Comparison of Ampicillin-Sulbactam and Imipenem-Cilastatin for the Treatment of *Acinetobacter* Ventilator-Associated Pneumonia

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*Acinetobacter* organisms, which are a common cause of ventilator-associated pneumonia (VAP) in some health care centers, are becoming more resistant to such first-line agents as imipenem-cilastatin (Imi-Cil). Sulbactam has good in vitro activity against *Acinetobacter* organisms; thus, ampicillin-sulbactam (Amp-Sulb) may be a viable treatment alternative. The outcomes for critically ill trauma patients with *Acinetobacter* VAP treated with either Amp-Sulb or Imi-Cil were compared retrospectively. A total of 77 episodes in 75 patients were studied. Fourteen patients were treated with Amp-Sulb, and 63 patients were treated with Imi-Cil. Treatment efficacy was similar in the Amp-Sulb and Imi-Cil groups (93% vs. 83%, respectively; $P > .05$). No statistically significant differences between groups were noted with regard to associated mortality, duration of mechanical ventilation, or length of stay in the intensive care unit or hospital. However, adjunctive aminoglycoside therapy was used more often in the Amp-Sulb group. Patients generally received Amp-Sulb because of imipenem resistance. Amp-Sulb was effective in treating a small number of patients with *Acinetobacter* VAP; however, more data are needed.

Ventilator-associated pneumonia (VAP) is a common and severe complication of critical illness that is associated with an increased length of stay in the hospital or intensive care unit and with a high mortality rate [1–5]. *Acinetobacter* species are a common cause of late-onset VAP, which occurs more than 5–7 days after admission to the hospital, and such species are associated with a higher mortality rate than are other bacteria [6, 7]. Imipenem and meropenem, which usually are the agents most active against *Acinetobacter* species, are considered the antibiotics of choice when they are used in combination with aminoglycosides for treatment [1, 8]. However, resistance to imipenem is becoming more common and has recently been reported in up to 11% of *Acinetobacter* isolates [8]. In anticipation of continued increases in resistance, alternatives to the use of carbapenems against *Acinetobacter* species should be studied.

Ampicillin-sulbactam (Amp-Sulb) is one of the few treatments that may retain activity against imipenem-resistant *Acinetobacter* organisms [9]. Amp-Sulb is a somewhat unconventional treatment option, because the β-lactamase inhibitor sulbactam is the agent that is active against *Acinetobacter* species [9]. To our knowledge, only a single case series report has described the use of Amp-Sulb for the treatment of clinical *Acinetobacter* pneumonia [9]. In that report, Amp-Sulb was found to be...
effective; however, the data were limited by the diagnostic techniques used and by the lack of a comparison group. More data are needed to determine whether Amp-Sulb is a viable option for the treatment of Acinetobacter pneumonia. The purpose of this study was to compare the outcomes for patients with Acinetobacter VAP treated with Amp-Sulb versus imipenem-cilastatin (Imi-Cil).

PATIENTS AND METHODS

Patients who were admitted to the intensive care unit of a level I trauma center (Presley Memorial Trauma Center, Memphis, TN) from January 1997 through November 2000 were the subjects of this retrospective study. Patients with Acinetobacter VAP were identified using an existing database of information on patients in the study center who had pneumonia. Identification of organisms was done by the staff of the hospital microbiology laboratory, by use of the Vitek system (bioMérieux). All isolates were identified as Acinetobacter baumannii; however, because of the limitations of automated identification of this organism, throughout the remainder of the present report, we will refer to the species by its genus name only. The antimicrobial susceptibility of Acinetobacter isolates was determined by the hospital microbiology laboratory staff, by use of a disk-diffusion method (Becton Dickinson Microbiology Systems), and it was interpreted by use of the guidelines of the National Committee for Clinical Laboratory Standards [10].

All patients received mechanical ventilation for >5 days before VAP developed. Diagnosis of VAP required the presence of the following criteria: fever, leukocytosis or leukopenia (WBC count, >10,000 or <4000 cells/mm³; or >10% bands), macroscopically purulent sputum, a new or changing infiltrate observed on a chest radiograph, and quantitative cultures of a bronchoalveolar lavage (BAL) specimen yielding $10^5$ cfu/mL. Follow-up BAL was performed, as clinically indicated, to exclude persistent or new episodes of VAP.

Empiric antibiotic therapy was initiated immediately after each diagnostic BAL was performed, and the type of therapy given was based on the day of hospitalization when BAL was performed. Amp-Sulb was administered if BAL was performed during the first 7 days of hospitalization. An antipseudomonal cephalosporin (cefepime or ceftazidime) and vancomycin were used if BAL was performed >7 days after hospitalization began. Empiric antibiotic therapy was changed to appropriate definitive therapy, as needed, on the basis of the results of culture and sensitivity testing. The choice of definitive therapy was made at the discretion of the attending physician, but Imi-Cil generally was used for imipenem-susceptible Acinetobacter isolates. Amp-Sulb generally was used for isolates with intermediate or full resistance to imipenem. Use of combination antimicrobial therapy was done at the discretion of the attending physician but was not routine.

Patient outcomes were defined as either “successful treatment” or “treatment failure.” Successful treatment outcomes were further defined as “clinical success” or “microbiologic success.” Clinical success was defined by a lessening of the signs and symptoms of Acinetobacter VAP, which allowed for discontinuation of antimicrobial therapy and for discharge of the patient from the hospital. No follow-up culture of a BAL specimen was performed. Patients who had resolution of signs and symptoms of Acinetobacter VAP but who later died of an unrelated event were considered to have clinical success. Microbiologic success was defined by the eradication or suppression of Acinetobacter organisms (to $1<10^3$ cfu/mL), as noted after follow-up BAL was performed, in addition to the presence of criteria for clinical success.

Treatment failure outcomes were further defined as “clinical failure,” “microbiologic failure,” or “microbiologic failure only.” Clinical failure was defined either by (1) death that was likely due to Acinetobacter VAP, or (2) persistence of signs and symptoms of VAP for >5 days, which necessitated a change in antibiotic therapy. Microbiologic failure was defined by persistence of Acinetobacter organisms ($10^5$ cfu/mL) on a follow-up culture of a BAL specimen, in addition to the presence of criteria for clinical failure. Microbiologic failure only was defined by persistence of Acinetobacter organisms ($10^5$ cfu/mL) on a follow-up culture of a BAL specimen, improvement in the patient’s clinical condition, and discharge of the patient from the hospital.

There was no category for treatment that produced microbiologic success only. Such a classification would have defined the outcome for a patient who had eradication or suppression of Acinetobacter organisms noted on a follow-up culture of a BAL specimen but who died as a result of the same episode of VAP. For such a patient, clinical failure would have been considered the outcome. Patients were considered unevaluable if they died of an unrelated event while receiving therapy for Acinetobacter VAP.

Discrete variables were compared between groups by use of Fisher’s exact test or the χ² statistic, as appropriate. Continuous variables were compared using Student’s t-test. A P value of <.05 was considered statistically significant.

RESULTS

The clinical characteristics of patients with Acinetobacter VAP treated with Amp-Sulb or Imi-Cil are summarized in table 1. A total of 77 episodes of Acinetobacter VAP occurred in 75 patients. Six patients who had Acinetobacter VAP treated with cefepime (2 patients), ciprofloxacin (2 patients), ceftazidime (1 patient), or trimethoprim-sulfamethoxazole (1 patient) were
not included in the study. In addition, 5 patients who received Imi-Cil were considered unevaluable because they died of unrelated causes (e.g., progression of traumatic brain injury and aortic dissection) while receiving therapy for Acinetobacter VAP. Fourteen patients with Acinetobacter VAP were treated with Amp-Sulb, and 63 patients were treated with Imi-Cil. One patient treated with meropenem was included in the Imi-Cil group. The baseline characteristics of the patients in the 2 treatment groups were statistically similar; however, there was a higher incidence of severe traumatic brain injury among patients in the Imi-Cil group.

Two patients had a second, independent episode of Acinetobacter VAP occur later in the course of their hospitalization. These second episodes were treated as independent events because of the large interval (14 and 27 days) between the end of treatment of the first episode and the onset of the second episode. For each of these patients, a first episode of VAP due to imipenem-susceptible Acinetobacter organisms was successfully treated with Imi-Cil, but a subsequent episode of VAP due to imipenem-resistant Acinetobacter organisms was treated with Amp-Sulb, which resulted in 1 treatment success and 1 treatment failure.

The clinical outcomes for patients treated with Amp-Sulb versus Imi-Cil are summarized in table 2. The percentage of successfully treated VAP episodes was similar in the 2 groups (93% for the Amp-Sulb group vs. 83% for the Imi-Cil group; $P > .05$). All clinical failures were the result of death due to the episode of VAP studied. Performance of follow-up cultures of BAL specimens was relatively common (50% of the Amp-Sulb group vs. 32% of the Imi-Cil group; $P > .05$), with persistence of Acinetobacter VAP seen in 0 of 7 patients in the Amp-Sulb group and in 6 of 20 patients in the Imi-Cil group ($P = .27$). No differences were seen in morbidity outcomes; however, statistical trends toward a longer stay in the intensive care unit ($P = .097$) and a longer hospital stay ($P = .07$) were seen in the Amp-Sulb group. Overall mortality was not statistically different between groups and was related to Acinetobacter VAP in all but 3 patients in the Imi-Cil group. For these patients, the cause of death was progression of traumatic brain injury (2 patients) and acute myocardial infarction (1 patient). Patients in the Amp-Sulb group were more likely to have been treated with combination therapy ($P = .01$). Overall, adjunctive antibiotic agents included aminoglycosides in 18 patients (aminoglycosides in 15 and tobramycin in 3) and ciprofloxacin in 1 patient. Outcomes for patients who received combination therapy versus monotherapy were compared within each treatment group as well as within the entire patient population. For all comparisons, clinical outcomes ($P > .05$) for patients who received monotherapy were similar to those for patients who received combination therapy.

Regarding antimicrobial susceptibility, all episodes of VAP in the Imi-Cil group were caused by isolates that were fully susceptible to Imi-Cil. Of the 14 VAP episodes that were treated with Amp-Sulb, 7 were fully resistant to Imi-Cil, 5 were intermediate resistant, and 2 were susceptible. All isolates in both groups were susceptible to Amp-Sulb. The 2 patients in the Amp-Sulb group who had imipenem-susceptible isolates received definitive Amp-Sulb therapy because they had previously received Amp-Sulb as empiric therapy for VAP. Isolates recovered from patients who were receiving combination therapy were susceptible to both antibiotics used.

**DISCUSSION**

The results of the present study show that Amp-Sulb appears to have been effective for the treatment of Acinetobacter VAP in a small group of critically ill trauma patients. These results are encouraging because of the potential for high mortality in association with Acinetobacter VAP [7], increasing imipenem-resistance among Acinetobacter isolates [8], and a lack of treatment options [9]. The strengths of these data include the robust diagnostic criteria for VAP and the high percentage of patients who had treatment success or failure confirmed by follow-up culture of a BAL specimen. Trends toward longer stays in the intensive care unit or hospital were observed in the Amp-Sulb group; however, these results are thought to have been because of a later onset of VAP (20 days vs. 14 days; $P = .07$) and not
Table 2. Clinical outcomes for patients treated with ampicillin-sulbactam (Amp-Sulb) versus imipenem-cilastatin (Imi-Cil).

<table>
<thead>
<tr>
<th>Outcome or variable affecting outcome</th>
<th>Patients treated with Amp-Sulb (n = 14)</th>
<th>Patients treated with Imi-Cil (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical success</td>
<td>6 (43)</td>
<td>35 (56)</td>
</tr>
<tr>
<td>Clinical and microbiologic success</td>
<td>7 (50)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (93)</td>
<td>52 (83)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical failure</td>
<td>1 (7)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Clinical and microbiologic failure</td>
<td>0 (0)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Microbiologic failure only</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>1 (7)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Received combination therapy</td>
<td>7 (50)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, mean days ± SD</td>
<td>33 ± 19</td>
<td>28 ± 18</td>
</tr>
<tr>
<td>Duration of intensive care unit stay, mean days ± SD</td>
<td>39 ± 17</td>
<td>31 ± 17</td>
</tr>
<tr>
<td>Duration of hospital stay, mean days ± SD</td>
<td>50 ± 17</td>
<td>42 ± 20</td>
</tr>
<tr>
<td>Deathb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to all causes</td>
<td>1 (7)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Due to all causes at day 14 after VAP development</td>
<td>0 (0)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Due to all causes at day 28 after VAP development</td>
<td>0 (0)</td>
<td>11 (17)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless indicated otherwise. For all comparisons between groups, \( P > .05 \), except for variable "received combination therapy" \( (P = .01) \).

a For outcome definitions, see the Patients and Methods section of the text.

b All but 3 deaths that occurred among patients in the Imi-Cil group were related to *Acinetobacter* VAP.

because of a difference in the efficacy of Amp-Sulb versus that of Imi-Cil.

The potential limitations of the present study include its retrospective design, the small number of patients in the Amp-Sulb group, and the potential differences between groups that may favor the use of Amp-Sulb. Although no statistically significant differences between the study populations were found, the patients in the Imi-Cil group may have been more severely ill, as was evidenced by the higher incidence of traumatic brain injury and the slightly higher mean Acute Physiology and Chronic Health Evaluation II score observed for such patients. Another important difference was the higher percentage of patients in the Amp-Sulb group who were receiving combination therapy. This disparity is not thought to have affected the results, because no differences in outcome were found for patients who were receiving combination therapy versus those who were receiving monotherapy. Similarly, combination therapy generally has not been shown to be more effective than monotherapy for the treatment of serious gram-negative infections [11–15], and it may even be associated with increased mortality rates among trauma patients [16]. The risks of aminoglycoside-induced nephrotoxicity and the increased costs of drug acquisition and monitoring are other reasons why combination therapy was not universally used.

Nonetheless, one-half of the patients in the Amp-Sulb group did receive concomitant aminoglycoside therapy. A conservative interpretation of the results of this study suggests that, until more data are known, it seems prudent to add an aminoglycoside to Amp-Sulb for the treatment of *Acinetobacter* VAP. Indeed, current guidelines recommend using combination therapy for *Acinetobacter* VAP, on the basis of the in vitro synergy between \( \beta \)-lactams and aminoglycosides [1].

In the only previous report of the use of Amp-Sulb for the treatment of *Acinetobacter* pneumonia, Urban et al. [9] reported a case series that showed clinical improvement in 8 of 8 patients with pneumonia or tracheobronchitis. As in the present study, Amp-Sulb was used because of imipenem resistance. The present study adds to the previously published data in 2 ways. First, the method for diagnosing VAP included evaluation of quantitative cultures of BAL specimens obtained from all patients, compared with such evaluation being done for only 2 of 8 patients in the previous report [9]. This is important because cultures of BAL specimens are superior to conventional diagnostic techniques for the differentiation of true pneumonia from bacterial colonization or a systemic inflammatory state [6, 17]. Second, the present study included a comparison group that was treated with the standard therapy, a carbapenem.

Small reports also exist that describe the use of Amp-Sulb for the treatment of other serious *Acinetobacter* infections.
Jiménez-Mejías et al. [18] reported that Amp-Sulb was successful in the treatment of 6 of 8 cases of meningitis caused by imipenem-resistant isolates. However, it should be noted that the susceptibility testing methods used by these investigators, as well as those used by Urban et al. [9], may falsely report imipenem resistance. Nonetheless, Amp-Sulb was found to be effective in both studies, regardless of whether the isolates were truly resistant to imipenem. Likewise, Cisneros et al. [19] showed that Amp-Sulb had an efficacy similar to that of Imi-Cil in patients with Acinetobacter bacteremia. Jellison et al. [20] and Corbella et al. [21] both took a somewhat different approach by using Amp-Sulb as an “imipenen-sparing” agent in patients with bacteremia due to imipenem-susceptible Acinetobacter organisms. Amp-Sulb was found to have an efficacy similar to that of Imi-Cil in both studies; however, many of the patients evaluated were not critically ill. Such an approach may be prudent because carbapenem restriction, when used as part of an infection-control program, may help decrease the incidence of Acinetobacter infections [22].

Other than Amp-Sulb, few options exist for the treatment of imipenem-resistant Acinetobacter pneumonia. To date, the only other agent that has been studied clinically is colistin [23], which had poor results in 14 patients (response rate, ~25%). Meropenem, cephalosporins, and extended-spectrum penicillins are not typically active against imipenem-resistant Acinetobacter organisms [9, 24]. Tetracyclines demonstrate good in vitro susceptibility and in vivo success in the treatment of experimentally induced cases of Acinetobacter pneumonia; however, these drugs are bacteriostatic, and clinical data are lacking [8, 25]. Another potential option, aminoglycoside monotherapy, is not suitable for the treatment of severe pneumonia because of poor pulmonary penetration and poor clinical outcomes [1, 11].

In conclusion, a small group of patients who received Amp-Sulb for the treatment of Acinetobacter VAP had outcomes similar to those for patients treated with Imi-Cil. Amp-Sulb was used primarily because of full or intermediate resistance to imipenem. Because of the large number of patients in the Amp-Sulb group who were receiving combination therapy, an adjunctive aminoglycoside should be considered if Amp-Sulb is used for the treatment of Acinetobacter VAP. Further data are needed to fully determine the role of Amp-Sulb in the treatment of Acinetobacter VAP.

References


