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Safety and efficacy of colistin in *Acinetobacter* and *Pseudomonas* infections: a prospective cohort study

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Abstract *Objective:* To assess renal dysfunction and outcome in patients treated exclusively with colistin vs. other antibiotics. *Design and setting:* Prospective cohort study in a mixed ICU in a university-affiliated hospital. *Patients:* 185 patients infected with *Acinetobacter baumannii* and *Pseudomonas aeruginosa* after an ICU stay longer than 48 h: 55 in the colistin group and 130 in the noncolistin group, similar in age, APACHE II, medical status, and SOFA score. *Measurements and results:* We recorded data on epidemiology and severity of illness, site of infection, renal function before and after treatment, clinical cure, and mortality. Clinical cure was defined as simultaneous normalization of central temperature ($\leq$38°), leukocyte count ($\leq$10,000/mm^3), and PaO_2/FIO_2 ratio (>187). Before treatment creatinine was 0.9±0.2 in the colistin group and 0.9±0.1 in the noncolistin group; after treatment the value was 1.0±0.3 in both groups. The most frequent infection was ventilator-associated pneumonia: 53% vs. 66% in colistin and noncolistin groups, respectively, *Acinetobacter* was the cause in 65% and 60% and *Pseudomonas* in 35% and 53%. In the noncolistin group 81% of patients were treated with carbapenems. Inadequate empirical antimicrobial treatment was more frequent in the colistin group (100% vs. 8%), but there were no differences in the frequency of clinical cure on day 6 of treatment (15% and 17%) or in mortality (29% and 24%). *Conclusions:* Colistin appears to be as safe and as effective as other antimicrobials for treatment of sepsis caused by *Acinetobacter* and *Pseudomonas* in critically ill patients.

Keywords Colistin · Renal failure · *Pseudomonas* · *Acinetobacter* · ICU-acquired infections

Introduction

Multidrug-resistant Gram-negative bacilli, mainly *Acinetobacter* species and *Pseudomonas aeruginosa*, are responsible for a significant proportion of nosocomial infections [1]. These micro-organisms have been found to be resistant to many currently available antimicrobial agents. Thus, the risk of an initially inappropriate antimicrobial treatment is also rising [2, 3]. Inadequate antimicrobial treatment of nosocomial infections is an independent determinant of mortality in the critically ill [4]. Recently there has been renewed interest in antimicrobial agents, which had earlier been abandoned for serious adverse effects. An example is colistin, a polimyxin that has excellent in vitro activity against many species of Gram-negative bacilli [5, 6, 7, 8, 9]. Colistin was extensively used from the 1960s to the early 1980s [10, 11]. Polimyxins are amphipathic molecules that interact with lipopolysaccharide in the outer membrane of many Gram-negative bacilli, leading to rapid permeability changes and ultimately to cell death, with additional potent antiendotoxin properties [12]. Colistin is usually pre-

scribed at 2.5–5 mg/kg per day divided into two or three doses. Toxicity involves the kidney and central nervous system, and because of serious adverse effects colistin systemic utilization has been discouraged [13, 14]. However, recent studies, mainly case-series, have reported the safe use of colistin [8, 9].

We performed this study to compare (a) the renal toxicity and (b) the outcome, measured as clinical response and survival, of intravenously administered colistin vs. conventional antibiotics in ICU patients with severe infections. Preliminary results about toxicity have been reported previously [15].

Methods

Study design

This prospective cohort study was conducted in the mixed medical/surgical intensive care unit (ICU) located in Hospital Interzonal de Agudos General San Martín, a university-affiliated hospital in La Plata, Buenos Aires, Argentina. The study period ran from January 2000 to January 2004. As there were no interventions, and measurements formed part of the usual care of patients, informed consent was waived by the hospital ethics committee. All patients acquiring infections with *Acinetobacter* and *Pseudomonas* after being in the ICU for more than 48 h were considered eligible and were prospectively followed from the date of infection to death or hospital discharge. During the study period 797 patients were admitted to the ICU, and 185 of these developed *Acinetobacter* or *Pseudomonas* infection 48 h after admission.

We recorded age, gender, admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and reason for initiating mechanical ventilation [16]. Preexistent illnesses were assessed according to the McCabe score [17] as: 1=not preexistent disease, 2=ultimately fatal disease, and 3=proximally fatal disease. Daily SOFA score [18], new sites of infection, type and duration of antimicrobial therapy, use of physiological doses of steroids for septic shock, use of α drotrecogin, renal dysfunction, clinical cure, and hospital mortality were recorded. These parameters were compared between patients treated exclusively with colistin (n=55) and those treated with other antibiotics (n=130), including carbapenems (81%), ampicilin/sulbactam (11.5%), piperacillin/tazobactam (3%), ceftazidime (3%), ciprofloxacin (1.5%), and cefepime (0.8%). Adjunctive treatment with aminoglycosides was prescribed in 36% of patients. Table 1 presents clinical characteristics of the colistin and noncolistin groups.

Table 1 General characteristics of patients in colistin and noncolistin groups (*APACHE II* Acute Physiology and Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease)

	Colistin group (n=55)	Noncolistin group (n=130)	p
Age (years)	40±16	41±16	0.2
Female gender	36 (66%)	73 (60%)	0.3
APACHE II	21±7	20±7	0.2
APACHE II risk of death (%)	42±22	36±22	0.06
Admission diagnosis			
Medical	28 (51%)	79 (61%)	0.14
Surgical	27 (49%)	51 (39%)	0.28
Elective	11 (20%)	15 (16%)	0.13
Emergency (nontrauma)	10 (19%)	14 (11%)	0.21
Emergency (trauma)	6 (10%)	22 (17%)	0.29
McCabe score	1.37±0.7	1.43±0.7	0.4
McCabe score (2+3)	15 (27%)	26 (20%)	0.08
SOFA score[a]	5±3	5±3	0.9
Septic shock	24 (44%)	35 (27%)	0.03
Physiological doses of steroids in septic shock	5 (9%)	3 (2%)	0.03
Use of α drotrecogin	1 (0.02)	1 (0.008)	0.51
Mechanical ventilation	55 (100%)	130 (100%)	0.9
Respiratory cause	17 (31%)	35 (27%)	0.58
ALI/ARDS	16	24	0.11
Asthma	1	7	–
COPD	–	4	–
Neurological cause	11 (20%)	39 (30%)	0.16
Cranial trauma	5	21	0.20
Hemodynamic cause	10 (18%)	28 (22%)	0.61
Postoperative	16 (29%)	28 (22%)	0.27

[a] On the day prior to the infection

Diagnosis of infection

ICU-acquired infection was defined as that occurring in a patient staying longer than 48 h in the ICU [19], with systemic inflammatory response syndrome, sepsis, severe sepsis or septic shock, according to ACCP/SCCM Consensus Conference [20] definitions. Septic shock at the moment of infection diagnoses was recorded. Possible sites of infections were:

- Ventilator-associated pneumonia (VAP), defined as the occurrence of a new or persistent radiographic infiltrate occurring more than 96 h after the onset of mechanical ventilation (late-onset VAP) [21] and macroscopically purulent tracheal secretions, plus a positive quantitative secretion sample culture yielding at least 10^4 cfu/ml in a broncoalveolar lavage [22] or at least 10^3 cfu/ml in a mini-broncoalveolar lavage [23] or at least 10^6 cfu/ml in a quantitative tracheal aspirate [24]. Due to the high incidence and mortality in VAP reportedly caused by *P. aeruginosa* [25], this entity was analyzed separately.
- Primary bacteremia: at least one positive blood culture without another site simultaneously infected with the same micro-organism [26].
- Catheter-related infection confirmed by growth of at least 15 cfu in a semiquantitative culture, or at least 10^3 cfu in a quantitative culture from a catheter tip and/or exit-site infection plus isolation of the same micro-organism from blood drawn from a peripheral vein [26].
- Central nervous system infection diagnosed by a glucose CSF less than 40 mg/dl or less than 50% from simultaneous blood level and/or neutrophilic pleocytosis (>100 cells/mm^3 or >50% neutrophils), with a positive or negative culture, primary or after neurosurgery or penetrating cranial trauma, or evidence of brain abscess on computed tomography [27, 28, 29].
- Urinary tract infection: defined by the presence of pyuria ($\geq$ 10 leukocytes/mm^3) and urine culture of at least 10^5 cfu/ml [19].

Therapy was considered adequate when at least one effective drug was included in the empirical antibiotic treatment within 24 h of developing infection, with dose and pattern of administration according to current medical standards [30].

The course of infection was assessed on day 6 of treatment since this has been shown to be the mean time to resolution of clinical parameters. Improvement was defined as simultaneous normalization of central temperature to 38° or lower, white blood cell count to 10,000/mm^3 or less, and PaO_2/FIO_2 ratio higher than187

(25 kPa), not only for VAP as originally described but also for the other infections since oxygenation alterations may represent ongoing multiorgan failure of nonpulmonary cause [31].

Bacteriological cure was not assessed, as colonization with Enterobacteriaceae and *P. aeruginosa* may persist despite therapy success [31]. Chest radiographic infiltrates were not evaluated due to the low specificity of radiographic criteria in diagnosing VAP [32]. Recurrent pneumonia was considered if a new infiltrate developed at least 72 h after clinical resolution, with positive quantitative culture for *P. aeruginosa or Acinetobacter* and two of the following: fever of 38° or higher, white blood cell count of10,000/mm^3 or higher, purulent respiratory secretions, and no extrapulmonary source of infection. It was not possible to distinguish between relapse of a previous clone with reinfection by the same micro-organism since chromosomal fingerprinting based on pulsed-field gel electrophoresis was not available. Superinfection was considered when a new, different micro-organism was isolated [33].

Renal function was monitored by daily measurement of serum creatinine. Renal failure was defined as a serum creatinine value of 2 mg/dl or higher, as a reduction in creatinine clearance of 50% compared to therapy initiation, or as a decline in renal function that prompted renal replacement therapy [34]. Concomitant use of potentially nephrotoxic drugs was recorded.

Use of colistin

The methanesulfonate polymyxn derivate [7] was administered intravenously to patients infected by strains *exclusively* susceptible to colistin. The daily colistin dose was adjusted to renal function as follows: less than 1.2 mg/dl, 5.0 mg/kg (maximum daily dose of 300 mg) divided into three doses; 1.3–1.5 mg/dl, 2.5–3.8 mg/kg divided into two doses; 1.6–2.5 mg/dl, 2.5 mg/kg in one or two doses; 2.6 mg/dl or higher, 1.5 mg/kg every 36 h [35]. Hemodialyzed patients received 1.0 mg/kg per day as a single dose. Length of treatments was determined by attending physicians.

Statistical Analysis

Categorical variables were compared between groups by χ^2 test for and continuous variables by *t* test. Data are expressed here as mean ±standard deviation or as median and interquartile range (25–75 percentiles) as appropriate. Differences with a *p* value less than 0.05 were considered significant. Comparisons within groups were adjusted by Bonferroni's correction.

Results

Sites of infection, Gram-negative bacilli, impact on renal function, and outcomes are displayed in Table 2. *Acinetobacter* was more frequent in both groups than *Pseudomonas*. Although all colistin-treated patients had initially inappropriate antibiotic treatment, no differences in outcomes were found compared to the noncolistin treated group. Mortality, clinical cure, course of physiological parameters, and their concomitant normalization were essentially the same in the two groups (Table 2, Figs. 1, 2). The only difference between groups was at the moment of infection diagnosis: fever was significantly higher in patients with micro-organisms respondent to noncolistin antimicrobials (38°6±0.7 vs. 38°2±0.2 for colistin, *p*=0.015). On day 6 of treatment a similar proportion of patients had normalized physiological parameters (Fig. 2).

Table 2 Outcomes and sites of infection in colistin and noncolistin groups (*LOS* length of stay)

	Colistin group (*n*=55)	Noncolistin group (*n*=130)	*p*
Treatment duration (days)	13±5	13±6	0.8
Basal creatinine (mg/dl)[a]	0.9±0.2	0.9±0.2	0.6
End creatinine (mg/dl)[b]	1.0±0.3	1.0±0.3	0.9
Day of diagnosis of infection[c]	12 (7–21)	7 (6–13)	0.0001[d]
Inappropriate empirical treatment	55 (100%)	10 (8%)	0.00001
Treatment delay (hours)[e]	96±24	12±4	0.00001
Alive at hospital discharge	39 (71%)	96 (74%)	0.2
Length of MV (days)[c]	28 (15–48)	20 (12–27)	0.02[d]
LOS ICU (days)[c]	40 (21–58)	26 (16–43)	0.03[d]
LOS hospital (days)[c]	61 (29–88)	36 (26–70)	0.54[d]
Acinetobacter infections	36 (65%)	69 (53%)	0.2
Mortality	10 (27%)	21 (30%)	0.8
Pseudomonas infections	19 (35%)	61 (47%)	0.3
Mortality	7 (37%)	17 (28%)	0.5
Ventilator-associated pneumonia	29 (53%)	86 (66%)	0.2
Mortality	10 (32%)	21 (24%)	0.2
Primary bacteremia	9 (16%)	25 (19%)	0.2
Mortality	2 (22%)	9 (36%)	0.1
Urinary tract infection	10 (18%)	11 (8%)	0.1
Mortality	2 (20%)	2 (20%)	0.2
Other infections[f]	7 (13%)	8 (6%)	0.3
Mortality	3 (43%)	3 (38%)	0.3

[a] Before start of treatment
[b] After end of treatment
[c] Median (*parentheses* interquartile range)
[d] Mann-Whitney test
[e] Delay in starting adequate antibiotics
[f] Catheter-related infections, central nervous system infections, peritonitis, surgical wound infection

No colistin-resistant micro-organisms were found in this study. Infections caused by *P. aeruginosa* were present in 48% of patients (88/185). Forty-eight patients (54%) of patients had VAP with an age of 40±17 years, APACHE II score of 21±7, and predicted risk of death of 39%. Comorbidities were present in 23%. Ten patients (21%) died, five in each group. Persistence of micro-organisms in respiratory samples and recurrent pneumonia are displayed in Table 3. No superinfection episodes were recorded. The small numbers preclude statistical analysis. Twenty-one patients had bacteremia by *Pseudomonas*, with a mean age of 40±17 years, APACHE II score of 20±7, and predicted risk of death 37%. Nine patients died (43%). Only 19% had comorbidities.

Mean creatinine levels were normal in both groups at the initiation of antimicrobial therapy and remained so after treatment (Table 2). Two patients in each group had previous renal failure, but none further deteriorated or needed renal replacement therapy. Creatinine levels before and after treatment were 2.3±0.5 and 2.5±0.6 in the

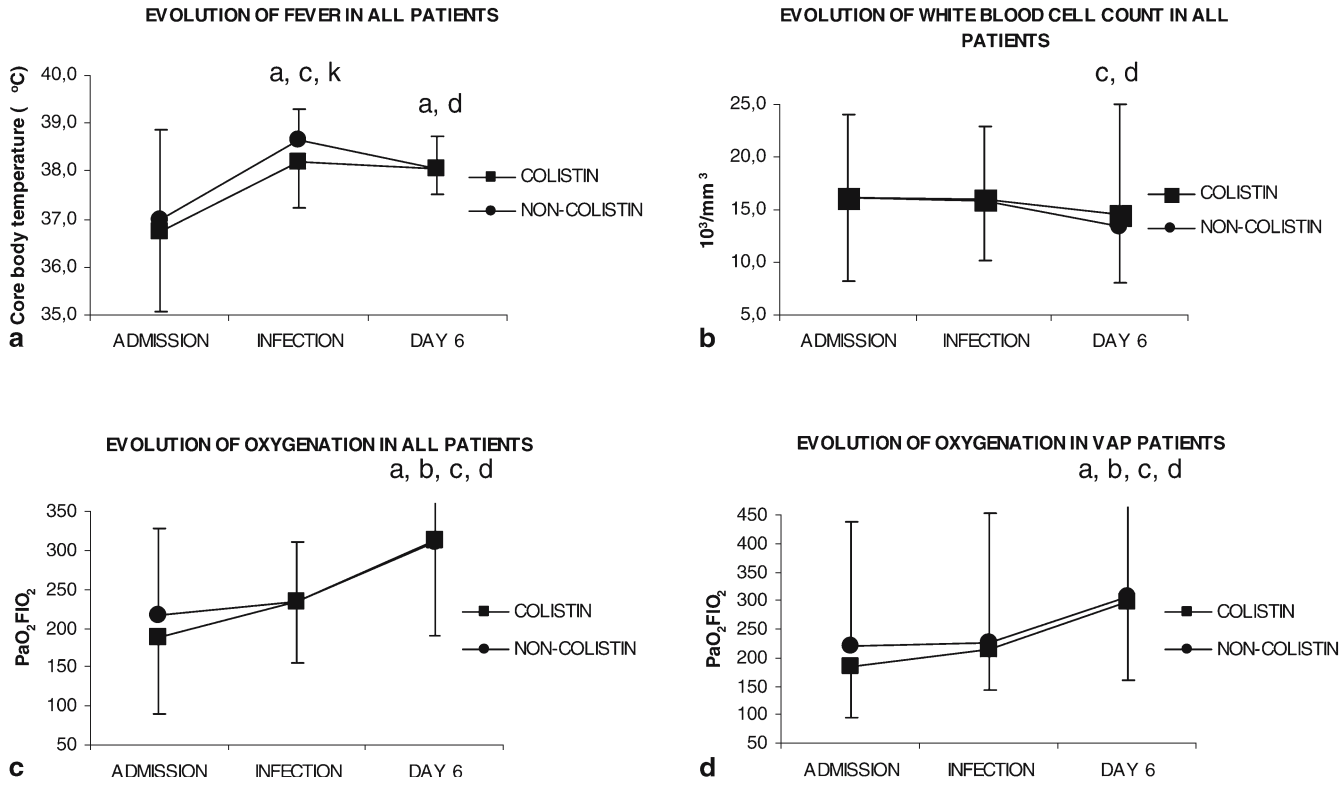

Fig. 1 A–C Temporal course of clinical parameters in all patients in colistin and noncolistin groups. **D** Evolution of oxygenation in VAP patients. [a]$p<0.01$ vs. admission for colistin group, [b]$p<0.01$ vs. infection for colistin group, [c]$p<0.01$ vs. admission for noncolistin group, [d]$p<0.01$ vs. infection for noncolistin group, [k]$p<0.05$ colistin vs. noncolistin

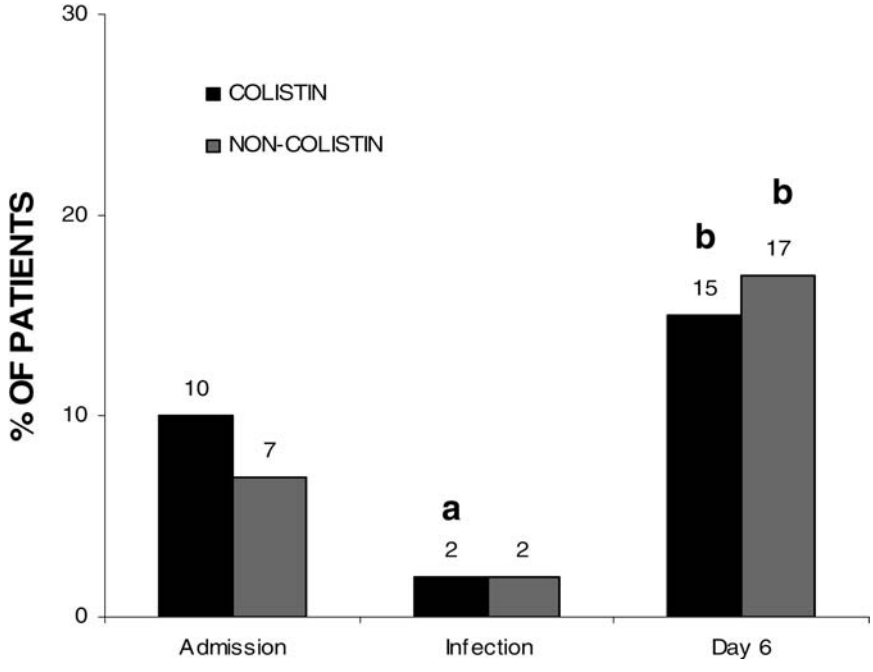

Fig. 2 Patients fulfilling the three criteria of improvement in colistin and noncolistin groups. Criteria of improvement [20]: simultaneous achieving of central temperature of 38° or below, white blood cell count of 10,000/mm^3 or less, and PaO_2/FIO_2 ratio greater than 187 (25 kPa). [a]$p<0.05$ with respect to admission, [b]$p<0.01$ with respect to infection

Table 3 Bacteriological findings and outcomes of 115 episodes of VAP, when a new infection was suspected

	n	Mortality	Persistent micro-organism[a]	Recurrent VAP
Colistin	29	10 (34%)	2	1
P. aeruginosa	14	5 (36%)	1	1
Acinetobacter	15	5 (33%)	1	
Noncolistin	86	21 (24%)	5	1
P. aeruginosa	34	5 (15%)		
Acinetobacter	52	16 (31%)	5	1

[a] All these patients finally had an extrapulmonary cause of infection, but the micro-organism that caused VAP was still isolated at 7.0±0.5 days

colistin group and 2.5±0.5 and 2.5±0.5 in noncolistin group (NS). Other potentially nephrotoxic drugs received by patients in colistin and noncolistin groups, respectively, were: vancomycin, 80% vs. 71% (p=0.2); aminoglycosides, 0 vs. 48% (p<0.001); and amphotericyn B, 9 vs. 2% (p=0.04).

Discussion

The most important findings of this study were the efficacy and lack of nephrotoxicity of colistin in treating severe sepsis caused by *Acinetobacter* and *P. aeruginosa*. Due to the recent emergence and worldwide spread of multidrug-resistant Gram-negative bacilli [36, 37] few antimicrobial drugs remain available for effective treatment [38]. Potential therapeutic indications for colistin have been restored, and three studies have assessed its use in the ICU [6, 8, 9, 39]. Levin et al. [6] in a case series examined 59 patients infected with *P. aeruginosa* and *A. baumannii* (52% ICU, 13% transplantation, 35% general-ward patients). These subjects were young (mean age 42 years, similar to 40 years in our study), but with less severe acute illness (APACHE II score 13±7 vs. 21±7). Good clinical outcome was obtained in 58% of cases. However, mortality was high for their APACHE II score (37%), possibly due to their high degree of comorbidities. Markou et al. [9] in a smaller and equally young case series (n=24, mean age 44 years, mean APACHE score 20.6) also reported 73% clinical cures (loosely defined as diminished fever and improvement in vital signs). Mortality was higher (47%), but it is difficult to draw a conclusion about colistin efficacy in this study because all patients received other antimicrobials for lack of trust in colistin monotherapy. Finally, Garnacho-Montero et al. [8] compared patients with VAP due to *A. baumannii*, with 21 episodes caused by micro-organisms susceptible exclusively to colistin and 14 susceptible to imipenem. These were older, severely ill patients (mean age 61 years, APACHE II 20). Clinical cure, defined as remission of pneumonia symptoms, was high (57%), crude mortality was 62%, and VAP-related mortality was 38%. No differences were found between colistin and imipenem groups. Of note, these VAP patients fared well, although Levin et al. [6] had found a suboptimal response to colistin in pneumonia.

Ours was the largest, prospective cohort reported, with youngest and most acutely ill patients, although preexistent illnesses were less frequent. Mortality was low (30%), and lower than the predicted risk of death based on APACHE II scores (36%). In addition, and differently than in other studies which define clinical cure as remission of clinical symptoms without further clarification [6, 8, 9], we used objective criteria of clinical cure [31]. We found no difference between colistin and noncolistin groups regarding mortality, renal function, temporal analysis of separate clinical parameters, and simultaneous normalization on the 6th day of treatment. Moreover, these results occurred despite a significantly higher septic shock rate in colistin group at the time of infection. This favorable effect of colistin on general outcome was similar to that described by Garnacho-Montero et al. [8], also extensive to *P. aeruginosa* infections.

Assessing infection response to treatment on the 6th day may still be regarded as early, at least in our patients, but symptoms of pneumonia are usually slow to resolve [31]. We found a significant pretreatment difference between groups only at the time of diagnosis infection: *Acinetobacter* or *Pseudomonas* respondent only to colistin infections caused less fever. It is difficult to determine the clinical significance of this finding, if any. The significant elevation in temperature during the infection period was expected, as it a diagnostic parameter. However, the high leukocyte count suggests the persistence of systemic inflammatory response syndrome, present as early as ICU admission in these severely compromised patients. Finally, although the increase in oxygenation seems puzzling, it may reflect an improving respiratory condition after treatment of the admission illness, or to the use of positive end-expiratory pressure.

No strains resistant to colistin were found in this study. This is in line with reports in the literature of an unusual appearance of resistance with colistin [5, 40]. Recurrent pneumonia was infrequent, and no superinfections occurred.

All patients in the colistin group received inadequate empirical antibiotic treatment. Adequate therapy was prescribed after a mean of 96 h; despite this, colistin and noncolistin groups had similarly good outcomes. The

reason for this undesirable, significant delay, reflects the fact merely that colistin was never considered as first-line therapy. This was an intriguing, unexpected finding that contradicts the well known effect of inadequate antimicrobial treatment on mortality [41, 42, 43]. A possible reason is that inadequate empirical antimicrobial therapy exerts its deleterious effect only in some subpopulations, for example, the less severely ill. Recently Clec'h et al. [44] found no significant difference in mortality among VAP patients with and without adequate early institution of antibiotics. However, prognosis was significantly worse in patients with inadequate early antibiotic therapy whose LOD score was 4 or less. In the sickest patients stronger predictors of mortality, such as old age, underlying diseases, and immunosuppression may be more important.

VAP caused by *Pseudomonas* is usually associated with higher mortality rates (>60%) than that of other causes [25]. Crouch et al. [25] hypothesize that the excess mortality of *Pseudomonas* pneumonia is related to the host defense response rather than to any characteristic of the infection. In this way patients' youth and lack of comorbidities may explain the 21% mortality in *Pseudomonas* VAP. In addition, the high survival rate in our patients may be due to the physiological selection process which they had already undergone, given that mortality peaks during the first days of ICU stay. These are chronically critically ill patients, with lower mortality than that of a general group of ICU patients, but who still carry a high degree of morbidity (severe infections, prolonged mechanical ventilation and ICU and hospital lengths of stay) [45, 46, 47], as is shown in Table 2. Infections caused by *Pseudomonas* and *Acinetobacter* were a late event. Bacteremia caused by *Pseudomonas* showed 43% of mortality, similar to previously reported figures [48, 49]. *Acinetobacter* infections do not have a worse prognosis than other causes [50, 51, 52, 53]; since these micro-organisms caused 52% of infections, they may have an affect on overall mortality. Nevertheless, mortality with *Acinetobacter* and *P. aeruginosa* was similar.

Despite long-standing fears of colistin-induced nephrotoxicity this drug has been reassessed and is being used increasingly to treat acute respiratory exacerbations of cystic fibrosis by multiresistant *Pseudomonas*. Interestingly, higher doses have been used in adults (5–8 mg/kg per day, administered every 8 h) without renal toxicity [54]. In our study mean creatinine level did not change significantly after treatment, nor was there further deterioration in patients with compromised renal function. No patient required renal replacement therapy after colistin therapy. Again, the young age of patients may be related to this good outcome.

Renal dysfunction after colistin use in ICU patients is reported at 14% [9], 24% (similar to an imipenem-treated group) [8], and 32%, but in the latter case many patients had prior severely compromised renal function [6]. This change in previously reported nephrotoxicity may be due to the new drug formulation, as methane sulfonate is less toxic than the sulfate salt used in earlier studies [5]. Moreover, diminished toxicity may also reflect the global improvement in hemodynamic resuscitation techniques in the critically ill over the past 25 years. Neurotoxicity, the other side effect of colistin, was not systematically assessed with neurophysiological evaluations, such as electromyography and repetitive stimulation.

Our study has several limitations. First, it was performed at only one hospital. Second, all our patients were younger than those of some other studies. This may limit the generalizability of our results to institutions that treat different groups of patients. Third, we did not assess bacteriological cure, which has been linked to resolution of clinical symptoms [55]. However, microbiological eradication in VAP caused by *P. aeruginosa* and Enterobacteriaceae is difficult to obtain as these micro-organisms can persist despite clinical cure [31]. Poor reliability of microbiological criteria for evaluating therapy success has recently been reinforced, although it has been suggested they be included in the assessment of treatment failures [56]. Fourth, as with most studies in this area [6, 8, 31, 44], we did not perform a power analysis to estimate sample size. A post-hoc calculation based in a difference between 60% [6] and 80% (due to a lower frequency of underlying diseases in our cohort) of probability of clinical cure, with a two-tailed α value of 0.05 and 0.8 power would yield 91 patients per group [57]. It took us 4 years to collect 55 patients with infective microorganisms susceptible only to colistin, but less than the 7-year period needed to gather 45 episodes of bacteremia caused by *A. baumannii* [52]. Rello et al. [53] have addressed this issue, noting the scarce number of *A. baumannii* infections. In addition, a prolonged length of patient recruitment is not advisable since standards of care may change and thus introduce unknown biases that can affect conclusions. Thus, although this study might be statistically unpowered, the conclusions may be still relevant: colistin seems to be as effective as other drugs commonly used in severe sepsis caused by *Acinetobacter* and *Pseudomonas* acquired in the ICU and also shows an acceptable level of toxicity.

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Conflict of interest: No information supplied

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