Cost-Effectiveness of Ampicillin/Sulbactam Versus Imipenem/Cilastatin in the Treatment of Limb-Threatening Foot Infections in Diabetic Patients

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A cost-effectiveness analysis was performed following a double-blind, randomized study of ampicillin/sulbactam (A/S) versus imipenem/cilastatin (I/C) for the treatment of limb-threatening foot infections in 90 diabetic patients. There were no significant differences between the treatments in terms of clinical success rate, adverse-event frequency, duration of study antibiotic treatment, or length of hospitalization. Costs of the study antibiotics, treatment of failures and adverse events, and hospitalization were calculated. Mean per-patient treatment cost in the A/S group was $14,084, compared with $17,008 in the I/C group (P = .05), primarily because of lower drug and hospitalization costs and less-severe adverse events in the A/S group. Sensitivity analyses varying drug prices or hospital costs demonstrated that A/S was consistently more cost-effective than I/C. Varying the clinical success rate for each drug revealed that I/C would have to be 30% more effective than A/S to change the economic decisions.

Foot and lower-limb infections, often complicated by gangrene and/or osteomyelitis, are a leading cause of morbidity and mortality in diabetic patients. Treatment may be complex and costly, as long-term intravenous antibiotic therapy and surgical interventions such as debridement and amputation are often necessary for cure [1–3]. In the United States 20% of hospitalized diabetics are admitted for foot problems, representing the single most common reason for hospitalization of diabetic patients [4].

In 1991 this was estimated to represent an annual cost of >$200 million [4]. Similar financial implications were demonstrated by data from the Netherlands, in which 20.4% of the 18,153 diabetic patients admitted to hospitals in 1988 had foot problems [3]. The economic consequences of these infections should be considered in evaluations of alternative treatment modalities. An intervention that could reduce costs associated with the treatment of diabetic foot infections would have significant financial benefit.

We reviewed the results of a clinical and bacteriologic study of ampicillin/sulbactam (A/S) vs. imipenem/cilastatin (I/C) for the treatment of limb-threatening infections in diabetic patients [5]. The purchase price of A/S is lower than that of I/C [6]; however, the question of cost-effectiveness has not been addressed. Although a statistically significant difference was not demonstrated in the previous study [5], there was a shorter duration of treatment and length of stay (LOS) associated with the use of A/S. Furthermore, adverse events requiring treatment or prolonging the LOS appeared more frequently in the I/C group.

Because this was a randomized, double-blind study, we considered it valid to subject the data to an economic analysis. While it is preferable to prospectively conduct an economic analysis to facilitate the inclusion of all costs and consequences [7], valuable information can be gained from careful retrospective analysis of controlled clinical studies [8–10]. Therefore, we conducted a cost-effectiveness analysis (CEA) of the above-referenced study [5] to compare A/S and I/C for the empirical treatment of limb-threatening foot infections in diabetic patients.

Methods

All patients enrolled in a completed randomized, double-blind study of A/S vs. I/C for the treatment of serious lower limb infections [5] were eligible for inclusion in this retrospective pharmacoeconomic analysis. Criteria for inclusion in the clinical study were a need for hospitalization, age of ≥ 18 years, and presence of diabetes mellitus and limb-threatening infection involving the lower extremity. Limb-threatening infection was defined clinically by the presence of cellulitis, with or without ulceration or purulent discharge.

Exclusion criteria were a known hypersensitivity to β-lactam antibiotics, a need for other (concomitant) antibiotic treatment, a serum creatinine level of ≥ 3.5 mg/dL, expected survival of <48 hours, and immunosuppression secondary to underlying disease or drug therapy. Patients were randomized to receive either A/S (3 g iv q6h) or I/C (500 mg iv q6h). Dosages were adjusted for impaired renal function.

Patients' routine care included adjunctive therapy such as tight control of diabetes mellitus, wound care, and surgical
drainage and debridement. A final assessment of treatment outcome was made at the end of intravenous antimicrobial therapy. The following clinical endpoints were used: cure (resolution of soft-tissue infection), failure (inadequate improvement necessitating a change in antibiotic therapy), and indeterminate (clinical assessment not possible, e.g., because of amputation of the entire site of infection).

The clinical and bacteriologic results of the trial have been published [5]. There were 98 episodes of infection treated in 93 patients, and we were able to obtain data from 90 of these patients for economic evaluation. The remaining patients were excluded; either they had been previously enrolled in the study or no pathogen was isolated. CEA with decision modeling was used to characterize, measure, and compare costs and potential economic differences between treatment groups. Sensitivity analysis was used to assess the strength of the model and whether the treatment decision changes when index variables are altered within a reasonable range.

Resource Utilization

A database to collect information necessary for the economic analyses was established. The economic evaluation period for each patient began on the day study-drug treatment was initiated. The study-drug regimen, including dosage, interval, and number of doses administered, was determined for each patient. If the patient was successfully treated and did not experience any adverse event, then data collection stopped when study-antibiotic administration was discontinued. If study-antibiotic treatment was not successful, costs of subsequent treatment with non-study antibiotics were calculated. Costs of treating adverse events caused by study treatment or of unknown etiology were also calculated.

The investigator assessing costs associated with treatment of adverse events and treatment failures extracted data from the adverse-experience page and the concomitant-medication page of the case report but was blinded to the treatment regimen. In the event of clinical failure, data collection continued until the completion of the secondary treatment.

The number of days of hospitalization during which an antibiotic is administered for the treatment of infection is known as the antibiotic-related length of stay (ALOS) [9]. The ALOS for each patient begins at initiation of study-antibiotic treatment and ends at discontinuation of all antibiotic therapy or at hospital discharge, whichever occurs first. Also included within the ALOS is any additional LOS associated with (1) treatment of adverse events resulting from use of the study antibiotic or (2) subsequent antimicrobial therapy for treatment failures. This additional LOS was calculated as the duration of the subsequent treatment, in days, up to but not exceeding the duration of hospitalization.

Resource Cost

Current standard costs in 1994 United States dollars were employed to determine the value of the resources used. Discounting was not necessary, as costs were incurred and outcomes occurred during the same time period. Pharmaco-economic analyses can be divided into three levels of costs [9]. Level I considers only the acquisition price of a medication. Because acquisition prices for medications can vary by purchaser, nationally published direct drug prices were used [6]. Level II adds all costs directly related to antibiotic use and infection treatment, exclusive of the cost for a hospital bed [9]. Antibiotic-related items include acquisition cost, medication preparation and administration, treatment of adverse events, and secondary treatment for failures. Medication preparation and administration was priced at an average figure of $4 per intravenous dose [11–14].

Level III costs include all Level II items plus hospital bed costs incurred during treatment [9]. The ALOS, as defined above, was used to calculate the costs of hospital stay directly related to treatment of infection [8–10]. Raw LOS data were also computed. The daily cost of occupying a hospital bed is highly variable and depends on the type of unit (intensive care or otherwise), the type and geographic location of the hospital, and the levels of technology and services provided. The most recently published average value for the daily cost of occupying a hospital bed in the United States, $852, was used [15].

Analytical Plan

An economic analysis should consider all resources consumed during the study period. Because this was a retrospective study, it was not possible to collect the data necessary for a comprehensive analysis of all resources consumed. The following items were not specifically accounted for: laboratory tests, surgeries and other procedures, physical or occupational therapy, radiology, and the myriad of other resources consumed while a patient is occupying a hospital bed. Furthermore, from the available data, it was not possible to discern the number of days spent in the intensive care unit. The United States average cost of a hospitalization day indirectly represents unaccounted resources while incorporating elements such as personnel and overhead expenses.

A CEA from the perspective of the institution was conducted. Because the hospital perspective was taken, physician charges were not considered. Similarly, costs of outpatient visits, treatments such as rehabilitation, and prosthetic devices were not included. However, it has been previously demonstrated that these costs are modest relative to costs incurred as an inpatient for the treatment of diabetic foot infections [2].

A decision tree categorized each case as a treatment success, a treatment failure, or of indeterminate outcome, according to the original investigators’ clinical assessment at the end of treatment [5]. Sensitivity analysis was employed to test the robustness of the model by varying drug price, hospital bed cost, and probability of success. Drug acquisition price was tested over a range of ~25% above and below the direct price for each antibiotic: $9–$15 for 3 g of A/S and $17–$30 for 500 mg of I/C. The
hospital bed cost was varied to bracket the per-day cost of $852 by $±$250, for a range of $600–$1,100. The probability of success for each drug was varied independently between 50% and 95% to encompass possible outcomes.

Statistical Analysis

Statistical analysis was performed with SYSTAT software (SYSTAT, Evanston, IL) on a personal computer. The probability of a type I error of 0.05 was used to determine statistical significance. Comparisons of the LOS, ALOS, and costs associated with the two regimens were made by means of the Kruskal-Wallis one-way analysis of variance test.

Results

Clinical Trial—Summary

Detailed demographic data and clinical results from the prospective trial have been published [5]. Included in the initial study were 47 patients (48 episodes of infection) in the A/S group and 46 patients (48 episodes of infection) in the I/C group, as shown in table 1. Patient demographics were similar in the two treatment groups, as were clinical characteristics such as insulin-requiring diabetes, peripheral vascular disease, and site of infection. Surgical interventions were similar between groups: ~25% of patients required surgical debridement alone, and ~65% of patients required amputation.

Of required amputations, the majority (>90%) were limited to the infected digits and metatarsal heads and were considered to be foot-sparing amputations. There were no statistically significant differences in clinical success rate, overall adverse event frequency, duration of study-antibiotic treatment, or length of hospitalization between the treatment groups [5]. The clinical success rate was 81% (39 of 48 episodes) for A/S-treated patients and 85% (41 of 48 episodes) for those treated with I/C.

Table 1. Summary of results of the previously conducted clinical trial [5] of ampicillin/sulbactam (A/S) vs. imipenem/cilastatin (I/C) for the treatment of infections in diabetic patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>A/S (%) of episodes or other data, per treatment group</th>
<th>I/C (%) of episodes or other data, per treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes of infection</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>32 (68)</td>
<td>27 (56)</td>
</tr>
<tr>
<td>Amputation</td>
<td>33 (69)</td>
<td>28 (58)</td>
</tr>
<tr>
<td>Foot-sparing amputation</td>
<td>30/33 (91)</td>
<td>27/28 (96)</td>
</tr>
<tr>
<td>Duration (no. of days) of treatment with study antibiotic (mean ± SD)</td>
<td>13 ± 6.5</td>
<td>15 ± 8.6</td>
</tr>
<tr>
<td>Cure rate</td>
<td>39 (81)</td>
<td>41 (85)</td>
</tr>
</tbody>
</table>

Table 2. Clinical outcomes and adverse events in the groups of diabetic patients treated with ampicillin/sulbactam (A/S) or imipenem/cilastatin (I/C).

<table>
<thead>
<tr>
<th>Variable</th>
<th>A/S (%) of patients per treatment group</th>
<th>I/C (%) of patients per treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>36 (80)</td>
<td>36 (80)</td>
</tr>
<tr>
<td>Failure</td>
<td>8 (18)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>1 (2)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Adverse effect(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economically significant*</td>
<td>7 (16)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Diarrhea (due to Clostridium difficile)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other*</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

* Requiring treatment and related to study drug or of unknown origin.
† Rash, nausea/vomiting, or fungal superinfection.

Economic Analysis

Data from the case report forms for 90 patients (45 patients from each treatment group) were available for economic analysis. Seven episodes of infection from the original study were not included in the economic analysis, either because they had been previously enrolled (n = 5; their second course was therefore not evaluated) or because no initial pathogen was isolated (n = 2). The clinical success rate was 80% for patients in the A/S group (usual dose, 3 g iv q6h) and 80% for patients in the I/C group (usual dose, 500 mg iv q6h). Clinical outcomes for these 90 patients are summarized in table 2.

Adverse events with potential economic consequences (defined as those that required treatment and were either drug-related or of unknown etiology) were identified from the patients’ case report forms. Adverse events meeting these criteria occurred in 16% of A/S-treated patients and 20% of I/C-treated patients, as shown in table 2.

Most identified adverse events were mild and transient: rash, diarrhea, nausea, vomiting, pain at injection site, fungal superinfection, and constipation. However, diarrhea related to Clostridium difficile contributed to increased cost and ALOS for 5 patients, 1 in the A/S-treated group and 4 in the I/C-treated group. The overall increase in LOS for treatment of patients with C. difficile–associated diarrhea was 3 days for the patient treated with A/S and 25 days (total) for the four patients treated with I/C.

Total and mean (per patient) data regarding study-drug treatment duration, ALOS, and LOS are shown in table 3. Mean perpatient data for ALOS, broken down by category, are shown in figure 1. The drug costs used for the initial analysis were $12.39 per 3-g dose of A/S and $23.34 per 500 mg dose of I/C [6]. As success rates were identical for each treatment group, cost-
Table 3. Treatment duration and length of stay for the ampicillin/sulbactam (A/S) and imipenem/cilastatin (I/C) treatment groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>A/S (n = 45)</th>
<th></th>
<th>I/C (n = 45)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total no. of days</td>
<td>Mean (±SD) no. of days (per patient)</td>
<td>Total no. of days</td>
<td>Mean (±SD) no. of days (per patient)</td>
</tr>
<tr>
<td>Duration of treatment with study drug</td>
<td>612</td>
<td>13.6 ± 7.6</td>
<td>679</td>
<td>15.1 ± 8.7</td>
</tr>
<tr>
<td>Increase in ALOS due to AEs</td>
<td>7</td>
<td>0.2</td>
<td>52</td>
<td>1.2</td>
</tr>
<tr>
<td>Increase in ALOS due to failures</td>
<td>72</td>
<td>1.6</td>
<td>78</td>
<td>1.7</td>
</tr>
<tr>
<td>ALOS</td>
<td>691</td>
<td>15.4 ± 8.9</td>
<td>809</td>
<td>18.0 ± 9.7</td>
</tr>
<tr>
<td>LOS</td>
<td>792</td>
<td>17.6 ± 9.9</td>
<td>949</td>
<td>21.1 ± 10.8</td>
</tr>
</tbody>
</table>

NOTE. No statistically significant difference was detected between the two groups by means of the Kruskal-Wallis one-way analysis of variance test. AEs = adverse events; ALOS = antibiotic-related length of stay (no. of hospitalization days during which study antibiotic was administered and for treatment of failures or adverse events); LOS = length of stay (total duration of hospitalization).

effectiveness ratios were not necessary to demonstrate differences.

Mean study-drug acquisition costs per patient were $603.35 for those treated with A/S and $1,306.92 for patients in the I/C group (P < .001). Resulting level I, level II, and level III costs per patient (mean ± SD) are shown in table 4. Total costs—broken down into level I, level II, and level III—are depicted in figure 2.

Results of the level III economic analysis are presented in a decision tree in figure 3. The decision tree, incorporating the actual clinical probabilities of success or failure in this trial, illustrates the consequences resulting from each treatment option. The boxes at the end of the terminal branches list the resulting mean cost and ALOS for each possible outcome. For each drug, successful treatment resulted in a shorter ALOS and lower cost than did treatment resulting in clinical failure.

Results of Sensitivity Analyses

Drug-acquisition costs were varied by ±25%, from $9 to $15 per 3 g of A/S and from $17 to $30 per 500 mg of I/C, but the overall economic decision did not change: the cost of treatment with A/S was consistently lower for all permutations. Hospital bed costs were varied between $600 and $1,100 per day for the ALOS analysis; again, the economic decision did not change.

Economic projections can be determined for a range of probabilities of success by applying costs associated with each outcome. Results obtained by varying the clinical success rate of each drug, independently, between 50% and 95% are shown in figure 4. On the graph, the point of intersection of the two lines reflects the breakpoint at which the cost-effectiveness decision changes. At this point, if success rates were ~87% for I/C and 57% for A/S, the two agents would be equally cost-effective. A/S remains cost-effective in the area to the left of the intersection. Overall, I/C would have to be ~30% more effective than A/S to be cost-effective under the conditions of this study.

Discussion

A CEA from the perspective of the hospital was used to assess the difference in economic outcome between two agents used to treat diabetic foot infections. A CEA is often used to consider costs (resources used) and consequences (outcomes) in medication comparisons. In a CEA, results of analysis are often expressed as the ratio of cost to effectiveness to demonstrate costs incurred for a given outcome. In this analysis the treatments provided equivalent efficacy; thus, an incremental CEA is not applicable and costs can be compared directly.

The mean total treatment cost was ~$3,000 less per patient in the A/S-treated group than in the I/C-treated group: $14,084 vs. $17,008 (P = .05). Whether comparing only antibiotic-acquisition (level I) costs, or those plus costs of preparation/administration and subsequent treatment (level II), or all of the above plus hospital bed costs (level III), the cost and sensitivity analyses consistently demonstrated that treatment with A/S was less costly than treatment with I/C. Since no difference between agents was found in this study and A/S consistently used fewer
Table 4. Level I, II, and III costs (in United States dollars) for treatment with ampicillin/sulbactam (A/S) or imipenem/cilastatin (I/C).

<table>
<thead>
<tr>
<th>Level</th>
<th>A/S Mean</th>
<th>A/S SD</th>
<th>I/C Mean</th>
<th>I/C SD</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>603</td>
<td>313</td>
<td>1307</td>
<td>816</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>II</td>
<td>982</td>
<td>650</td>
<td>1654</td>
<td>913</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>III</td>
<td>14,084</td>
<td>8,262</td>
<td>17,008</td>
<td>9,064</td>
<td>.05</td>
</tr>
</tbody>
</table>

* Per Kruskal-Wallis one-way analysis of variance test.
1 Total study-drug acquisition cost per patient.
2 Level I cost plus cost of drug preparation/administration and treatment of adverse events and failures.
3 Level II cost plus hospital bed costs for ALOS.

resources, cost-effectiveness is maintained for A/S throughout the cost-sensitivity analyses.

Sensitivity analysis tests the robustness of the decision model. By altering the value of key data, or changing outcome probabilities, one can ascertain the conditions that will cause the decision to change. This technique gives strength to the conclusions drawn and facilitates extrapolation of existing data to other populations. With use of sensitivity analysis, it was demonstrated that I/C would need to achieve 30% greater efficacy than A/S to change the economic decision in favor of I/C.

While this magnitude of difference would not be expected in the empirical treatment of diabetic foot infections of moderate severity, in the specific case of an organism resistant to A/S but susceptible to I/C, one could likely justify the cost-efficacy of I/C. Certain patient factors may give a clinician reason to suspect that an infection is caused by resistant organisms. The most appropriate therapy for a given patient will be determined by consideration of patient-specific information as well as the cost and efficacy of each regimen.

There are advantages and disadvantages associated with performing a retrospective economic analysis [16, 17]. One limitation to a retrospective analysis is that some of the data necessary for a comprehensive analysis may not have been collected at the time of the initial clinical trial. In this analysis we have considered study-drug price, preparation and administration costs, antibiotics used for failures, treatment of adverse events, and the ALOS. The average cost of a day of hospitalization was used; not accounted for were any potential differences in LOS in intensive care units.

For level I and level II analyses, the cost of the drug itself is the predominant factor contributing to cost. It has been determined that the cost of a hospital day is the major component of hospitalization costs for infected patients, comprising 78% of total costs in one comprehensive study [9]. This is consistent with our findings in the level III analysis, where the most significant expense was attributable to hospital bed cost. Therefore, although not all resource costs are included, this analysis

Figure 2. Cost-analysis levels, expressed as mean costs per patient, in United States dollars (U.S. $); □ = level I, □ = level II, and □ = level III.

Figure 3. A decision tree presenting the results of the level III economic analysis. Dollar figures shown are the mean costs per branch; the number of days represents the antibiotic-related length of stay (Succ = clinical success (cure); Fail = clinical failure; Indt = indeterminate outcome; □ = choice node; ⊙ = chance node).
Figure 4. Sensitivity analysis of the probability of success of treatment with either A/S (— — —) or I/C (-----), assessing level III costs in United States dollars (U.S. $).

offers important and useful information because at each level it considers the most important cost factors.

The design of a clinical trial may determine its suitability for CEA. When the initial investigation was performed, there was no specific impetus for shortening the length of intravenous therapy with an early switch to oral antibiotics. Protocol guidelines did not mandate duration of treatment, and no conscientious attempt was made by the investigators to shorten either duration of therapy or length of stay. Since economic analysis was not an objective of the initial study and the study was both randomized and double-blind, there is less chance that bias was introduced to affect the economic analysis [8].

In the original clinical study, no difference was detected between the groups with regard to duration of study-drug treatment or overall LOS. Our level III analysis included costs for additional LOS associated with treatment failures or adverse events. As shown in table 3, the additional LOS for secondary treatment (ALOS minus duration of treatment with study-drug) was greater for I/C than for A/S. The mean number of days that ALOS was longer than study-drug treatment was 2.9 days per patient for I/C and 1.8 days per patient for A/S. The greater additional ALOS with use of I/C is due in part to prolonged hospitalization for treatment of C. difficile—associated diarrhea, which occurred more frequently in the I/C-treated group.

In an economic analysis it is desirable for the comparison to involve real-life situations, comparing commonly used treatments for a given disease state. This is in contrast to some clinical studies in which investigational treatments are compared with an uncommon treatment option for the purpose of demonstrating efficacy. Diabetic foot infections are most often polymicrobial, with a mix of aerobic and anaerobic bacteria [18–23]. Furthermore, for diabetic patients it is desirable to avoid nephrotoxic agents (such as the aminoglycosides) whenever possible [24–27]. The agents utilized in this study are considered valid treatment options because they exhibit broad-spectrum activity against commonly isolated pathogens and are relatively free of renal toxicity [24–27].

The patients included in the clinical study were determined to have limb-threatening infections of moderate severity. Severe or life-threatening infections were excluded from the initial trial [5]. The authors offer the caveat that their results may not apply to patients with more severe infections or overwhelming sepsis secondary to extensive disease. Similarly, the economic results should be cautiously extrapolated to these patients.

Conclusions

The economic burden of climbing health-care costs has placed hospitals under increased pressure to contain costs. Simple price comparisons are not appropriate for economic assessment of treatments. Outcome evaluation provides necessary information for performing a CEA. In this retrospective evaluation we have shown that A/S is a cost-effective alternative to I/C for the empirical treatment of limb-threatening infections in diabetic patients.

One must always exercise sound clinical judgement to determine when a patient may be among those who might benefit from treatment with an agent with a broad spectrum of activity such as that provided by I/C. CEAs add to our database to be utilized in making rational choices of antimicrobial agents.

Acknowledgment

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References