Pharmacoeconomic Comparison of Sequential IV/Oral Ciprofloxacin Versus Ceftazidime in the Treatment of Nosocomial Pneumonia

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ABSTRACT

A retrospective, cost-effectiveness analysis was performed on 106 clinically evaluable patients who participated in a multi-centre, randomized study of sequential IV/oral ciprofloxacin therapy versus ceftazidime for the treatment of nosocomial pneumonia. Although nearly half of the ciprofloxacin patients received sequential therapy, the majority were treated with a full IV regimen. Clinical success rates and antibiotic-related adverse events were similar for the ciprofloxacin and ceftazidime groups. Per patient and per day costs of antibiotic acquisition; preparation and administration; treatment of adverse events, and clinical failures were compared. Decision analysis revealed that ciprofloxacin therapy was cost-effective compared to ceftazidime 2 g q8h. Varying the probability of clinical success between 60-99% failed to change the economic decision; costs for ciprofloxacin were always lower than for ceftazidime. Further sensitivity analyses demonstrated that if the ceftazidime price was reduced by 50% (equivalent to 1 g q8h), treatment costs would be similar to ciprofloxacin therapy. Increasing the ciprofloxacin price by 50% (equivalent to a q8h frequency) produced per patient costs similar to ceftazidime, although ciprofloxacin therapy retained a lower cost per day ($p<0.0002$). For the treatment of nosocomial pneumonia, ciprofloxacin therapy was cost-effective compared to ceftazidime.

Key words: *cost-effectiveness, ceftazidime, nosocomial pneumonia, sequential ciprofloxacin*

RÉSUMÉ

Une analyse rétrospective coûts-efficacité a été menée auprès de 106 patients cliniquement évaluables qui ont participé à une étude multicentres, randomisée, visant à comparer le traitement séquentiel i.v./oral à la ciprofloxacine et à la ceftazidime, dans la pneumonie nosocomiale. Bien que près de la moitié des patients du groupe ciprofloxacine aient reçu le traitement séquentiel, la plupart d'entre eux ont reçu le traitement complet par voie i.v. Les taux de succès clinique et de réactions indésirables associées aux deux antibiotiques étaient semblables dans les deux groupes. Les coûts d'acquisition des antibiotiques, de préparation et d'administration; de traitement des effets indésirables et ceux associés aux échecs cliniques, par patient et par jour, ont été comparés. L'analyse de décision a révélé que le traitement à la ciprofloxacine avait un rapport coûts/efficacité favorable comparativement à celui de la ceftazidime administrée à raison de 2 g q8h. La variation de la probabilité de succès clinique entre 60 et 99 % n'a pas réussi à modifier la décision économique; les coûts associés à la ciprofloxacine étaient toujours inférieurs à ceux associés à la ceftazidime. Des analyses de sensibilité détaillées ont montré qu'en réduisant le prix de la ceftazidime de 50 % (équivalent à 1 g q8h), les coûts du traitement à la ceftazidime étaient semblables à ceux du traitement à la ciprofloxacine. Parallèlement, en augmentant le prix de la ciprofloxacine de 50 % (équivalent à 750 mg q8h), les coûts du traitement à la ciprofloxacine par patient étaient semblables à ceux du traitement à la ceftazidime, bien que ces coûts, par jour, aient été moins élevés avec la ciprofloxacine ($p < 0,0002$). Le traitement à la ciprofloxacine d'une pneumonie nosocomiale a donc un rapport coûts/efficacité avantageux comparativement à celui de la ceftazidime.

MOTS CLÉS : *analyse coûts-efficacité, ceftazidime, pneumonie nosocomiale, traitement séquentiel à la ciprofloxacine*

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INTRODUCTION

The price of pharmaceuticals has long been a target of cost-containment activities.[1,2] Certainly, any program to reduce the purchase price of an item is a worthwhile venture. However, to simply focus on drug purchase price without considering the costs and consequences of outcomes may lead one to make an economically inaccurate and clinically inappropriate decision when comparing alternative medications.[3,4] It is now recognized that along with assessments of efficacy and adverse events, the complete evaluation of a medication should include a proper economic analysis.[5] Unfortunately, there are a limited number of pharmacoeconomic studies published and they frequently employed flawed methodologies or made inappropriate conclusions.[6,7] This is changing as the present economic movement in the health-care field has fostered an increasing number of well-designed, prospectively conducted studies. Nonetheless, published and peer-reviewed economic information is sparse or lacking for many compounds. A review of the literature did not reveal an economic analysis of ciprofloxacin versus ceftazidime.

Until prospective economic comparisons are more widely available, there is a role for properly conducted, retrospective analyses of existing data sets.[8] It should be recognized that retrospective evaluations are not comprehensive since information necessary for a thorough economic study is missing.[9,10] Still, because cost savings are not a goal of purely clinical studies, retrospective pharmacoeconomic evaluations of the studies are relatively free from economic bias. The potential for bias can be further reduced by an agreement between the owner of the data set/sponsor of the study and an independent researcher, granting him intellectual freedom in the study design, control over the analysis, and freedom to publish regardless of the result.[11] The study described herein is the result of such an agreement between the manufacturer/developer of ciprofloxacin (Bayer Health Care) and the investigator.

There is additional controversy in economically analyzing a randomized, controlled clinical trial (RCT). It has been inferred that the conditions under which a controlled trial is performed are artificial and not reflective of daily clinical practice.[12] While every study needs to be carefully evaluated for its applicability, one should not blindly discount an economic analysis of a RCT. If a study truly is not grounded in reality, the clinical results would be as invalid as the economic results and the work would have no real value. On the other hand, the highest quality evidence for establishing effectiveness is provided by well-done RCTs, which address *efficacy* (used in near-optimal circumstances in a homogeneous sample) rather than *effectiveness* (usual, uncontrolled use).[5] A negative consideration in economically analyzing uncontrolled use is that inappropriate or suboptimal practices may be assessed. For example, it has been established in a RCT that oral ciprofloxacin can abbreviate IV antibiotic therapy, resulting in significant cost savings.[13] Yet others report that under uncontrolled conditions the same compound may not result in a decrease in costs.[14]

The purpose of this study was to evaluate the cost-effectiveness of sequential IV/oral ciprofloxacin and ceftazidime in the treatment of nosocomial pneumonia.

METHODS

All patients enrolled into a multicentre study of nosocomial pneumonia were eligible for inclusion into this retrospective pharmacoeconomic analysis. The clinical study was conducted in association with members of the Canadian Infectious Diseases Society in five hospitals in Ontario and one hospital each in Alberta and Quebec. Data from the case report forms of patients whose courses were clinically evaluable comprise the economic study population. A cost-effectiveness analysis was conducted from the perspective of the institution. Decision analysis was utilized to provide a framework for the assessment. Sensitivity analysis was employed to test the robustness of the model by varying drug acquisition costs and the probability of success. The sensitivity analyses determined and defined the conditions under which each antibiotic would be cost-effective.

Review of Methods for the Clinical Study

The prospective clinical study compared the safety and efficacy of sequential IV-to-oral ciprofloxacin with IV ceftazidime for the treatment of moderately severe to severe nosocomial pneumonia caused by gram negative or gram positive organisms susceptible to both antimicrobials, in adult patients. Detailed results of the clinical trial (data on file, Bayer Health Care) are to be published separately.

In an unblinded fashion, patients were randomized to receive either IV ciprofloxacin 300 mg q12h or ceftazidime 2 g q8h. Patients randomized to receive IV ciprofloxacin were eligible to be switched to oral ciprofloxacin 750 mg BID when they were able to take oral medications. Oral ciprofloxacin was instituted at the discretion of the investigators. Initial therapy for all patients included clindamycin 600 mg q6h IV which could be discontinued at the discretion of the investigator. Erythromycin 500 mg - 1 q6h IV could be substituted for the clindamycin to treat atypical pneumonia, although this modification would cause the patient's course to be classified as a failure.

Duration of antibiotic therapy was dependent on the severity of the infection as well as the patient's clinical and microbiological response. Criteria necessary for evaluation of efficacy required the following: respiratory tract infection confirmed by the presence of clinical signs and symptoms of infection; infecting organism sensitive to study antibiotics as confirmed by broth or agar dilution susceptibility tests; chest x-rays before and after therapy; minimum of four days treatment with study antibiotic; culture taken after conclusion of drug therapy if sputum could be obtained. The clinical investigators' assessment of overall patient response was based on clinical and bacteriological responses of all sites of infection identified in a patient.

Methods for the Economic Study

A database to collect information necessary for the economic analyses was established. The economic evaluation period for each patient begins on the day the study drug treatment was initiated. The study drug regimen, including dosage, interval, and number of doses administered, was determined for each patient.

Overall patient response was assessed by the original clinical investigators' assessment of treatment outcome. If the patient was successfully treated and without adverse event, economic data collection stopped when the study antibiotic was discontinued. In the event of clinical failure, data collection continued until completion of the subsequent treatment with whichever non-study antibiotic was used after discontinuing the study antibiotic. Clinical failure was also declared if the occurrence of an adverse event required discontinuation of the study antibiotic and subsequent treatment with a non-study antibiotic, and data collection was continued as above. Regimen information was collected for any additional antibiotics administered. Any costs incurred for the treatment of any adverse events caused by study antibiotics or due to an unknown etiology were calculated. All IV antibiotics were administered in hospital.

Thus, the costs of antibiotic acquisition; antibiotic preparation and administration, and treatment of failures and adverse events were considered. Because this is a retrospective analysis, it was not possible to obtain the data necessary for a comprehensive accounting of resource consumption. Information on length-of-stay was not available as this was not recorded on the case report forms. Examples of other data not available include intensive care unit admission and length-of-stay; routine laboratory tests; invasive procedures; therapies (physical, occupational, respiratory, etc.), and primary physician and consultant visits.

Thus, the documented duration of treatment included the number of days

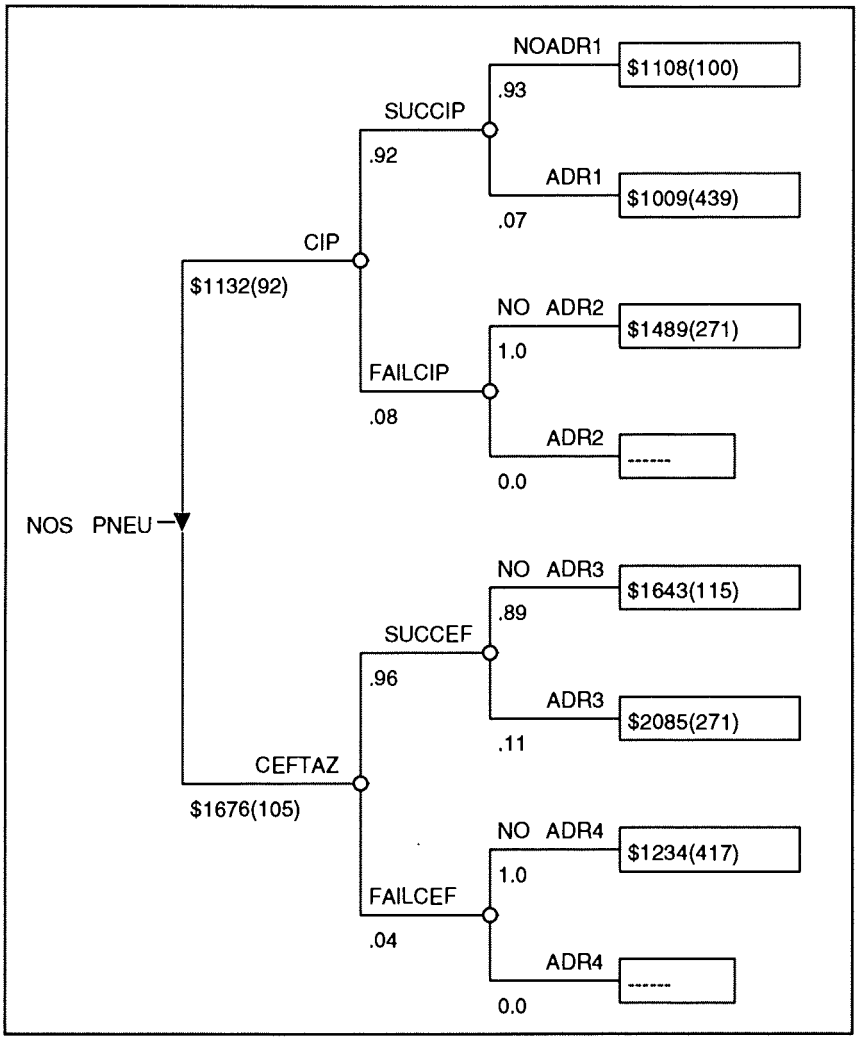

Figure 1. Decision Tree of Mean Cost-per-Patient.
∇ = choice node, o = chance node, data presented as $ ( ) are mean ± SEM, NOS PNEUMO: nosocomial pneumonia, NOADR1-4 = no adverse event; ADR1-4 = an adverse event was reported; CIP = ciprofloxacin, SUCCIP = successful outcome of ciprofloxacin treatment, FAILCIP = clinical failure of ciprofloxacin treatment; CEFTAZ = ceftazidime, SUCCEF = successful outcome of ceftazidime treatment, FAILCEF = clinical failure of ceftazidime treatment.

of treatment with IV ciprofloxacin, ceftazidime, or clindamycin, sequential IV-oral ciprofloxacin, other antibiotics used for treatment failures, and treatment of adverse events.

Pharmacoeconomic analyses can be divided into three levels. Level I considers only drug acquisition prices. Level II calculates direct and ancillary resources related to medication use (purchase, preparation, administration, monitoring, treatment of adverse events and failures). While Level III evaluates all health care resources consumed without regard to disease state, including overall hospitalization costs.[15] This study is a Level II analysis. Study antibiotics, post-study antibiotics, and medications to treat adverse events were computed at their standard direct prices, in 1994 Canadian dollars, obtained from a reference hospital in Ontario; discounting was not necessary. At the time of this study, IV ciprofloxacin was an investigational drug and a 300 mg dose was administered. It has since been approved at a 400 mg dose, so the price for a 400 mg dose ($33) was used. The price for ceftazidime was obtained as $20.19/g. It is understood that actual acquisition prices vary among institutions, so a range of prices was considered in the sensitivity analysis. The cost of preparing and administering a dose of IV medication varies widely, depending on medication formulations and hospital systems. For this study, resource utilization for medication preparation and administration (materials and personnel times) was conservatively priced at $4 per IV dose.[16-19]

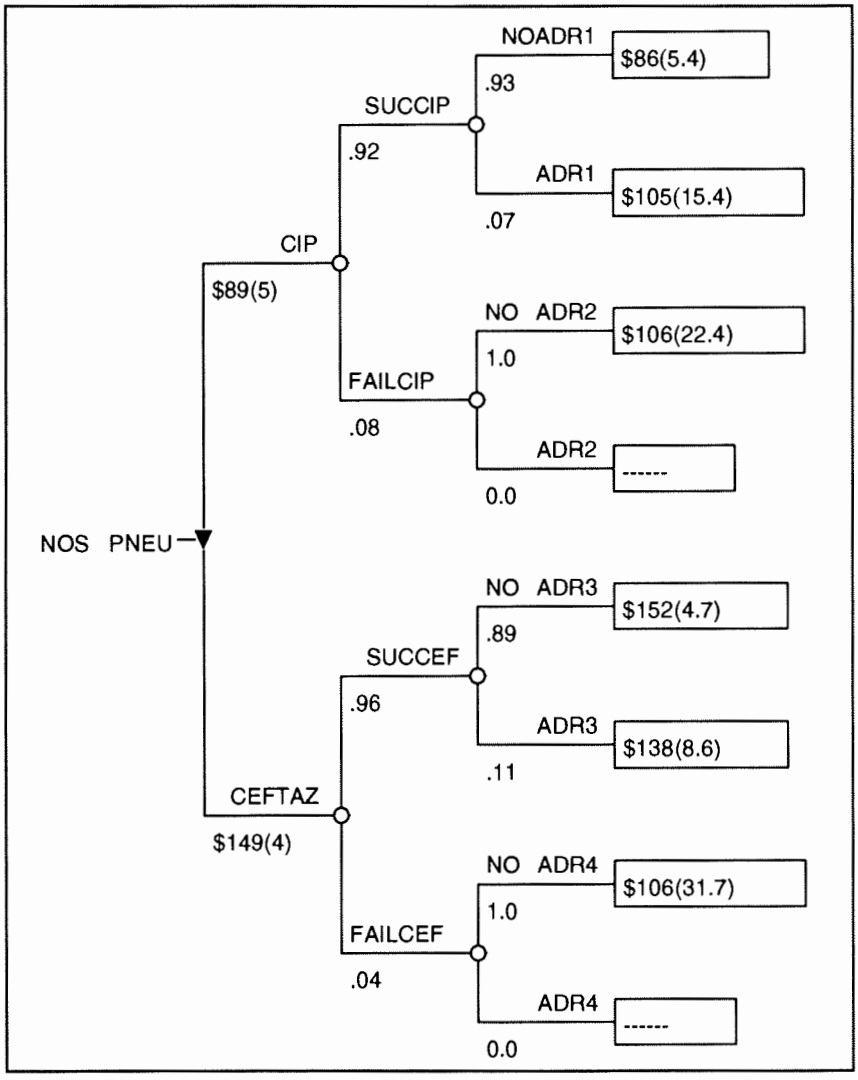

Figure 2. Decision Tree of Mean Cost-per-Day.
∇ choice node, o = chance node, data presented as $ ( ) are mean ± SEM, NOS PNEUMO: nosocomial pneumonia, NOADR1-4 = no adverse event; ADR1-4 = an adverse event was reported; CIP = ciprofloxacin, SUCCIP = successful outcome of ciprofloxacin treatment, FAILCIP = clinical failure of ciprofloxacin treatment; CEFTAZ = ceftazidime, SUCCEF = successful outcome of ceftazidime treatment, FAILCEF = clinical failure of ceftazidime treatment.

Decision and Sensitivity Analyses

Patient outcomes were categorized in decision trees (Figures 1 and 2) as a success or failure and whether or not an adverse event occurred, according to the clinical investigators' assessments. Each decision tree illustrates the probability of the possible outcomes occurring and the costs of the consequences, from the study treatment options. The boxes at the end of the terminal branches list the mean ± SE values for cost-per-patient (Figure 1) or cost-per-day of treatment (Figure 2).

Sensitivity analysis was performed by altering the probability of success and drug acquisition costs. The probability of success was varied between 60% and 99% to encompass likely outcomes under various clinical conditions. Drug acquisition cost was tested over a range that would include the cost of dose alternatives used in clinical practice. Ceftazidime costs were reduced by 50% (to $10.10/g), which also would reflect dosing of 1 g q8h at the original cost, while holding ciprofloxacin at the 400 mg q12h regimen. Then, ceftazidime costs were maintained at the 2 g q8h regimen while the ciprofloxacin cost was increased by 50% (to $49.50/400 mg), which would also reflect dosing at 400 mg q8h at the original price.

Statistical Analysis

Differences in efficacy rates between the two groups were tested by constructing 95% confidence intervals. The Kruskal-Wallis test was used to detect differences between nodes of the decision tree. Wilcoxon two-sample tests were used to assess cost differences between the study groups. The probability of a type 1 error = 0.05 was used to determine statistical significance.

RESULTS

The principal investigators of the clinical study were able to make outcome assessments on 106 of the 149 patients entered into the randomized comparison. Data from the case report forms of the 50 clinically evaluable patients in the ciprofloxacin group and 56 clinically evaluable patients in the ceftazidime group were used in the economic analysis.

There were no apparent demographic differences between the groups for age, sex, race, or ventilator status (Table I). The documented duration of antibiotic treatment was (mean ± SE) 13.2 ± 0.9 days for ciprofloxacin-treated patients and 11.2±0.6 days for ceftazidime-treated patients. The mean duration of IV antibiotic therapy for the 50 ciprofloxacin-treated patients was 9.3 days, while 22 of the patients received sequential oral ciprofloxacin (mean of 7.1 days). The median duration of treatment was 13.5 days overall for ciprofloxacin-treated patients and 11 days for ceftazidime-treated patients.

The 95% confidence interval for the difference in response rates for the 106 patients was -13.38%, 4.95%. The clinical success rate was 92% for patients in the ciprofloxacin group and 96% for patients in the ceftazidime group (NS). Antibiotic-related adverse events occurrred in 6% of ciprofloxacin and 10.7% of ceftazidime patients (NS). The adverse events were predictably mild and transient, predominately rash and diarrhea.

Decision analysis of the cost-per-patient (Figure 1) revealed a mean ± SE cost of $1132 ± 92 for the ciprofloxacin-treated patients and $1676 ± 105 for the ceftazidime-treated patients ($p<0.0003$). Decision analysis of the cost-per-day (Figure 2) revealed a mean ± SE cost of $89 ± 5 for the ciprofloxacin-treated patients and $149 ± 4 for the ceftazidime-treated patients ($p<0.0001$). Decision trees (not shown) were also constructed for median values. The results coincided with the decisions obtained from mean values. The median cost-per-patient was $1035 for ciprofloxacin-treated and $1559 for ceftazidime-treated patients. The median cost-per-day was $80 for ciprofloxacin-treated patients.

A disparity in original data collection that would affect the economic analysis was discovered. Although no provision was made in the protocol, most patients in the ceftazidime group received subsequent oral antibiotic therapy. Insufficient data were provided on the case report forms to allow for an economic analysis of these regimens. However, sequential oral therapy was recorded for patients in the ciprofloxacin group. This disparity has at least three consequences. First, because the length of total antibiotic therapy was documented for a longer period of observation in the ciprofloxacin group and oral antibiotic therapy was not imputed for the ceftazidime group, an economic advantage was given to ceftazidime. Conversely, including oral antibiotic costs decreases the average cost-per-day, an advantage to ciprofloxacin. Correction for the cost-per-day inequity was accomplished by a cost-minimization analysis of the IV study medications. Disregarding oral follow-up removes any ciprofloxacin advantage in this analysis. Third, anibiotic length-of-stay (ALOS), a marker for duration of hospitalization necessary for infection treatment,[9,15] cannot be applied under these unequal conditions.

Table I. Demographic Data

	Ciprofloxacin Patients	Ceftazidime Patients
Entrolled patients	72	77
Evaluable patients	50	56
Age		
Mean ± SEM (Years)	59.8 ± 2.5	60.2 ± 2.3
Range (years)	22-90	19-91
Sex		
Male (N, %)	35, 70%	34, 60.7%
Female (N, %)	15, 30%	22, 39.3%
Race		
Caucasian (N, %)	46, 92%	52, 92.9%
Other (N, %)	4, 8%	4, 7.1%
Ventilator Status		
Dependent (N, %)	27, 54%	26, 46.4%
Independent (N, %)	23, 46%	30, 53.6%

Cost-Effectiveness Analysis

There are various methods to compute cost-effectiveness.[20,21] The cost-effectiveness ratio is the cost divided by the effectiveness of a particular treatment, while incremental cost-effectiveness describes the additional cost and effectiveness obtained when one treatment is compared to another.

The results of the cost-effectiveness ratios (Table II) indicate that one would have to spend more to use ceftazidime. The incremental cost to achieve an additional efficacy benefit with ceftazidime was $516 more per patient, or $58 more per day.

Sensitivity Analyses

The decision model was subjected to three sensitivity analyses. Varying the probability of clinical success between 60-99% failed to change the economic decision; ciprofloxacin 400 mg q12h costs were always lower than ceftazidime 2 g q8h. Drug acquisition costs were varied in two fashions to favour ceftazidime. Costs of a lower-dose ceftazidime regimen, 1 g q8h, compared to ciprofloxacin at the 400 mg q12h regimen, resulted in no differences in mean cost-per-patient or cost-per-day ($p>0.05$). Then, costs of a higer-dose regimen of IV ciprofloxacin, 400 mg q8h, were compared to ceftazidime 2 g q8h. There was no difference in mean cost-per-patient ($p>0.05$) while the cost-per-day was lower for the ciprofloxacin-treated patients ($p<0.0002$).

Cost-Minimization Analysis

As stated previously, there was a disparity in the original data collection of oral antibiotic follow-up regimens. Thus, a straight price comparison representing likely IV regimens was performed, considering drug acquisition price and the costs of medication preparation and administration. Table III shows the sensitivity analysis of drug cost as a result of varying the acquisition costs. Because this was a straight price comparison, no statistical tests were performed on the raw data.

Table II. Cost-Effectiveness Analysis Results

	Cost-Effectiveness Ratios (CER)		
Treatment	**Cost/Day**	**% Effectiveness**	**CER (per day)**
Ceftazidime	$149	96%	155
Ciprofloxacin	$89	92%	97
	Cost/Patient	**% Effectiveness**	**CER (per patient)**
Ceftazidime	$1676	96%	1746
Ciprofloxacin	$1132	92%	1230

Table III. Cost-Minimization Analysis: Drug Acquisition Costs[a]

Antibiotic	P	Dose	Day	Prep & Admin[b]	Daily Total
Ciprofloxacin	S	33.00	66	8	74
Ceftazidime	S	40.38	121	12	133
Ciprofloxacin	S	33.00	66	8	74
Ceftazidime	↓	20.19	61	12	73
Ciprofloxacin	↑	49.50	99	8	107
Ceftazidime	S	40.38	121	12	133
Ciprofloxacin	↑	49.50	99	8	107
Ceftazidime	↓	20.19	61	12	73

Regimens: Ciprofloxacin 400 mg q12h
Ceftazidime 2 g q8h

[a] Prices in 1994 $CAN
P = Price
S = Standard Price
↑ = 50% Increase
↓ = 50% Decrease
[b] Preparation and administration costs (per dose) = $4.00

DISCUSSION

Clinical outcomes and their associated economic consequences resulting from the use of a medication must be considered for a proper economic assessment.[20-23] A cost-effectiveness analysis is often used to consider costs (resources used) and consequences (outcomes) in medication comparisons. In this study, the treatments provided essentially equivalent efficacy while one, ciprofloxacin, utilized less resources.

This study evaluated the costs of antibiotic acquisition, preparation and administration as well as the subsequent treatment of failures and adverse events. Discounting, a technique used to normalize comparisons when costs and consequences occur at different times,[24] was not necessary in this study of acute infections.

The cost applied to each IV dose administered ($4) can only be considered illustrative. The relevant studies referenced in this paper[16-19] are only representative of a sizeable body of literature. Moreover, they were performed some years ago and adjusting the results for 1994 dollars reveals that the mean costs for preparing and administering an IV dose range from >$3.50 to >$12. The overall 1994 mean is more likely to be $6-7 which would further penalize ceftazidime in this comparison because of its more frequent dosing regimen.

Information on hospital length-of-stay for these patients was not available. When hospital costs are included in an analysis such as this, the economic outcome is actually insensitive to changes (within a reasonable range) in drug price.[10,15] Not considering hospital costs may actually have the benefit of teasing out the economic differences attributable to the prices of similarly-effective medications.[9] In a previous economic study of an investigational cephalosporin, it was determined that antibiotic price was the most powerful component of costs exclusive of the

cost of a hospital day (a Level II analysis).[15] Thus, although not all resource costs are figured, this analysis offers important and useful information because it does consider the most important costs directly related to antibiotic use.

The clinical study tested 300 mg of IV ciprofloxacin, but the compound was approved at a 400 mg dose. The price used in this analysis is that for 400 mg. An obvious question is what effect the extra 100 mg may have on efficacy, adverse events, and the economic consequences of changes to either or both of those outcomes. Pharmacodynamic data would suggest that the increased dosage could result in a more rapid eradication of pathogens with higher minimum inhibitory concentrations and consequently increase the efficacy rates,[25] although to what degree and extent is unknown. Similarly, there may be an increase in dose-dependant adverse events, although 33 adult patients who received IV ciprofloxacin 400 mg q8h, six had virtually the same adverse event profile as seen after standard fluoroquinolone dosing.[27]

Sensitivity analysis on the probability of success, usually expected to eventually attain a threshold value to change the decision, could not do so in this study because the costs for the patients who failed ceftazidime therapy were lower than for those who were treated successfully. This finding is unusual. Thus, as the success rate with ceftazidime was incresed, mean costs increased as well. Possible explanations for this include: treatment regimens for failures cost less than the study regimen; more patients died in the failure group, consuming less resources than survivors; or a simple data artifact due to sample size.

This economic analysis is derived from a clinical study that compared ceftazidime q8h with ciprofloxacin q12h. These regimens resulted in essentially equivalent clinical outcomes. Again, one could logically question whether the conomic result would be different if the antibiotics were administered in regimens of equal frequency or potency. Sensitivity analyses of drug regimens, despite the fact that they were manipulated in a manner to favour ceftazidime, consistently demonstrated that ciprofloxacin was equally cost-effective or more cost-effective compared to ceftazidime. In one scenario, ceftazidime dosage was reduced while in the other, ciprofloxacin frequency was increased. In either case, the costs of ceftazidime were diminished relative to those of ciprofloxacin. By not altering efficacy or adverse reaction rates, the effect would favour ceftazidime, but the decision did not change.

Without direct comparative data, there is no evidence that q8h regimens of ciprofloxacin and ceftazidime would result in equal outcomes in serious infections, or that reducing ceftazidime to a 1 g dosage would not decrease efficacy or adverse event rates. Prospective clinical and economic evaluations of the two antibiotics in randomized studies of these alternative regimens is needed to assess the relative efficacy, adverse events, treatment duration, and economics. Such a study should include follow-up oral antibiotics since early conversion to oral antibiotic therapy has been shown to be a cost-effective component of streamlining antibiotic therapy.[13]

This study found that IV ciprofloxacin, with some patients changing to sequential oral therapy, was cost-effective compared to ceftazidime 2 g q8h in patients with moderately severe to severe nosocomial pneumonia.

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