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Ventilator-associated pneumonia due to colistin susceptible-only microorganisms

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ABSTRACT: **Acinetobacter spp. and *Pseudomonas aeruginosa* are common pathogens of ventilator-associated pneumonia (VAP). The presentation and outcome of VAP due to Acinetobacter spp. and *P. aeruginosa* susceptible to carbapenems (Carb-S; imipenem and/or meropenem) and to colistin only (Col-S) were compared in the present retrospective study in three intensive care units.**

A total of 61 episodes of VAP caused by Acinetobacter spp. or *P. aeruginosa* were studied, of which 30 isolates were Carb-S and 31 were Col-S.

Demographics, worsening of renal function and mortality were not different. The univariate analysis showed that a later onset and a previous episode of VAP, prior antimicrobial therapy for >10 days and previous therapy with carbapenems during the present admission were more frequent in patients with Col-S strains. On multivariate analysis, prior antimicrobial therapy for >10 days and a previous episode of VAP remained significantly associated with Col-S VAP. Approximately 41% of the infections caused by Col-S isolates, but none of those due to Carb-S isolates, had received prior carbapenem therapy.

Colistin-susceptible ventilator-associated pneumonia episodes can be effectively treated using colistin without significant renal dysfunction. This susceptibility pattern could be suspected in patients with a previous ventilator-associated pneumonia episode or prior antibiotic therapy for >10 days preceding the present ventilator-associated pneumonia episode.

KEYWORDS: **Antibiotic resistance, antibiotic treatment of pneumonia, bacterial infections, ventilator-associated pneumonia**

The isolation of multiple drug resistant (MDR) Acinetobacter spp. and *Pseudomonas aeruginosa* is an increasing phenomenon observed in different intensive care units (ICUs) around the world [1–3]. In recent years, strains of Acinetobacter spp. and *P. aeruginosa* nonsusceptible to nearly all classes of drugs, including carbapenems, one of the most effective antimicrobials for these pathogens [3, 4], were identified more frequently as the pathogens of ventilator-associated pneumonia (VAP) [2, 3, 5]. Colistin appears as an appropriate therapeutic alternative. The amount of data available regarding epidemiological and clinical characteristics of VAP due to Gram-negative bacilli susceptible only to colistin (Col-S) is limited [6, 7]. The mortality rate of VAP increases when the initial antimicrobial therapy is inappropriate [8–11], so it is extremely important to identify patients at risk and to begin the appropriate empiric antimicrobial therapy as soon as possible.

Colistin is an antibiotic of the polymyxin family and it is produced by *Bacillus colistinus*. It has been available since 1959 for the treatment of infections caused by Gram-negative bacteria [12]. It is thought to act by altering the cell wall permeability producing bacterial lysis [13]. *In vitro* colistin has a broad spectrum of action against Gram-negative bacteria, including some strains resistant to penicillins, carbapenems, aminoglycosides and fluoroquinolones. However, *Proteus mirabilis,* Providencia spp., Serratia spp., *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are naturally nonsusceptible to colistin [14]. Severe adverse effects (*i.e.* nephrotoxicity and neurotoxicity) have been reported which led to the discontinuation of parenteral use of this drug in the 1970s [7, 14]. Acquisition of resistance to colistin is uncommon; it has been described in cystic fibrosis patients chronically treated with nebulised colistin for tracheal colonisation with MDR *P. aeruginosa*. Sodium colistin methanesulphonate is the commercially available form for *i.v.* use [15].

Since colistin has been associated with severe adverse effects and an inappropriate initial

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empirical antibiotic treatment is consistently associated with increased mortality, the identification of factors associated to Acinetobacter spp. and *P. aeruginosa* Col-S, compared with strains susceptible to other antibiotics, would assist in choosing the initial antimicrobial therapy.

The aim of the present study was to compare the epidemiological conditions and clinical presentation of patients with VAP caused by MDR Acinetobacter spp. or *P. aeruginosa* that preserve their susceptibility to carbapenems (Carb-S) with Col-S strains, focusing on worsening serum creatinine concentration identified during therapy.

METHODS

The present retrospective study was based on the clinical and microbiological records of ICU patients from three different hospitals (Profesor Alejandro Posadas Hospital, Hospital de Clínicas and HIGA Eva Perón Hospital) located in the metropolitan area of Buenos Aires, Argentina, during a 26-month period (December 2001–January 2004). Episodes of VAP caused by Carb-S or Col-S Acinetobacter spp. or *P. aeruginosa*, fulfilling the inclusion criteria detailed hereafter, were studied. In these ICUs, the rate of VAP due to MDR microorganisms was ~69%, according to a previous multicentre prospective study on VAP [16]. In such previous studies, VAP incidence in mechanically ventilated patients was 14.8%, of which ~40% was due to Acinetobacter spp. or *P. aeruginosa* and one third was due to Col-S. Empirical antimicrobial therapy included a carbapenem in ~60% of the cases and other β-lactams were used in most of the remaining cases. In the present study, a combined therapy with an aminoglycoside, a fluoroquinolone in combination with a carbapenem, or colistin was used in 12 cases as empiric therapy. In 16 cases, colistin was used after the culture report showing Col-S Acinetobacter spp. or *P. aeruginosa*. In the remaining 15 cases, the initial therapy with colisitin was empirical according to the decision of the attending physician.

Inclusion criteria were as follows. 1) Aged >18 yrs with a new or progressive pre-existent radiographic infiltrate. 2) The isolation, bronchoscopically obtained, of $\geq 10^4$ colony forming units (cfu).mL^{-1} of MDR Acinetobacter spp. or *P. aeruginosa* from bronchoalveolar lavage (BAL) fluid or 10^3 cfu·mL^{-1} of MDR Acinetobacter spp. or *P. aeruginosa* from protected specimen brush (PSB). 3) Presenting with at least one of the following: purulent secretions, abnormal temperature (>38°C or <36°C) and/or abnormal leukocyte count (>10,000 or <4,000 white blood cell count·mm^{-3}). Microorganisms were considered MDRs when they were resistant to two or more antimicrobial classes to which they are naturally susceptible. The Carb-S Acinetobacter spp. or *P. aeruginosa* group includes VAPs due to MDR organisms that were consistently susceptible to imipenem and/or meropenem. The Col-S Acinetobacter spp. or *P. aeruginosa* group includes VAPs due to MDR organisms that were susceptible to colistin but resistant to carbapenems and to all other parenteral available antibiotics.

All patients initiated antimicrobial therapy empirically. Treatment was eventually modified when pathogens were identified and their antimicrobial susceptibilities were available (definitive therapy). The onset of appropriate antibiotic therapy, empiric or definitive, was taken into account to evaluate the therapy and to determine its duration and the time elapsed until the detection of adverse events. The definitive therapy for patients with VAP due to Carb-S bacteria consisted of imipenem 2 g·day^{-1} (n=11) or meropenem 3 g·day^{-1} (n=19), while patients with VAP due to Col-S were treated with *i.v.* colistin 5 mg·kg^{-1}·day^{-1}. Doses were corrected in patients with renal failure according to formulas published elsewhere [7].

Demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) II score at ICU admission, underlying diseases, aetiological agent, reasons for mechanical ventilation, previous VAP episodes and number of days spent in hospital, in the ICU and on mechanical ventilation (before and after the diagnosis of VAP), were recorded. Data on previous antimicrobial therapy during the 10 days preceding VAP onset, reasons for such antimicrobial therapy, days receiving antibiotics for VAP with carbapenems or colistin and the impact on renal function were also taken into consideration. Since the initiation of colistin or carbapenem could happen 2–3 days after the diagnosis of VAP, when the result of cultures and antimicrobial susceptibility studies became available, serum creatinine change during follow-up was evaluated taking into account the day of onset of appropriate antibiotic therapy.

Serum creatinine concentration was obtained at the onset of appropriate therapy and 3, 5, 7, 10 and 14 days later. The bacterial antimicrobial susceptibility was established by disk diffusion. It was considered that antimicrobial therapy was inappropriate when the isolated microorganisms were not susceptible to the initial empiric antimicrobial therapy. A 28 day overall mortality after the diagnosis of VAP was evaluated.

Statistical analysis

Data are noted in absolute numbers, with or without percentages, as mean±SD or as medians with 1–3 quartiles. Unpaired t-tests were used to compare continuous variables, whereas Chi-squared or Fischer exact tests were used to compare categorical data and proportions. Univariate and multivariate analysis with forward stepwise logistic regression analysis for the variables that were significantly different in patients with Col-S, were applied in order to better understand the risk factors related to the development of Col-S VAP episodes. Variables were entered into the model when $p<0.05$. Adjusted odds ratios and 95% confidence intervals (CI) were calculated. The variation of serum creatinine concentration at 3, 5, 7, 10 and 14 days compared with the day of onset of antimicrobial therapy was recorded in patients receiving colistin or carbapenems by using a two-way ANOVA.

RESULTS

A total of 61 patients fulfilling the clinical and microbiological criteria for MDR Acinetobacter spp. or *P. aeruginosa* VAP in the BAL (n=55) or in the PSB culture (n=6) were included. Of the 61 cases, 30 were due to Carb-S and 31 to Col-S strains. Demographic and clinical data of the two groups are displayed in table 1. More than one pathogen was isolated in 11 specimens (1.18 per patient; table 2). Among the remaining 50 cases, 36 were due to Acinetobacter spp. and 14 were due to *P. aeruginosa.* All the Carb-S pathogens were susceptible to

TABLE 1 Demographic and clinical characteristics from patients with ventilator-associated pneumonia (VAP) due to multiple drug-resistant Acinetobacter spp. or *Pseudomonas aeruginosa* susceptible to carbapenem (Carb-S) and susceptible to colistin only (Col-S)

	Carb-S	Col-S	p-value
Subjects n	30	31	
Age yrs	61.3±17.8	55.3±19.5	0.142
APACHE II	18.2±6.9	20.1±8.4	0.548
Creatinine 10 days after VAP onset mg·dL^{-1}	1.21±0.89	1.32±1.29	0.754
Overall hospitalisation days	23 (17–28)	37 (25–70)	<0.001
Overall ICU stay days	21 (16–23)	30 (19–64)	<0.001
Days on mechanical ventilation	16 (10–22)	24 (14–55)	<0.001
Appropriate empiric antibiotic therapy	24	17	0.056
Overall mortality	13 (45.1)	16 (51.6)	0.696
Characteristics present at VAP onset			
Creatinine at the time of VAP diagnosis mg·dL^{-1}	1.31±0.92	1.42±1.45	0.749
Days on mechanical ventilation	7 (5–10)	16 (12–34)	<0.001
Days elapsed from admission to VAP diagnosis	6 (1–9)	15 (10.5–28.5)	<0.001
Days on prior antibiotics	5.0±3.1	13.3±7.1	<0.001
Previous episode of VAP	4 (12.5)	16 (51.6)	0.004
Prior antimicrobial therapy	22 (73.3)	30 (96.8)	0.026
Prior use of carbapenems	0 (0)	13 (41.9)	<0.001

Data are presented as mean±SD, mean (range) or n (%), unless otherwise stated. APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit.

imipenem and/or meropenem and to colistin. Additionally, among the 20 Carb-S Acinetobacter spp. isolates, nine were susceptible to ampcillin-sulbactam, three to piperacillin and/or tazobactam, two to levofloxacin and one to amikacin. Among the 11 Carb-S *P. aeruginosa* isolates (two cases with mixed aetiology due to Acinetobacter spp. and *P. aeruginosa*), six were susceptible to piperacillin and/or tazobactam, four to cefoperazone, three to ciprofloxacin, three to amikacin, two to levofloxacin and two to gentamicin. The 26 Acinetobacter spp. isolates and 11 *P. aeruginosa* Col-S isolates (seven cases with mixed aetiology due to Acinetobacter spp. and *P. aeruginosa*) were resistant to all the other parenteral available antibiotics (a small number were susceptible to minocycline, not available for parenteral use). In total, 29 patients died within 28 days after VAP onset (mortality=47.5%). Mortality rates for Acinetobacter spp. and *P. aeruginosa* were 41.7 and 61.3%, respectively (p=0.361), when they were the only isolated microorganism. Length of hospital stay after VAP diagnosis in survivors was 45.8±110.2 days. Admissions were due to medical (62%) and surgical (38%) reasons. Demographic and clinical data from the patients for the Carb-S and Col-S groups of patients are displayed in table 2.

TABLE 2 Microorganisms isolated in respiratory specimens obtained by bronchoalvelolar lavage[#] or protected specimen brush[¶]

	Total	Carb-S	Col-S
Subjects	61	30	31
Acinetobacter baumannii	46	20	26
Pseudomonas aeruginosa	24	13	11
Staphylococcus aureus	1	1	
Klebsiella pneumoniae	1	1	
Microorganisms per VAP episode	1.18	1.17	1.19

Data are presented as n. Carb-S: carbapenems susceptible; Col-S: colistin susceptible only; VAP: ventilator-associated pneumonia. [#]: n=55; [¶]: n=6.

Antimicrobial therapy

The duration of therapy in patients who survived ⩾15 days was 12.0±6.2 and 12.2±5.8 days for the Carb-S group and the Col-S group, respectively. No difference was observed in the mortality rate between the Carb-S and the Col-S groups, but hospital and ICU length of stay were significantly longer for patients in the Col-S group (table 1). In most cases, initial empirical antimicrobial therapy included a β-lactam active against MDR Gram-negative bacilli (carbapenem or piperacillin-tazobactam). Some patients also received an aminoglycoside or ciprofloxacin and/or colistin as part of this empirical antimicrobial therapy. In 20 patients this therapy was inappropriate, 14 from the Col-S group and six from the Carb-S group (p=nonsignificant). However, a significantly higher mortality rate was identified in patients who received an initial inappropriate therapy (70 *versus* 36.6%; p=0.014). This difference persisted in patients who had switched to an appropriate therapy a few days after the starting point (fig. 1). The mortality rate for the VAP episodes caused by Acinetobacter spp. or *P. aeruginosa* treated with appropriate empiric antimicrobial therapy was exactly the same (*i.e.* 33.3%; eight out of 24 patients and three out of nine patients, respectively).

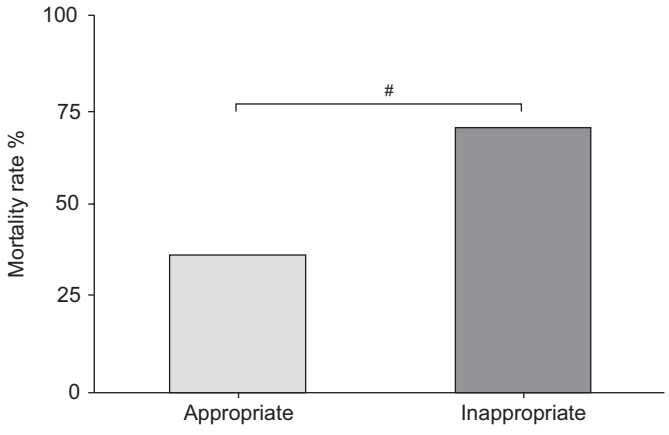

FIGURE 1. Mortality rates in the overall population of 61 patients related to empirically prescribed antimicrobial therapy appropriateness (36.6% in the appropriate therapy and 70.0% in the inappropriate therapy groups, respectively) at the time of ventilator-associated pneumonia diagnosis. The therapeutic measure taken prior to confirming the nature of the microorganisms involved and their antimicrobial susceptibility was taken into account. Appropriate antimicrobial therapy was administered more commonly to patients with carbapenems-susceptible rather than colistin-susceptible pneumonia. #: p=0.014.

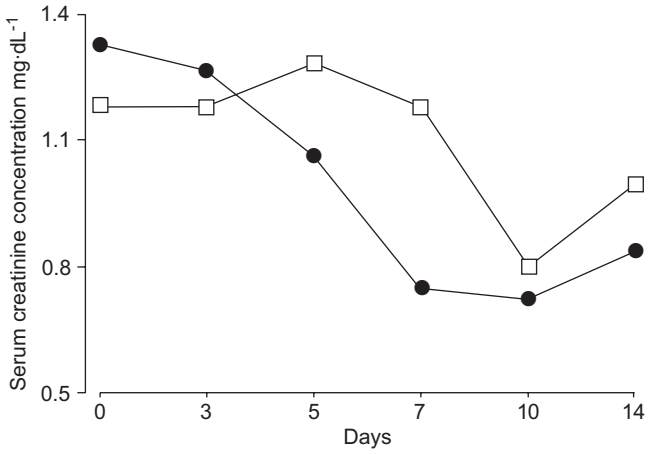

FIGURE 2. Mean serum creatinine concentration evolution in both carbapenem-susceptible (□) and colistin-susceptible (●) groups from the onset of ventilator-associated pneumonia to 14 days after administration of the initial appropriate antimicrobial therapy (carbapenem or colistin). There was no difference in the serum creatinine concentration between the two groups compared (two-way ANOVA).

Other characteristics during hospitalisation

The APACHE II score at ICU admission and the mortality rate were similar in both groups (table 1). In the present cohort, hospitalisation was very long (28 (23–41) days). During the ICU stay (23 (17–34) days), patients remained on mechanical ventilation for 19 (14–28) days. Comparing both VAP groups, hospitalisation time, time in ICU, days on mechanical ventilation and days in the ICU before VAP onset were significantly shorter in patients with Carb-S isolate compared with those Col-S Acinetobacter spp. or *P. aeruginosa* (table 1). Prior antimicrobial treatment, particularly with carbapenems, and a previous VAP history were significantly more frequent in the Col-S groups.

TABLE 3 Reasons for prior antimicrobial therapy in 52 patients

	Carb-S	Col-S	p-value
Subjects	21	31	
Nosocomial pneumonia including VAP	1	15	0.001
Community-acquired pneumonia	5	7	1.000
Intra-abdominal infection	3	5	1.000
Other lower respiratory tract infections	4	1	0.145
Acute exacerbation of COPD	4	0	0.022
Bacteremia or sepsis	1	2	1.000
Miscellaneous	3	1	0.291

Data are presented as n. Carb-S: carbapenems susceptible; Col-S: colistin susceptible; VAP: ventilator-associated pneumonia; COPD: chronic obstructive pulmonary disease.

In total, 30 Col-S and 25 Carb-S patients had received antimicrobial therapy prior to VAP diagnosis (p=0.012). The duration of prior therapy was 9.2±6.8 days (5.2±2.5 and 12.3±4.3 days for the Carb-S and the Col-S groups, respectively; p<0.0001). The two most common causes for prior antimicrobial treatment were community- and hospital-acquired respiratory tract infections. All antimicrobial therapy causes are listed in table 3. Approximately 41% of the Col-S episodes, but none of the Carb-S episodes, had received prior carbapenem therapy.

Renal function evaluation

By the time of onset of appropriate VAP therapy, the mean serum creatinine concentration was within the normal range (1.32±1.19 mg·dL^{-1}) and there was no difference between the Carb-S and Col-S groups. Comparing the value observed at onset of appropriate therapy with the levels observed 3, 5, 7 and 10 days later, there was a trend towards a reduction of serum creatinine concentration in both groups (fig. 2). Twelve (seven in the Carb-S and five in the Col-S group) patients had an initial serum creatinine level >1.4 mg·dL^{-1}(normal limit). On days 3 and 5, there were five (two Carb-S and three Col-S) and six (two Carb-S and four Col-S) patients, respectively, with a creatinine level ⩾1.4 mg·dL^{-1}. Considering the 34 patients with normal renal function at onset of appropriate antibiotic therapy remaining in the study for ⩾5 days, and taking into account the creatinine level on days 0, 3 and 5, it was observed that on day 3, there were four patients with a creatinine level ⩾1.4 mg·dL^{-1} (two in each group) and on day 5 there were two patients in each group with a creatinine level ⩾1.4 mg·dL^{-1}. Four patients (one in the Carb-S and three in the Col-S group) had a serum creatinine value ⩾4.0 mg·dL^{-1}, but none of them presented worsened renal function during the antimicrobial therapy (data not shown). None of the 61 patients who participated in the present study required dialysis either at onset or during the follow-up of VAP.

TABLE 4 Categorical variables significantly associated with colistin-susceptible ventilator-associated pneumonia (VAP) in univariate and multivariate analysis

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	β-coefficient (95% CI)	p-value
Duration of mechanical ventilation >30 days	17.7 (1.7–179.4)	0.016		
Overall hospitalisation >50 days	17.7 (1.7–179.4)	0.001		
Overall ICU stay >40 days	20.5 (2.0–205.5)	<0.001	31.6 (31.5–495.9)	0.014
Characteristics present at VAP onset				
Duration of prior antimicrobial therapy >10 days	31.5 (2.9–340.4)	<0.001	13.2 (2.2–78.7)	0.005
Time from admission to VAP diagnosis >16 days	27.1 (2.7–269.5)	<0.001		
Previous episode of VAP	27.7 (2.8–273.5)	<0.001	6.0 (1.0–35.7)	0.047
Prior use of carbapenems	21.7 (2.2–212.9)	<0.001		

OR: odds ratio; CI: confidence interval; ICU: intensive care unit.

Multivariate analysis

A multivariate logistic regression model was applied to the categorical variables to disclose which conditions were significantly related to Col-S isolates. The forward stepwise model using the therapy with colistin or carbapenems as the dependent variable demonstrated that duration of prior antimicrobial therapy >10 days remained significantly associated with the Col-S condition at VAP onset. Overall ICU stay for >40 days was also associated to Col-S VAP (table 4).

DISCUSSION

Although *i.v.* colistin is accepted as an antimicrobial option for specific MDR pathogens [17], the clinical experience with this antibiotic is poor. In fact, it has practically been discontinued due to the occurrence of serious adverse effects and the availability of other suitable alternatives. The development of MDR Col-S Gram-negative infections, particularly in critically ill patients, has led to a renewed interest on this drug.

It has been acknowledged that VAP episodes caused by the so-called ''high-risk pathogens'', particularly the nonfermenting Gram-negative bacilli Acinetobacter spp. and *P. aeruginosa*, are associated with a higher mortality rate when compared with other microorganisms. A relative risk of 2.5 has been recorded [18]. The increased incidence of nosocomial infections due to MDR pathogens has grown impressively during recent decades [19–23]. This microbiological data has resulted in a more frequent use of inappropriate antimicrobial therapy [8, 10, 24]. Imipenem and meropenem have been the most effective antimicrobials against Acinetobacter spp. and *P. aeruginosa* during the last decade. Resistance to these antimicrobials is nearly always associated with nonsusceptibility to other β-lactams, fluoroquinolones and aminoglycosides [3, 4]. It remains unknown whether bacterial resistance to carbapenems has an intrinsic higher risk of morbidity or mortality. Similarly to previous studies, the results of the present study concerning this topic indicate that the mortality rate is comparable between patients with severe infections due to Carb-S and Col-S Acinetobacter spp. or *P. aeruginosa* [6, 25]. It was observed, however, that inappropriate therapy was consistently associated with higher mortality, regardless of which antimicrobial was used.

TROUILLET *et al.* [21] identified several factors related to the acquisition of VAP due to MDR microorganisms, including a duration of mechanical ventilation >7 days, prior antimicrobial therapy and the use of broad-spectrum antibiotics. Similarly, RIOS *et al.* [22] identified hospitalisation prior to VAP onset during >5 days and the use of prior antimicrobial therapy as risk predictors of VAP caused by MDR pathogens.

Reports about colistin-related toxicity pointed out a variable incidence and established that their adverse effects are transient [6, 26, 27]. CONWAY *et al.* [28] considered that the first reports of adverse events could be erroneously attributed to colistin due to the complexity of the clinical background observed in those patients. Aminoglycosides and glycopeptidic antimicrobials are commonly used in critically ill patients, but these highly effective antibiotics may also produce nephrotoxicity in a large number of patients [29, 30]. The knowledge of the pharmacokinetics and pharmacodynamics of colistin administered intravenously is limited. In an experimental mice comparative model about the efficacy of different antibiotics against pneumonia caused by MDR Acinetobacter spp., MONTERO *et al.* [31] reported that, disregarding its *in vitro* microbiological activity according to its minimum inhibitory concentration, the results were discouraging with regards to the use of colistin to treat Acinetobacter spp. pneumonia. These results require careful interpretation and any extrapolation to humans should be done with caution.

Several studies on efficacy and/or safety of parenteral colistin for critically ill patients with VAP or other severe infections due to MDR Acinetobacter spp. or *P. aeruginosa* have been published in recent years [6, 25, 32, 33]. GARNACHO-MONTERO *et al.* [6] compared 21 carbapenem-resistant strains of Acinetobacter spp. VAP episodes treated with colistin with 14 carbapenem-susceptible VAP episodes treated with imipenem, but no differences were found regarding efficacy, nephrotoxicity or neurotoxicity. LINDEN *et al.* [33] studied 23 critically ill patients infected with MDR *P. aeruginosa* and treated with colistin, including 18 who had pneumonia. Out of these 23 patients, 14 had a favourable clinical response. In that study, bacteremia was the only factor associated with therapeutic failure. KASIAKOU *et al.* [32] studied 54 episodes

of severe infections in cystic fibrosis patients due to MDR Gram-negative bacteria treated with a combination therapy, which included parenteral colistin. It was reported that 8% of the patients worsened their renal function during therapy, while 67% improved or were cured, showing colistin's safety and effectiveness. Finally, in a study of 185 critically ill patients with Acinetobacter spp. or *P. aeruginosa* infections (55 were treated with colistin and 105 of the remaining 130 were treated with a carbapenem), REINA *et al.* [25] concluded that colistin was as safe and effective as other antibiotics. However, the authors did not find an association between inappropriate antimicrobial therapy, more common in the colistin group, and poorer outcome.

Regarding renal function, serum creatinine concentration was thoroughly examined. No significant adverse effects attributable to colistin were found in the present cohort. Regarding patients with normal renal function at the onset of appropriate antibiotic therapy, a few of them showed a mild and transient elevation of serum creatinine levels. Approximately half of the patients that presented an abnormal initial serum creatinine concentration observed a decrease in their levels during colistin therapy.

Multivariate analysis demonstrated that previous VAP episodes and prior antimicrobial therapy for >10 days are risk factors for VAP due to Col-S *P. aeruginosa* or Acinetobacter spp. This group also showed a longer stay in the ICU.

Delay in the initiation of antimicrobial therapy increases the VAP mortality rate [29, 34]. A higher mortality rate was found in patients who did not receive appropriate therapy or received it with delay, in comparison with those that received appropriate therapy. It is believed that in patients with a high risk of harbouring MDR nonfermenting Gram-negative bacteria admitted to ICUs with similar epidemiological conditions to patients included in the present study, it could be appropriate to begin the empiric initial antimicrobial therapy using colistin. In fact, the current American Thoracic Society/Infectious Diseases Society of America guidelines for hospital-acquired, ventilator-associated and healthcare-associated pneumonia recommend considering colistin as a therapy for patients with VAP attributed to carbapenem-resistant Acinetobacter spp. [17].

The present study has several limitations. It is a retrospective study on a relatively reduced number of patients that were recruited at three different institutions, thus many factors were not controlled and it may present biases inherent to this kind of study. The analysis of Acinetobacter spp. and *P. aeruginosa* together could be inappropriate, as these are different microorganisms and could have different response to therapy. A prospective randomised study with more patients is necessary to analyse in depth the factors associated with the development of Col-S Acinetobacter spp. or *P. aeruginosa* VAP and to confirm the findings of the present study. The results of the current study are limited by the high incidence of MDR pathogens in the participating institutions and the local ICU practice, as evidenced by a high rate of carbapenem use as empiric therapy for VAP (24 Carb-S patients received carbapenems empirically, while 12 Col-S patients had also received previous carbapenem therapy). Carbapenems often represent the last line of β-lactam therapy due to their greater resilience against common resistance mechanisms (*e.g.* β-lactamases).

Colistin should not always be recommended as first-line therapy. Physicians should know their own ecology and should only consider colistin use as an option when there are risk factors for Col-S isolates and, as a consequence, there is no other choice (*i.e.* highly selected patients with a previous VAP episode and prior use of antimicrobial therapy, especially carbapenems, for >10 days).

In summary, patients with multiple drug-resistant colistin-susceptible *Pseudomonas aeruginosa* or Acinetobacter spp. ventilator-associated pneumonia are characterised by presenting some of the following: previous ventilator-associated pneumonia episodes; prior broad-spectrum antimicrobial therapy for >10 days (particularly carbapenems); and delayed onset of ventilator-associated pneumonia from the intensive care unit admission. Under these conditions, in intensive care units with the ecological characteristics described in the present study, colistin could be a suitable antibiotic for initial empiric antimicrobial therapy.

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