Intravenous Colistin as Therapy for Nosocomial Infections Caused by Multidrug-Resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

Anna S. Levin, Antonio A. Barone, Juliana Penço, Marcio V. Santos, Ivan S. Marinho, Erico A. G. Arruda, Edison I. Manrique, and Silvia F. Costa

Sixty nosocomial infections caused by *Pseudomonas aeruginosa* and *Acinetobacter baumannii* resistant to aminoglycosides, cephalosporins, quinolones, penicillins, monobactams, and imipenem were treated with colistin (one patient had two infections that are included as two different cases). The infections were pneumonia (33% of patients), urinary tract infection (20%), primary bloodstream infection (15%), central nervous system infection (8%), peritonitis (7%), catheter-related infection (7%), and otitis media (2%). A good outcome occurred for 35 patients (58%), and three patients died within the first 48 hours of treatment. The poorest results were observed in cases of pneumonia: only five (25%) of 20 had a good outcome. A good outcome occurred for four of five patients with central nervous system infections, although no intrathecal treatment was given. The main adverse effect of treatment was renal failure; 27% of patients with initially normal renal function had renal failure, and renal function worsened in 58% of patients with abnormal baseline creatinine levels. Colistin may be a good therapeutic option for the treatment of severe infections caused by multidrug-resistant *P. aeruginosa* and *A. baumannii*.

The emergence of multidrug-resistant gram-negative organisms causing nosocomial infections is a growing problem worldwide [1, 2]. In our hospital, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* resistant to all commercially available antimicrobial drugs have been important causes of infections acquired mainly in intensive care units [3, 4]. Hospital das Clínicas is a 2,200-bed tertiary care hospital attached to the University of São Paulo (São Paulo, Brazil). Infection due to multidrug-resistant *A. baumannii* has been a problem since 1993 when an outbreak occurred. All isolates were one clone, and the outbreak was initially controlled; however, clusters of cases have been occurring since then [3]. Multidrug-resistant *P. aeruginosa* infections have been investigated in our hospital; four different typing methods have revealed that these infections are caused by multiple clones (authors’ unpublished data).

Colistin, a polymyxin, was used from the 1960s to the early 1980s. Because of toxicity considerations (mainly nephrotoxicity, neuromuscular blockade, and neurotoxicity), its systemic use has been all but abandoned [5, 6]. The mechanism of action of colistin is not very clear; however, it is believed that its bactericidal activity is due to a detergent effect on the cell membrane [6, 7]. In vitro colistin has shown excellent activity against a variety of gram-negative rods including those resistant to other classes of antimicrobials (penicillins, cephalosporins, quinolones, aminoglycosides, and carbapenems), although very little activity has been demonstrated against *Serratia* species, *Providencia* species, and *Proteus mirabilis* [5, 6].

All the multidrug-resistant isolates of *P. aeruginosa* and *A. baumannii* in our hospital were susceptible in vitro to colistin. The objective of this study was to evaluate the use of colistin in the treatment of infections caused by these multidrug-resistant microorganisms.

**Methods**

Patients with infections caused by multidrug-resistant *P. aeruginosa* or *A. baumannii* who were hospitalized during the period from January 1993 to December 1994 were treated with intravenous colistin (colistimethate sodium, Parke-Davis, Morris Plains, NJ; or colistin sodium methane sulfonate, Bellon, Rhône-Poulenc Rorer, Neuilly sur Seine, France). All infections were diagnosed according to the criteria of the Centers for Disease Control and Prevention [8]. On the basis of their etiologies, the cases were considered confirmed or probable. A confirmed case was defined as a nosocomial infection with a culture of a specimen obtained from a usually sterile site (e.g., blood or CSF) that was positive for *P. aeruginosa* or *A. baumannii*. A probable case was defined as an infection whose etiology could not be confirmed because the positive culture was of a specimen from a usually nonsterile site for which there was no evidence of another cause.

Identification of *P. aeruginosa* and *A. baumannii* was performed by using classic biochemical methods [9, 10]. Susceptibility testing was done according to an automated method (bioMérieux Vitek, Hazelwood, MO); susceptibility to various antimicrobials (gram-negative susceptibility cards PA and GD) was analyzed. Susceptibility to colistin was tested by means of the disk diffusion method with use of a 10-μg colistin disk.
(Oxoid, Basingstoke, Hants, England), and isolates were considered susceptible if the inhibition zone was \( \geq 11 \) mm.

Only infections for which there was no other therapeutic option were treated with colistin. Patients were evaluated at the beginning of treatment for the following data: age, gender, identity of infectious agent, and severity of clinical condition according to the APACHE (Acute Physiological and Chronic Health Evaluation) II scoring system [11]. Patients were followed up until the end of the treatment for outcome that was considered improved or worsened based on clinical criteria, the evaluation of the attending physician, and adverse events.

The patients were treated with 2.5 to 5.0 mg of colistin/kg daily up to a maximum dose of 300 mg, which was divided in two or three doses intravenously. When the patients presented with renal failure, the daily dose was adjusted as follows: serum creatinine level from 1.3 to 1.5 mg/dL, daily dose of 2.5 to 5.0 mg/kg; 1.6 to 2.5 mg/dL, 2.5 mg/kg; and \( \geq 2.5 \) mg/dL, 1.0 to 1.5 mg/kg.

The isolates were resistant to the following antimicrobials on the basis of the MICs: ticarcillin and piperacillin (MIC, \( \geq 64 \) \( \mu \)g/mL), ceftazidime (MIC, \( \geq 64 \) \( \mu \)g/mL), aztreonam (MIC, \( \geq 32 \) \( \mu \)g/mL), gentamicin (MIC, \( \geq 8 \) \( \mu \)g/mL), ciprofloxacin (MIC, \( \geq 4 \) \( \mu \)g/mL), and imipenem (MIC, \( \geq 8 \) \( \mu \)g/mL). The MIC breakpoints for susceptibility according to the National Committee for Clinical Laboratory Standards [12] are as follows: 64 \( \mu \)g of ticarcillin/mL or 64 \( \mu \)g of piperacillin/mL, \( P. \) aeruginosa; 16 \( \mu \)g of piperacillin/mL or 16 \( \mu \)g of ticarcillin/mL, \( A. \) baumannii; 8 \( \mu \)g of ceftazidime/mL, both microorganisms; 8 \( \mu \)g of aztreonam/mL, both microorganisms; 16 \( \mu \)g of amikacin/mL, both microorganisms; 4 \( \mu \)g of gentamicin/mL, both microorganisms; 1 \( \mu \)g of ciprofloxacin/mL, both microorganisms; and 4 \( \mu \)g of imipenem/mL, both microorganisms.

**Results**

Sixty infections in 59 patients were treated with colistin (one patient had two infections that are included as two different cases); 21 (35%) were caused by \( P. \) aeruginosa, and 39 (65%) were caused by \( A. \) baumannii. The mean age \( \pm \) SD of the patients was 42.1 \( \pm \) 21.4 years (range, 2–85 years), and 39 (65%) were male. The specimens from which the microorganisms were isolated are listed in table 1.

The etiology of 42 infections (70%) was confirmed, and 18 cases (30%) were probable.

The underlying diseases in the 59 patients are listed in table 2. The mean APACHE II score \( \pm \) SD was 13.1 \( \pm \) 7.0 (range, 2–34). Thirty-one infections (52%) occurred in intensive care units, 8 (13%) in transplant units, and 21 (35%) in medical or surgical wards. The mean hospital stay before infection \( \pm \) SD was 38.4 \( \pm \) 37.1 days (range, 0–237 days). Fifty-six infections (93%) had been previously treated with other antimicrobials: imipenem, 30 (54%) of the treated cases; aminoglycosides, 20 (36%); ceftazidime, 16 (29%); quinolones, 16 (29%); and third-generation cephalosporins, 15 (27%).

A good outcome occurred in 35 (58%) of the cases. Of the confirmed cases, 28 (67%) had a good outcome, and of the probable cases, seven (39%) had a good outcome. The infections and their outcomes are shown in table 1. In the cases with a good outcome, fever lasted for a mean duration \( \pm \) SD of 5.5 \( \pm \) 5.8 days (range, 0–21 days). Follow-up cultures of specimens from the original positive site were performed in 29 cases; 27 (93%) of these cultures were negative. Death occurred in 22 cases (37%); three of the patients died within the first 48 hours of treatment.

The mean daily dose of colistin \( \pm \) SD was 152.8 \( \pm \) 62.8 mg (range, 60–300 mg); the mean duration of treatment \( \pm \) SD was 12.6 \( \pm \) 6.8 days (range, 2–34 days). The mean duration of treatment \( \pm \) SD for the surviving patients was 14.0 \( \pm \) 5.1 days (range, 5–25 days).

The mean baseline serum creatinine level \( \pm \) SD was 1.5 \( \pm \) 1.5 mg/dL (range, 0.1–9.1 mg/dL), and 19 (32%) of the patients presented with renal failure defined as a creatinine level of \( \geq 1.5 \) mg/dL or a urea level of \( > 50 \) mg/dL. Eleven (27%) of the 41 patients with normal renal function at the initial evaluation presented with worsening renal function during treatment (mean increase in creatinine level \( \pm \) SD, 0.9 \( \pm \) 0.6 mg/dL; range, 0.3–2.4 mg/dL). Follow-up was possible for six of these 11 patients, and the creatinine levels became normal in three within 1 month after the end of treatment. Of 19 patients with abnormal baseline creatinine levels, 11 (58%) had worsening renal function during treatment (mean increase in creatinine level \( \pm \) SD, 1.5 \( \pm \) 1.4 mg/dL; range, 0.1–4.0 mg/dL). Nephrotoxicity did not cause discontinuation of treatment. No neuromuscular disorders were observed.

**Discussion**

The emergence of multidrug-resistant \( P. \) aeruginosa and \( A. \) baumannii causing nosocomial infections poses a very serious therapeutic problem in Brazil as there are no commercially available alternatives for treatment. Until the early 1980s, colistin was used for treating infections caused by gram-negative rods. The use of colistin was dropped when second- and third-generation cephalosporins became available, mainly because of toxicity [5]. Ticarcillin was commercialized only in the 1990s. Colistin is not available in Brazil, although it is an approved drug (thus allowing importation from other countries).

Colistin was reported as a new agent in 1952 and was shown to be polymyxin E, belonging to the polymyxins (a polypeptide antibiotic group discovered in 1947–1948). Polymyxin E is sulfomethylated, obliterating its cationic nature and rendering it ineffective as an antibiotic. The sulfomethyl polymyxin must be hydrolyzed to release the active free base, and this release occurs at body temperature and at physiological pH in aqueous systems. The sulfomethylated form of the drug is called colistimethate sodium or colistin sodium methane sulfonate [13]. The
Table 1. Nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: isolates and outcomes.

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. (%) of infections</th>
<th>No. (%) with good outcome</th>
<th>Specimen(s) (no.)</th>
<th>No. of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>20 (33)</td>
<td>5 (25)</td>
<td>Tracheal secretion (14), pleural fluid (3), blood (2), BAL fluid (1)</td>
<td>6 14</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 (20)</td>
<td>10 (83)</td>
<td>Urine (12)</td>
<td>4 8</td>
</tr>
<tr>
<td>Primary bloodstream infection</td>
<td>9 (15)</td>
<td>7 (78)</td>
<td>Blood (9)</td>
<td>7 2</td>
</tr>
<tr>
<td>CNS infection</td>
<td>5 (8)</td>
<td>4 (80)</td>
<td>CSF (5)</td>
<td>0 5</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>5 (8)</td>
<td>3 (60)</td>
<td>Surgical site specimen (5)</td>
<td>1 4</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>4 (7)</td>
<td>2 (50)</td>
<td>Peritoneal fluid (4)</td>
<td>1 3</td>
</tr>
<tr>
<td>Catheter-related infection</td>
<td>4 (7)</td>
<td>3 (75)</td>
<td>Central venous catheter (4)</td>
<td>1 3</td>
</tr>
<tr>
<td>Otitis media</td>
<td>1 (2)</td>
<td>1 (100)</td>
<td>Middle ear fluid (1)</td>
<td>1 0</td>
</tr>
<tr>
<td>Total</td>
<td>60 (100)</td>
<td>35 (58)</td>
<td></td>
<td>21 39</td>
</tr>
</tbody>
</table>

NOTE. BAL = bronchoalveolar lavage.

antibacterial action of colistin is poorly understood, but the bacterial cell membrane is disrupted by the binding of the drug to phospholipids, leading to the death of the organism. The drug binds to acidic phospholipids in mammalian tissue, where it has no antibacterial activity [7] but may account for the persistent detectable levels of the free form that might be slowly released from binding sites. Colistin has no effect against gram-positive bacteria, has an insignificant antifungal effect, and is effective against gram-negative bacilli (including *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Salmonella* species, *Shigella* species, *Vibrio* species, *Pasteurella* species, *Haemophilus* species, and *Bordetella* species); *Proteus* species, *Providencia* species, and most *Serratia* isolates are resistant to colistin [14, 15].

In the past (1960s and 1970s), colistimethate sodium was used to treat infections caused by *P. aeruginosa* resistant to other available drugs as well as infections due to other gram-negative bacilli. These infections included septicemia and urinary tract, wound, and respiratory tract infections [16–20]. There are also studies reporting good results of colistin treatment of children and newborns [21, 22]. In our study, colistin was used only in cases in which there were no therapeutic alternatives. The patients treated were mostly from intensive care units, which are mostly affected by multidrug-resistant organisms, and were severely ill as can be seen by their underlying conditions and APACHE II scores. A good outcome occurred in 35 (58%) of 60 cases. Three patients died within the first 48 hours of treatment, and these patients’ treatments cannot really be considered as failures.

The infection associated with the poorest results was pneumonia, for which 15 of 20 treatments failed. This occurrence cannot be explained by the fact that in most of these cases the etiologies were probable and not confirmed, because four of five confirmed cases had a bad outcome. Results were good for a variety of different infections, and surprisingly, four of five cases of CNS infection (meningitis and ventriculitis) had a good outcome, although no intrathecal therapy was given. Colistin has been reported to have poor penetration through the blood-brain barrier [6], but our study and other investigators [22] who reported good results of colistin treatment suggest that further studies are needed to clarify this issue. A possible explanation is the improvement of penetration with inflammation.

Toxicity is an important concern with colistin, and it has never been a first choice for treatment of infections due to gram-negative bacteria because of this concern, although toxicity was not recognized at first [13]. Nephrotoxicity is the most important adverse effect. In normal subjects, transient renal im-

Table 2. Underlying diseases in 59 patients with infections caused by multidrug-resistant microorganisms who were treated with colistin.

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological disorder</td>
<td>14 (24)</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Transplantation (bone marrow, kidney, or liver)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Burn</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Trauma</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Chagas’ disease</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>59 (100)</td>
</tr>
</tbody>
</table>
Impairment may occur during therapy, but in patients with pre-existing renal disease, severe renal impairment with residual damage occurs more frequently. Doses for patients with renal insufficiency must be adjusted, as colistin is excreted principally by the kidneys and elevated blood levels of the drug may further impair renal function [23–25]. In our study, nephrotoxicity was observed in 22 patients (37%), occurring more frequently in patients with preexisting alterations of renal function. No treatments were stopped because of adverse effects of the drug. Neurotoxicity and neuromuscular blockade have also been reported with the use of colistin [25, 26], but these effects were not observed in our study; however, the fact that many patients were receiving support with mechanical ventilation and were sedated made evaluation difficult.

This study shows that colistin may be a good therapeutic option in the treatment of severe infections caused by multidrug-resistant *P. aeruginosa* and *A. baumannii*.

### References


