.4±22.2	4.7±24.3	0.774
Chest radiograph	11.1±27.5	11.5±28.2	0.936
Total outpatient care	64.1±66.2	48.0±57.3	0.208
Total charges	4742.2±9278.2	3768.9±2757.0	0.543
Indirect			
Patient inability to work	746.2±1883.7	507.4±1426.3	0.201

Data are presented as n and mean±SD, unless otherwise stated.

below those observed in the sequential therapy group, but the difference was not statistically significant.

Treatment of CAP has come a long way from a full course of *i.v.* antibiotics to switch therapy and now, tentatively, to a full course of oral fluoroquinolone. Treatment with oral antibiotics helps to minimise the use of *i.v.* catheters, reducing nursing time and improving the patient's comfort and mobility, and, thus, contributing to prevent complications of *i.v.* therapy, such as phlebitis, catheter-related infections, bedsores and thrombo-embolic events.

Economic studies have assessed the full cost of CAP for healthcare systems [3, 4] and shown it to be important. Hospitalisation costs represent an important share of total costs. FINE *et al.* [16] found that these costs are greatest in the first 3 days after admission, with room costs amounting to 59% of the median daily costs and remaining stable throughout the hospital stay, suggesting that substantial savings would result from a 1-day decrease in the length of stay (US\$680 per patient). Using a critical pathway, including a prediction rule to assist the admission decision and guidelines for an early switch from *i.v.*-to-oral therapy, was shown to result in a 1.7-day reduction in the hospital length of stay (4.4 days *versus* 6.3 days, $p=0.01$) and an estimated cost saving of US\$1,700 per patient [1].

Surprisingly, only two studies addressed the cost of the different antibiotic regimen used in practice [17] or proposed in guidelines [18]. Similarly, few economic comparisons were carried out for fluoroquinolones *versus* β -lactam or macrolide regimens in CAP. DRESSER *et al.* [10] examined the cost-effectiveness of gatifloxacin *versus* ceftriaxone with a macrolid and found similar efficacy, length of stay and antibiotic-related length of stay. The cost-effectiveness ratio for gatifloxacin was US\$5,236 for each patient cured, as compared with US\$7,047 for ceftriaxone. Cost of hospitalisation was the key factor in this analysis. DRUMMOND *et al.* [11] assessed the costs over 21 days of sequential *i.v./p.o.* moxifloxacin therapy compared to *i.v./p.o.* co-amoxiclav with or without clarithromycin in the patients of the

TARGET study in two different healthcare systems (Germany and France). The authors found that moxifloxacin treatment resulted in 5.3% more patients being clinically cured after 5–7 days, apyrexia achieved 1 day sooner and a 0.81-day reduction in hospital stay, resulting in a cost saving of €266 and €381 for Germany and France, respectively.

Several factors can explain why the current authors' study found no difference in costs between the two groups. First, in these severe CAP patients not requiring treatment in an ICU, the hospital length of stay was no longer influenced by the kind of the treatment for CAP, but rather by the age of the patients, the severity of the acute disease, as well as the presence of co-morbidities, as already described by FINE *et al.* [5]. The need for rehabilitation in a quarter of these patients and the length of this second stay are arguments to support this influence. Similarly, the inability to work, which affected nearly all of the current authors' active patients, is a second argument in favour of this explanation.

A second factor that deserves further study may be that physicians using the full course of oral levofloxacin may have been overcautious in assessing the success of the new kind of therapy and, as a consequence, observed the patients in hospital for a longer period than was absolutely necessary. As a safeguard against a risk of underdosing due to a less than optimal absorption of oral antibiotic in these severely ill patients, levofloxacin (500 mg) was given *b.i.d.* instead of *q.d.* as is usually prescribed in patients with CAP. The high proportion of patients with a PSI of IV and V (>60%) with co-morbidities (>70%) and the elevated median age (77 yrs) indicate that the patients enrolled had severe non-ICU CAP [5]. This situation may change with accumulated experience and a slight decrease in length of stay may be observed in the future.

Thirdly, practice patterns have not been adapted to capture the full advantages of this new kind of treatment. Barriers to the adoption of new strategies, such as clinical practice guidelines, have already been described in CAP, where physician adherence was shown to be far from perfect [19].

In particular, the fact that all patients had an *i.v.* line inserted suggests that the admission procedures have to be changed in the future to more effectively select patients who really need *i.v.* therapy and avoid inserting a line for commodity purposes only, such as drawing blood for laboratory tests. A trend to use more procedures in teaching and in urban hospitals, as compared with rural hospitals, is well known [20] and should be addressed to reach maximal benefit.

Finally, the different results of the moxifloxacin study [11] may be due to differences in fluoroquinolone potency or to the fact that, despite excellent bioavailability of fluoroquinolones, an initial *i.v.* administration may be necessary to achieve early clinical improvement and earlier hospital discharge.

This study presents some obvious limitations: it involved only two hospitals and a relatively small numbers of patients, of which only a minority was still professionally active. In addition, the dose of levofloxacin (500 mg *b.i.d.*) was higher than that commonly used for treating CAP, and other characteristics of the current authors' healthcare system, such as the availability of rehabilitation beds and outpatient treatment possibilities, may have influenced the pattern of care. Therefore, the ability to generalise results for both direct and indirect costs will have to be assessed in different settings.

However, the fact that the clinical outcome of these patients with community-acquired pneumonia was not different when treated with a full course of oral levofloxacin will open new perspectives in treating this disease. If these results are confirmed in other studies, they may eventually lead to interesting savings for the whole healthcare system.

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