Effectiveness and Safety of Colistin for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections

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Abstract

Purpose: To describe the clinical and microbiological outcomes of patients infected with multidrug-resistant *Pseudomonas aeruginosa* (MDRP) treated with colistin (colistimethate sodium) and the adverse events observed with this treatment.

Methods: Retrospective study of MDRP infections treated with colistin from 1997 to 2006.

Results: 121 episodes were identified. The median daily intravenous dose was 240 mg/day; 28.9% of patients received intravenous and nebulized colistin. Clinical outcome was favorable in ten cases of bacteremia (62.5%, n = 16), 43 cases of bronchial infection (72.9%, n = 59), 13 cases of pneumonia (65%, n = 20), 11 cases of urinary infection (84.6%, n = 13), eight cases of skin and soft tissues (72.7%, n = 11), and in the one case of arthritis and one case of otitis. Eradication was achieved in 31 (34.8%) of the 89 patients with available bacteriologic data. Factors associated with bacteriological failure were smoking, chronic obstructive pulmonary disease (COPD), and previous infection with *P. aeruginosa*. Nephrotoxicity occurred in ten cases (8.3%), with the associated factors being previous chronic renal insufficiency, diabetes mellitus, and aminoglycoside use. Crude mortality was 16.5%, and related MDRP was 12.4%, and was higher in patients with pneumonia or bacteremia (36.1%) than in other types of infections (8.2%).

Conclusions: Colistin is a safe option for the treatment of MDRP infections, with acceptable clinical outcomes. However, bacteriological eradication is difficult to achieve, especially in COPD patients.

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Introduction

Colistin is a bactericidal polypeptide that is effective against multiple strains of aerobic Gram-negative bacteria, interacting with and altering the structure of the phospholipids of the bacterial cell membrane [1]. It was discovered in 1949 and used in the 1950s, subsequently falling out of favor in the 1980s due to its toxicity profile [2], particularly on the renal and peripheral nervous systems [3]. However, the emergence of multidrug resistant Gram-negative microorganisms, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and the resultant significant increase in the prescribing rate for colistin, has prompted the need to reintroduce this drug into the pharmaceutical market [4].

This situation has generated a number of recent publications on the effectiveness and safety of colistin for the treatment of infections caused by multidrug-resistant microorganisms in intensive care setting [5, 6]. However, to date, well-designed controlled clinical trials to evaluate the effectiveness of colistin for treating infections with multidrug-resistant *P. aeruginosa* (MDRP) are not available. Moreover, data in non-intensive care units (ICU) patients are scarce.

The purpose of this study was to describe the clinical and microbiological outcomes of patients infected with MDRP who were treated with colistin, including non-ICU patients, and the adverse events observed with treatment. Factors associated with clinical and microbial outcomes and toxicity are analyzed.

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Materials and Methods

A retrospective study was conducted at a university hospital (450 beds). All patients treated with colistin (colistimethate sodium) between January 1997 and December 2006 were identified in the pharmacy database. The inclusion criteria were to have received treatment with colistin for more than 3 days following an episode of active infection with MDRP. MDRP was defined as *P. aeruginosa* resistant to carbapenems, β-lactams, quinolones, tobramycin, and gentamicin and sensitive to colistin and amikacin. Colistin susceptibility was defined as a MIC $\leq$ 2 mcg/ml according to the U.S. Clinical and Laboratory Standards Institution. Susceptibility testing of culture isolates was performed by the broth microdilution method using the MicroScan system (Dade Behring, Brookfield CT).

Infections were defined according to criteria established by the Centers for Disease Control and Prevention (CDC) [7]. Active infection with MDRP was defined as the presence of local and/or systemic symptoms of infection attributable to MDRP together with the isolation of MDRP in validated samples.

Once the inclusion criteria were applied, medical charts were reviewed. Analyzed factors included age, gender, tobacco, and alcohol use and the following clinical data: diabetes mellitus, arterial hypertension, chronic renal insufficiency (glomerular filtration rate [GFR] < 60 ml/min per 1.73 m^2 in no less than two measurements at least 3 months apart), hemodialysis at the time of MDRP detection or in the previous 4 weeks, chronic obstructive pulmonary disease (COPD), previous solid or hematologic neoplasia diagnosed in the previous 5 years and currently not free from disease, neutropenia (neutrophil count < 500 cell/µl at the time of MDRP detection and/or over the previous 10 days), a history of chronic liver disease and hepatic cirrhosis, serologies for hepatitis C virus (HCV) and/or HIV, AIDS according to CDC criteria (stage C3), and solid organ transplant. Other variables recorded were number of days from admission to detection of MDRP, diagnosis at hospital admission, admission in the previous 3 months, previous isolation of non-MDRP, and clinical sample where MDRP was isolated.

All patients were treated with colistimethate sodium available as powder, and the equivalence is 80 mg of colistimethate per million units (12,500 units/mg). The usual dose used was in the range of 2.5–5 mg/kg in three doses per day. For patients with renal insufficiency, the doses were adjusted taking into account the estimated GFR. Data reviewed on colistin treatment were days of treatment, route of administration (parenteral, parenteral + nebulized), dosage (in milligrams), and simultaneous treatment with other antimicrobial agents.

Clinical effectiveness was evaluated according to the clinical course described in the patient's chart and assessed to be favorable response, failure, or not assessable. A favorable response was defined as the resolution of fever, leukocytosis, and local signs of infections or an improvement of these conditions. Microbiological response was evaluated according to results from subsequent cultures: eradication or presumed eradication (negative culture), persistence (isolation of MDRP with the same antibiogram), and undetermined (subsequent cultures not available).

The following data were analyzed to evaluate colistin toxicity: neurotoxicity (appearance of either central or peripheral nervous system-related symptoms during treatment). Nephrotoxicity, defined by creatinine $\geq$ 2 mg/ml in patients without prior renal insufficiency or an increase of $\geq$ 50% of basal creatinine levels in patients with chronic renal insufficiency (Naranjo's algorithm was used to attribute nephrotoxicity to colistin [8]. The simultaneous use of potential nephrotoxic agents (cyclosporin, aminoglycosides, angiotensin-converting enzyme (ACE) inhibitors, and tacrolimus) was recorded. Factors related to clinical outcome, microbiological response, and toxicity were also studied.

Statistical Analysis

The independent variables were analyzed as dichotomic. Age was analyzed as a dichotomic variable where the cutoff was the median age. The remaining quantitative variables were expressed as mean and standard deviation or as median and interquartile range according to their distribution. Qualitative variables were expressed as percentages. Proportions were compared using χ^2 tests with a continuity correction or Fisher's exact test when appropriate. Two-sided significance was used for all statistical analyses. Multiple logistical regression analysis of dependent variables was performed, including in the model those independent variables with p-value $\leq$ 0.05. Furthermore, crude inpatient mortality and mortality related to MDRP infection were evaluated. The death was not considered to be directly related to MDRP when the clinical and/or microbiological data did not justify the cause of death.

Results

188 patients treated with colistin during the study period were identified and, after applying the inclusion criteria, we selected 121 of these for inclusion in the study. The excluded patients were those only treated with nebulized therapy, infected by other bacteria, or considered to have been colonized but not infected by MDRP. Table 1 shows the characteristics of the studied population. All of the infections were nosocomial acquired.

Table 1
Characteristics of patients with MDRP infections treated with colistin

Characteristics of study population	Values
Demographic characteristics	
Age, mean (SD)	65.34 (14.1)
Men, n (%)	95 (78.5)
Women, n (%)	26 (21.5)
Admission to ICU, n (%)	23 (19)
Baseline conditions	
Hypertension, n (%)	56 (46.3)
Diabetes mellitus, n (%)	31 (25.6)
Chronic renal insufficiency, n (%)	14 (11.6)
COPD, n (%)	63 (52.1)
HIV infection, n (%)	4 (3.3)
Hematologic neoplasia, n (%)	8 (6.6)
Solid neoplasia, n (%)	24 (19.8)
Neutropenia, n (%)	7 (5.8)
Sites of infection	
Respiratory, n (%)	79 (65.2)
Bronchial infection	59 (48.8)
Pneumonia[a]	20 (16.5)
Bacteremia, n (%)	16 (13.2)
Urinary, n (%)	13 (10.7)
Skin and soft tissues, n (%)	11 (9.1)
Otitis, n (%)	1 (0.8)
Arthritis, n (%)	1 (0.8)

MDRP Multidrug-resistant *P. aeruginosa*; COPD chronic obstructive pulmonary disease; [a] 40% associated with mechanical ventilation

Table 2
Characteristics of treatment

Characteristics of treatment	Values
Routes of administration	
Intravenous route, n (%)	86 (71.1)
Intravenous and nebuilzed, n (%)	35 (28.9)
Total daily dose of colistin, mg/day (range)	
Intravenous administration, median	240 (120–480)
nebulized administration, median	120 (80–480)
Duration of colistin treatment, days (range)	
Intravenous route, median	15 (3–92)
Nebulized route, median	14.5 (3–63)
Association with other antibiotics	
Only colistin, n (%)	37 (30.6)
Bi-therapy, n (%)	70 (57.8)
Three-therapy, n (%)	14 (11.6)
With aminoglycosides, n (%)	57 (47.1)
With b-lactams, n (%)	25 (20.7)
With quinolones, n (%)	8 (6.6)
With carbapenems, n (%)	8 (6.6)

Routes of administration, dosage, duration of treatment, and associated treatment are described in table 2.

The clinical outcome was favorable in 87 patients (71.9%); the clinical response-by-type of infection is shown in table 3. The analyzed factors for clinical response were gender, age > 68 years, smoking, alcohol, chronic renal insufficiency, diabetes mellitus, COPD, HIV infection, neutropenia, neoplasia, previous admissions, admission to ICU, and combination with other antimicrobial agents. No factors were associated with the lack of clinical response. The proportion of clinical response was 73%, 71.9%, 72%, 75%, and 65.5% for colistin monotherapy, colistin associated with aminoglycosides, β-lactams, quinolones, and carbapenems, respectively. The combination of intravenous and nebulized colistin was not associated with a better response to therapy. The relatively higher dose of colistin (> 240 mg/day) was administered to only 20 patients, 17 (85%) of whom had a favorable clinical response; in comparison, 69.3% of the patients whose colistin dose was $\leq$ 240 mg/day had a favorable clinical response ($p = 0.1$).

Information on bacteriological outcome after treatment was available in 89 patients, with eradication of MDRP confirmed in 31 of these (34.8%). Table 3 shows the proportion of eradication by type of infection. In the multivariate analysis, factors related to non-eradication of MDRP were smoking (OR 3.5; 95% CI 1.1–10.4; $p = 0.02$); COPD (OR 2.8; 95% CI 1–7.6), and previous infection with *P. aeruginosa* (OR 3.2; 95% CI 1.1–9.3). Although the dose of colistin was not associated with a statistically significant difference in bacteriological outcome, patients who had taken a dose >240 mg (n = 14) had a 50% proportion of eradication compared with 33.3% ($p = 0.2$) for the other patients.

Crude inpatient mortality was 16.5% (20 patients), while the mortality related to MDRP was 12.4% (15 patients). The crude mortality by site of infection is shown in table 3. The mortality was higher for patients with pneumonia and/or bacteremia (36.1%) than for those with other type of infections (8.2%) (OR 4.9; 95% CI 1.7–14; $p = 0.004$).

No cases of neurotoxicity were detected, but ten patients (8.3%) developed nephrotoxicity. Table 4 shows the univariate analysis of factors potentially related to nephrotoxicity. In the multivariate analysis, the factors related to nephrotoxicity were chronic renal insufficiency (OR 7.1; 95% CI 1.4–35.7; $p = 0.02$), diabetes mellitus (OR 6.9; 95% CI 1.3–35.3; $p = 0.02$), and combination with aminoglycosides (OR 6.1; 95% CI 1–37.4; $p = 0.05$); in this context, the use of ACE inhibitors was close to statistical significance (OR 6.5; 95% CI 0.9–45.2; $p = 0.06$).

Discussion

Several studies have demonstrated the effectiveness and safety of colistin for treating multidrug resistant Gram-negative microorganisms, most of which were carried out in the ICU environment [6, 9]. The clinical response reported in these studies varied between 60% and 80% [10, 11], which is similar to the effectiveness found in our study, which analyzes a significantly large sample (121 patients) and includes a majority of patients from conventional hospital wards. The clinical response in relation

Table 3
Clinical and microbiological outcomes of patients infected with multi-drug resistant *P. aeruginosa* treated with colistin

Nosocomial infections	Favorable clinical response, n (%)	Crude mortality, n (%)	Microbiological outcome, n (%)		
			Eradication	Non-eradication	Indeterminate[a]
Bacteremia (n = 16)	10 (62.5)	6 (37.5)	7 (43.8)	6 (37.5)	3 (18.8)
Pneumonia (n = 20)	13 (65)	7 (35)	6 (30)	7 (35)	7 (35)
Bronchial infection (n = 59)	43 (72.9)	6 (10.2)	9 (15.3)	36 (61)	14 (23.7)
Urinary (n = 13)	11 (84.6)	1 (7.7)	3 (23.1)	6 (46.2)	4 (30.8)
Skin and soft tissues (n = 11)	8 (72.7)	0	5 (45.5)	3 (27.3)	3 (27.3)
Otitis (n = 1)	1 (100)	0	1 (100)	0	0
Arthritis (n = 1)	1 (100)	0	0	0	1 (100)

[a] Indeterminate: No microbiological sample available to evaluate eradication

Table 4
Factors associated with colistin nephrotoxicity

Associated factors	Nephrotoxiciy (n = 10)	Absence of nephrotoxicity (n = 111)	OR	95% CI	*p*
Men, n (%)	8 (80)	87 (78.4)	0.96	0.18–4.55	1
Age >68 years, n (%)	8 (80)	52 (46.8)	4.5	0.92–22.3	0.054
Smoking, n (%)	4 (40)	44 (39.6)	1	0.27–3.8	1
Alcohol, n (%)	2 (20)	5 (4,5)	5.3	0.88–31.75	0.1
Hypertension, n (%)	8 (80)	48 (43.2)	5.2	1–25.85	0.04
Chronic renal insufficiency, n (%)	5 (50)	9 (8.1)	11.3	2.75–46.63	0.002
Diabetes mellitus), n (%)	6 (60)	25 (22.5)	5.1	1.3–19.73	0.018
COPD, n (%)	4 (40)	59 (53.2)	0.58	0.15–2.19	0.51
Solid neoplasia, n (%)	3 (30)	21 (19.8)	1.8	0.43–7.7	0.31
Previous admission, n (%)	7 (70)	46 (41.4)	3.29	0.8–13.42	0.1
Previous *P. aeruginosa*, n (%)	5 (50)	41 (36.9)	1.7	0.46–6.2	0.5
Aminoglycosides, n (%)	8 (80)	49 (44.1)	5	1–24.92	0.045
ACE inhibitors, n (%)	3 (30)	8 (7.2)	5.5	1.1–25.53	0.04
Colistin dose > 240 mg/day, n (%)	3 (30)	17 (15.3)	2.3	0.55–10.08	0.36
Treatment > 15 days, n (%)	7 (70)	47 (42.3)	3.1	0.78–12.93	0.1
ICU admission, n (%)	0 (0)	23 (20.7)	0.79	0.72–0.87	0.09

ACE Angiotensin-converting enzyme; ICU intensive care unit

to the specific site of infection in our study was similar to that found in two other studies – 73% [50] and 74% [12] – and better than reported by *Levin* et al. [13] – 58%.

Among the factors that we analyzed in relation to clinical response, neither simultaneous parenteral and nebulized administration or the use of colistin in combination with other antimicrobials showed statistical significant differences. A number of *in vitro* studies have demonstrated a synergistic activity against MDRP strains when colistin is combined with rifampicin [14, 15] or with amikacin [16, 17]. However, no clinical studies carried out to date have demonstrated the superiority of combining colistin with other antimicrobials over monotherapy [18].

In contrast to the acceptable clinical response, microbiological eradication was low (34.8%). A high proportion of the samples studied were respiratory (65.2%) in origin, obtained mostly from patients with exacerbated COPD. This would largely explain the low rate of microbiological eradication. The COPD patient is similar to the patient with cystic fibrosis, where persistent colonization with *P. aeruginosa* is frequent, despite treatment [19, 20]. In support of this, we found that the factors independently related to low rate of eradication were COPD and previous isolation of *P. aeruginosa*.

The median dose of colistin used in our population of patients without renal insufficiency was 240 mg/day (3.4 mg/kg per day). Only 20 patients were treated with a dose > 240 mg/day, and only 14 patients of this latter dose group could be evaluated for the relation between eradication and this higher dose. A tendency of better clinical response and better eradication rate was observed when the higher dose was used. *Falagas* and other authors reported that the use of higher daily doses of colistin (up to 720 mg/day) administered intravenously was related to high rates of clinical response and eradication [4, 5, 12, 21]. Another factor supporting the use of higher dose is that colistin is poorly distributed to the pleural cavity and pulmonary parenchyma. However, no systematic analyses have been reported on the effect of different dosage of colistin on the effectiveness and toxicity outcomes.

We did not found any case of neurotoxicity, which is in agreement with the results of some earlier studies [22]. Ten patients developed nephrotoxicity (8.3%). The reported rate of nephrotoxicity with colistin varies from 0% to 37% among patients with normal renal function [3, 9, 23]. In our study, the independent factors related to nephrotoxicity were previous chronic renal insufficiency, diabetes mellitus, and aminoglycoside use. It should be highlighted that no nephrotoxicity was detected among those patients admitted to the ICU, possibly because of the close monitoring of hydroelectrolytic balance in these patients.

We found a crude mortality rate of 16.5%, and mortality related to MDRP was 12.4%; however, the latter varied according to the specific localization of the infection. The mortality reported for infections caused by MDRP oscillates from 24% to 60% [9, 24, 25], and the factors associated to higher mortality are age and the presence of acute renal insufficiency. Most of these earlier studies focused on patients admitted to ICUs.

The main limitations of our are its retrospective design and the heterogeneity of the patients included, with several types of infections, different prognoses, and different treatment approaches (diverse doses and routes of administration and different combinations with other antimicrobials). The advantages are its sample size and the fact that the results are extracted from routine medical practice in a field where it is difficult to conduct controlled clinical trials.

The results of this study confirm that colistin is a safe and effective drug for treating infections due to multidrug-resistant strains of *P aeruginosa*, which is a clinical field with limited therapeutic options. Because colistin was developed many years ago, the studies conducted at those times do not provide sufficient information, and many important questions remain to be answered on the pharmacokinetics and pharmacology of this ''old'' antibiotic. Therefore, well-designed studies focusing on dosage, pharmacodynamics, pharmacokinetics, efficacy, and toxicity are needed.

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