Treatment of Multidrug-Resistant
Acinetobacter baumannii Ventilator-Associated Pneumonia (VAP)
with Intravenous Colistin: A Comparison with Imipenem-Susceptible VAP

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(See the editorial commentary by Kollef on pages 1119–21.)

We prospectively evaluated the efficacy and toxicity of intravenously administered colistin in 35 episodes of ventilator-associated pneumonia (VAP) due to multidrug-resistant Acinetobacter baumannii. Microbiological diagnosis was performed with use of quantitative culture. In 21 patients, the episodes were caused by a strain susceptible exclusively to colistin (the CO group) and were all treated with this antimicrobial intravenously. In 14 patients, the episodes were caused by strains that remained susceptible to imipenem and were treated with imipenem-cilastatin (the IM group). Acute Physiology and Chronic Health Evaluation II scores at the time of admission and Sequential Organ Failure Assessment scores at time of diagnosis were similar in both groups. VAP was considered clinically cured in 57% of cases in both groups. In-hospital mortality rates were 61.9% in the CO group and 64.2% in the IM group, and the VAP-related mortality rates were 38% and 35.7%, respectively. Four patients in the CO group and 6 in the IM group developed renal failure. Neurophysiological evaluation was performed during 12 episodes in the CO group, but it revealed no signs of neuromuscular blockade. Intravenous colistin appears to be a safe and effective alternative to imipenem for the management of VAP due to carbapenem-resistant strains of A. baumannii.

Ventilator-associated pneumonia (VAP) due to a multidrug-resistant microorganism is one of the most dreadful complications that occurs in the critical care setting. Several studies have suggested that the occurrence of VAP increases the risk of death in critically ill patients, especially when the episode of pneumonia is due to a multidrug-resistant pathogen [1, 2].

Acinetobacter baumannii is a nonfermenting, gram-negative, aerobic cocobacillus found extensively in natural environments that has assumed an increasing importance in nosocomial infections in general and in VAP in particular [1, 3, 4]. This microorganism is characterized by the rapid development of resistance to the majority of antimicrobials, including aminoglycosides, fluoroquinolones, and carbapenems [5]. The virulence of this pathogen is enhanced by the frequent appearance of multiple-antimicrobial resistance, which can make therapy extremely difficult.

Carbapenems are currently considered the antimicrobials of choice, although epidemic outbreaks and
endemic situations involving carbapenem-resistant *Acinetobacter* species have been described elsewhere [6, 7]. In this situation, alternative options are scarce, and only colistin (polymyxin E) is highly active against these multidrug-resistant strains. Intravenous colistin was used in the 1960s and 1970s, but its use was abandoned because of concerns about side effects, mainly nephrotoxicity and neurotoxicity. Although experience with systemic polymyxin is limited, it has been effective for clearing bacteremia and curing infections of diverse localizations [8]. However, its effectiveness for treatment of pneumonia has been questioned because of its inadequate penetration into the pulmonary parenchyma. To the best of our knowledge, no previous study has assessed the use of this drug for treatment of very serious infections, such as VAP. The aims of this study were to evaluate the efficacy and safety of intravenously administered colistin as therapy for VAP caused by multidrug-resistant *A. baumannii*, in comparison with cases treated with imipenem- cilastatin, the conventional therapy for this infection.

**METHODS**

This prospective study was performed at the intensive care unit (ICU) of the Hospital Virgen del Rocío (Seville, Spain), a 40-bed medical-surgical unit in a large urban hospital with teaching accreditation. This ICU is divided into 6 units according to the types of patients admitted. This study was performed in an 8-bed polyclinic unit where patients with serious infections are preferentially admitted.

**Design.** All episodes of VAP caused by *A. baumannii* during the study period were included. Diagnosis of pneumonia required radiographic appearance of a new and persistent pulmonary infiltrate and ≥2 of the following criteria: temperature of ≥38°C or ≤35°C, leukocytosis (leukocyte count, >12,000 cells/mm³) or leukopenia (leukocyte count, <4000 cells/mm³), and the presence of purulent bronchial secretions. Pneumonia was considered to be ventilator-associated when onset occurred 48 h after the initiation of mechanical ventilation and was judged not to have been incubating before the initiation of mechanical ventilation.

Microbiological documentation of every episode of VAP was made by examination of a protected specimen brush (PSB) or a quantitative tracheal aspirate. To be accepted for culture, tracheal aspirates were required to have >25 neutrophils present on a Gram stain and ≤10 epithelial cells per high-power field. The etiologic agent of VAP was considered to have been determined if the PSB yielded >10⁵ cfu/mL or if the tracheal aspirate culture yielded >10⁶ cfu/mL. Episodes of VAP in which *A. baumannii* was isolated in conjunction with another microorganism were also included in the study. Patients who had *A. baumannii* isolated but whose cases did not meet the criteria of infection were considered to be noninfected and were not treated with antibiotics [9].

The hospital’s microbiology laboratory determined the antimicrobial susceptibilities for isolates by the microdilution method (MicroScan system; Baxter Health Care). Results were interpreted according to breakpoints defined by the NCCLS [10]. Imipenem resistance was defined as an MIC of ≥16 µg/mL.

The severity of illness was evaluated by the APACHE II score on the basis of the worst data point of the first 24 h in the ICU [11]. Organ failure and severity of multiple-organ dysfunction syndrome (MODS) were evaluated using the Sequential Organ Failure Assessment (SOFA) scale at the time of admission to the ICU and during the subsequent clinical course [12]. The clinical presentation of the VAP was classified as sepsis, severe sepsis, or septic shock [13].

The following variables were recorded for every patient enrolled in this protocol: age, sex, dates of admission and discharge from the ICU and the hospital, the presence of chronic organ-function insufficiencies (as defined by the APACHE II scale), and the presence of other comorbidities (i.e., alcoholism, smoking habit, diabetes mellitus, noncured malignancy, and previous surgery) [14].

Empirical therapy was considered to be adequate if ≥1 effective antimicrobial was included in the initial antibiotic regimen. After culture results were known, the antimicrobial regimen was maintained or adapted on the basis of the results of susceptibility testing.

**Administration of antimicrobials.** Episodes of VAP due to *A. baumannii* that were susceptible to carbapenems were treated with imipenem-cilastatin at dosages of 2–3 g per day. The attending physician, on the basis of the susceptibilities provided by the microbiology laboratory, had the option to add a second antibiotic to the regimen.

Colistin sulphomethate sodium (Bellon; Rhône-Poulenc Rorer) was administered intravenously only for episodes of VAP caused by strains that were susceptible exclusively to colistin. The dosage of colistin was adjusted for renal function. For patients with normal renal function, the dosage was 2.5–5.0 mg/kg per day divided into 3 doses. If the serum creatinine level was 1.2–1.5 mg/dL, the dosage administered was 2.5–3.8 mg/kg per day divided into 2 doses. If the serum creatinine level was 1.6–2.5 mg/dL, the dosage was 2 mg/kg per day in 1 dose, whereas, if the serum creatinine level was ≥2.6 mg/mL, the dosage was 1.5 mg/kg every 48 h.

**Evaluation of outcome.** The physician in charge of the patient decided on the duration of treatment. The primary outcome measure was the clinical cure of VAP. Infection was considered to have been cured if there was remission of pneumonia-related symptoms. As secondary end points, we evaluated microbiological cure, VAP-related mortality, and crude
mortality. VAP-related mortality was defined as death that occurred during the treatment period, death that occurred when the signs of pneumonia remained, and death due to septic shock.

If the patient was still undergoing intubation at the end of antimicrobial therapy, tracheal aspirates were examined to confirm the eradication of the microorganism. Microbiological eradication was considered to have occurred if the aspirate culture was negative for *A. baumannii*. If the culture result was positive but the patient was clinically cured, treatment was stopped, and the case was considered to be a microbiological failure.

Renal function was monitored by daily measurement of the serum creatinine level. The creatinine clearance rate was calculated using the equation of Cockcroft and Gault [15]. In patients with normal renal function (serum creatinine level, <1.2 mg/dL, or 110 \( \mu M \)), renal failure was defined as a serum creatinine value of >2 mg/dL (171 \( \mu M \)), as a reduction in the calculated creatinine clearance of 50% relative to the value at antibiotic therapy initiation, or as a decline in renal function that resulted in the need for renal replacement therapy (i.e., intermittent hemodialysis or continuous venovenous hemofiltration). In patients with preexisting renal dysfunction, renal failure was defined as an increase of \( \geq 50\% \) of the baseline creatinine level, as a reduction in the calculated creatinine clearance of 50% relative to the value at antibiotic therapy initiation, or as a decline in renal function that resulted in the need for renal replacement therapy. The decision to initiate renal replacement therapy was made by the physician in charge of the patient and always as part of the management of acute renal failure. Total bilirubin levels and platelet counts were determined daily to monitor liver function and coagulation.

An electrophysiological study (EPS) was performed during the last days of antibiotic therapy to detect the presence of neuromuscular transmission blockade and critical illness polyneuropathy (CIP) [16]. The study included measurement of sensory and motor nerve conduction; calculation of conduction velocities, amplitude, and shape of the compound muscle ac-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient data, by treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colistin ((n = 21))</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>56.9 ± 13.1</td>
</tr>
<tr>
<td>Male sex</td>
<td>14 (66.6)</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
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<tr>
<td>Sepsis</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>3 (14.2)</td>
</tr>
<tr>
<td>Neurological failure</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Surgical patients</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
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<tr>
<td>Diabetes mellitus</td>
<td>4 (19)</td>
</tr>
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<td>Immunosuppression</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
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</tr>
<tr>
<td>Prior receipt of antibiotic therapy</td>
<td>20 (95.2)</td>
</tr>
<tr>
<td>Prior receipt of imipenem</td>
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</tr>
<tr>
<td>Duration of imipenem therapy, range in days</td>
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</tr>
<tr>
<td>Presence of bacteremia</td>
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</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (19.1)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td>Adequate empirical therapy received</td>
<td>2 (9.5)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. \( P \) values were not significant for all variables except adequate empirical therapy received, for which \( P = .001 \). COPD, chronic obstructive pulmonary disease.
tion potential (CMAP); measurement of the distal latencies; and repetitive nerve stimulation at 3 Hz and 20 Hz, to exclude neuromuscular transmission defects. Signs of denervation were also sought using needle electromyography. All of these studies were performed at bedside with a transportable apparatus (Nic- olet Compass Portabook; Nicolet Biomedical).

Statistical analysis. Quantitative variables are expressed as mean values ± SDs. Categorical variables were compared using χ² test or Fisher’s exact test, as appropriate. Continuous variables were compared using Student’s t test. Statistical significance was defined as P<.05.

RESULTS

From January 1997 through June 2001, 1205 consecutive patients were prospectively evaluated. Seventy-three episodes of VAP were diagnosed in 69 patients.

Thirty-seven episodes of VAP were due to A. baumannii. Two cases were treated with sulbactam and were excluded from this analysis. Thus, 35 episodes of VAP due to A. baumannii were investigated: in 21 patients, the infections were caused by multidrug-resistant strains susceptible exclusively to colistin and were treated with this antimicrobial (the CO group), and, in 14 patients, the infections were caused by strains susceptible to imipenem-cilastatin and were treated with this antibiotic (the IM group). In 6 patients in the IM group, a second antimicrobial was added to the treatment regimen, as follows: sulbactam (for 3 patients), amikacin (for 2), and tobramycin (for 1). Primary diagnoses, comorbidities, and clinical characteristics of patients with these episodes are listed in table 1.

The mean ICU stay before diagnosis of VAP was 10.1 ± 18.5 days for the CO group and 6.1 ± 6 days for the IM group (P = .30). Severity of illness at time of admission to the ICU was similar: the APACHE II score was 19.6 ± 7.2 in the CO group and 20.5 ± 7 in the IM group (P = .72). There was no significant difference in the severity of the process, as evaluated by the SOFA scale on the day of the VAP diagnosis (10 ± 4.9 and 11.7 ± 6.6, respectively; P = .44).

In 2 cases from the CO group, A. baumannii was isolated with another microorganism (P. aeruginosa in one case and Serratia marcescens in the other); for treatment of these episodes of infection, a second antimicrobial was added to the regimen (pipercillin-tazobactam and ciprofloxacin, respectively). Twelve patients (57%) ended therapy with colistin because VAP was judged to be clinically cured. We tested 9 of these subjects for microbiological eradication of infection at the end of therapy. Culture results were negative for 6 patients (66.7%), and they remained positive for 3 patients, although the patients were clinically cured; these latter cases were considered to be microbiological failures. For these 12 patients, the mean duration of treatment was 14.7 ± 4.1 days (range, 10–21 days). No polymyxin-resistant isolates were detected during the study period.

In the IM group, 8 patients (57%) ended antibiotic therapy because VAP was judged to be cured, with a mean treatment duration of 13.2 ± 4.2 days (range, 10–21 days). Testing for microbiological eradication of infection was done for 4 patients. Culture results were negative only for 2 patients.

Length of stay in the ICU was similar for both groups: 32.6 ± 20.5 days for the CO group and 32 ± 25 days for the IM group (P = .10). The length of hospital stay was also similar, at 45.2 ± 30.7 days for the former and 53.9 ± 50 days for the latter (P = .55). The crude in-hospital mortality rates were 61.9% (13 of 21 patients) in the CO group (11 patients died in the ICU) and 64.2% (9 of 14 patients) in the IM group (7 subjects died in the ICU; P = not significant [NS]). The corresponding figures for the VAP-related mortality rate were 38% (8 of 21 patients) and 35.7% (5 of 14 patients), respectively (P = NS).

At the initiation of antimicrobial therapy for VAP, serum creatinine levels were 1.91 ± 1.65 mg/dL in the CO group and 2.27 ± 1.36 mg/dL in the IM group (P = .10). After receipt of treatment with colistin or imipenem, the highest creatinine levels were 2.1 ± 1.7 mg/dL in the CO group and 3.2 ± 2.1 mg/dL in the IM group (P = .1). Five patients in the CO group (24%) and 6 patients in the IM group (42%) presented with renal failure (P > .05); 3 patients in each group required dialysis. The presence of renal toxicity did not provoke discontinuation of treatment. Table 2 describes patients who developed renal failure case by case. An insignificant decrease in the platelet count and an insignificant increase in the serum bilirubin level were observed in both groups.

Twelve patients in the CO group underwent neurophysiological evaluation. Ten of the 12 patients who had finished therapy with colistin underwent neurophysiological evaluation; for the other 2 patients, electrophysiological study was not performed because of technical problems. Of the other 9 patients in the CO group, who died before the treatment had finished, the neurophysiological evaluation was performed for only 2 who had received colistin for ≥ 7 days. Among these 12 patients, no evidence of neuromuscular junction blockade was observed, whereas 6 patients (50%) exhibited typical features consistent with CIP. Two patients in the IM group had CIP diagnosed on the basis of the results of neurophysiological studies, which were performed for only 5 subjects (40%).

DISCUSSION

The most notable finding of the present study is that intravenous colistin is at least as effective as imipenem-cilastatin, the conventional treatment of choice for VAP caused by multidrug-resistant strains of A. baumannii. In addition, nephro-
Table 2. Case-by-case description of patients with ventilator-associated pneumonia (VAP) who developed renal failure.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
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<tbody>
<tr>
<td>Age, years</td>
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<td>57</td>
<td>70</td>
<td>35</td>
<td>51</td>
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<td>79</td>
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<td>Ideal body weight, kg</td>
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<td>80</td>
<td>45</td>
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<td>90</td>
<td>75</td>
<td>75</td>
<td>72</td>
<td>82</td>
</tr>
<tr>
<td>Treatment received</td>
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<td>CO</td>
<td>CO</td>
<td>CO</td>
<td>CO</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
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<tr>
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<td>Septic shock</td>
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<tr>
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<td>Yes (5)</td>
<td>Yes (2)</td>
<td>Yes (3)</td>
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<td>Yes (0)</td>
<td>Yes (1)</td>
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<tr>
<td>Creatinine clearance&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>26</td>
<td>82</td>
<td>37.5</td>
<td>100</td>
<td>41</td>
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<td>47</td>
<td>43</td>
<td>32</td>
<td>26</td>
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<tr>
<td>Baseline</td>
<td>17</td>
<td>20</td>
<td>26</td>
<td>14</td>
<td>47.5</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>23</td>
<td>26</td>
<td>13</td>
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<tr>
<td>Day of nadir&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>2</td>
<td>10</td>
<td>7</td>
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<td>1</td>
<td>2</td>
<td>2</td>
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<td>3</td>
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<td>None</td>
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<td>—</td>
<td>HD</td>
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<td>—</td>
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<tr>
<td>Renal function recovered</td>
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<td>No</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Clinical cure achieved</td>
<td>No</td>
<td>No</td>
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<td>No</td>
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</table>

**NOTE.** AM, aminoglycosides; AMP, amphotericin B; CO, colistin; CVVHF, continuous venovenous hemofiltration; HD, intermittent hemodialysis; ICA, iodinated contrast agents; IM, imipenem-cilastatin; VAN, vancomycin.

<sup>a</sup> Days after the initiation of treatment for VAP.

<sup>b</sup> Creatinine clearance was calculated using the equation of Cockcroft and Gault [15], with adjustment for sex, as follows: 

\[ \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine concentration in mg/dL}} \]
toxicity and neurotoxicity were not observed, although these adverse events have been reported with the systemic use of colistin.

A. baumannii is a prevalent nosocomial pathogen, especially in patients who undergo mechanical ventilation. Nowadays, imipenem therapy is the “gold standard” for pneumonia due to A. baumannii [17–19]. However, because this microorganism rapidly develops resistance to the majority of antibiotics, including carbapenems, the management of VAP caused by multidrug-resistant A. baumannii is an ongoing challenge. Sulfactam therapy is another option that has recently been validated in a study that enrolled exclusively patients with VAP [20]. Nevertheless, the majority of the isolates in our study were resistant to sulfactam, which has been a common finding in other studies [21, 22].

Actually, the polymyxins remain an exception with regard to the emergence of resistance to all available antibiotics [21]. Nevertheless, use of these agents is restricted, because there are limited data on their efficacy and their potential associated toxicity. Moreover, the treatment of pulmonary infection with polymyxins is also discouraged, because these agents have inadequate penetration into the lung parenchyma [19].

Our results show that, in terms of clinical response, the success rate was similar for both arms of treatment. The outcome for patients treated with colistin did not differ from the outcome for patients treated with imipenem; VAP-related mortality and crude mortality rates were almost identical. These figures are higher than mortality data reported by previous clinical trials that involved critically ill patients with VAP [23, 24]. However, when cases of VAP caused by A. baumannii or other multidrug-resistant pathogens were evaluated, mortality rates were similar to those in our study [1, 25, 26]. Moreover, as in previous studies [24, 27], bacteriological eradication rates were lower than clinical cure rates, although the rates were not significantly different between treatment groups.

Levin et al. [8] reported that, for a group of patients treated with intravenous colistin for nosocomial infections caused by multidrug-resistant P. aeruginosa and A. baumannii, the poorest results were observed in cases of pneumonia, compared with other types of infections. Conversely, intravenous colistin was an effective therapy for patients with cystic fibrosis who had exacerbation of acute respiratory infection due to P. aeruginosa [28].

Establishing a definitive diagnosis of VAP is difficult because of the lack of specific clinical and microbiological markers. Moreover, the accurate diagnosis of VAP caused by A. baumannii is especially difficult, given that this pathogen frequently colonizes inanimate surfaces and body fluids [9]. In our series, all patients exhibited overt clinical symptoms and signs of VAP; A. baumannii was always isolated in quantitative cultures, and it was the only pathogen isolated in 33 of the 35 episodes. Moreover, it is noteworthy that 27 of 35 patients developed severe sepsis or septic shock attributable to the pulmonary infection.

It is notable that, in our series, the mortality rates did not differ between treatment groups, although empirical antibiotic therapy was more frequently inadequate in the CO group than it was in the IM group. This is in disagreement with the findings of other studies, which have demonstrated that the appropriateness of the initial antibiotic regimen is a vital factor in determining outcome, although none of these studies have exclusively evaluated VAP caused by A. baumannii [29–31]. We acknowledge that the small number of patients included, the open design of the study, and the lack of randomization are limitations of our study, especially for drawing conclusions about associated mortality.

With regard to adverse effects, our data show that renal failure was not more common in the CO group than in the IM group. We presume that the cases of renal failure were mostly secondary to septic shock and MODS. Although renal failure associated with systemic use of colistin was reported in the 1960s and 1970s [32, 33], recent studies do not corroborate this finding. Although Levin et al. [8] found that 37% of patients developed renal dysfunction, the majority of the cases occurred in patients with preexisting alterations of renal function, the increase in the creatinine level was very slight, and none of the treatment regimens were discontinued because of this adverse event. Intravenous colistin was also well tolerated, with a small incidence of renal dysfunction, which did not give rise to therapy discontinuation in patients with cystic fibrosis and acute respiratory infection [28, 34, 35].

Recent series have found no clinically evident abnormalities in the peripheral nervous system after the systemic use of colistin [8, 28]. With a methodical neurophysiological evaluation, we did not find episodes of neuromuscular blockade, and the incidence of CIP was similar in both treatment groups. In the 1960s, several cases of reversible paralysis associated with the use of polymyxins were reported [32, 36]. Although we cannot rule out the possibility that use of polymyxins could have been responsible for these episodes, we speculate that other possible causes, such as use of muscle relaxants or CIP, could be implicated.

We do not suggest that colistin should be used as first-line therapy for A. baumannii VAP. If the causative strain remains susceptible to carbapenems, they should continue to be the antimicrobials of choice. Certainly, imipenem exhibits greater bactericidal efficacy than does colistin for treatment of pneumonia caused by A. baumannii [37]. However, this does not contradict our results, which show that colistin is a valid option for treating episodes of VAP due to carbapenem-resistant strains. Furthermore, concerns over colistin resistance have been raised, and anecdotal cases of infection with...
polymyxin-resistant strains of *A. baumannii* have been reported [22]. Studies evaluating new therapeutic options against these “panresistant” strains are scarce. In experimental models, synergy between colistin and rifampin has been demonstrated, although this combination has not been tested clinically [38, 39].

In summary, intravenously administered colistin is an effective option for the treatment of VAP caused by multidrug-resistant *A. baumannii*. Colistin therapy yielded good clinical and microbiological success rates, which were similar to those obtained with imipenem–cilastatin. We also found that this drug is safe, and our results do not support the current widespread concern about colistin and the reluctance to administer colistin intravenously.

**References**


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