A Closer Look at Aerosolized Colistin

To the Editor—With great interest I read a recent article by Kofteridis et al [1], who investigated the effect of aerosolized colistin in addition to intravenous colistin on clinical cure and mortality

rates in multidrug resistant gram-negative ventilator-associated pneumonia. I do have some concerns about the statistics, presentation of data, and conclusion, however.

One omission was that total colistin dose was not taken into account. Clearly, the aerosolized-plus-intravenous-colistin group received higher cumulative colistin dose, as treatment duration was median 3 days longer and 2 million aerosolized colistin units were added to 9 million intravenous units. Also, there was more renal failure in the intravenous-colistin group, which probably led to lower dosing in that group. As Nation and Li recently already pointed out in their review on the reemergent use of colistin, more research is needed on colistin's precise dose-effect relationship and the influence of different routes of administration [2].

Curiously, the Kaplan–Meier curves show survival for the deceased persons as they all end at 0% and the numbers of deaths in each group that can be derived from them do not correspond to the numbers given in Table 2.

Subgroup analysis, as with the *Acinetobacter baumannii* subpopulation, is not very informative when absolute numbers with corresponding confidence intervals are not given. Results are nearly always nonsignificant in small groups due to large β error.

Most importantly, I disagree with the authors' overall conclusion there was no added benefit of aerosolized colistin. In multivariate analysis, the authors found a nearly significant odds ratio for clinical cure in the aerosolized-plus-intravenous-colistin group of 2.375 (95% CI, .901–6.258; $P = .08$), which seems a rather strong effect in a small group of 86 patients. Absolute and relative mortality differences were also large (7 vs 11 out of 43, 16% vs 26%) but didn't reach 5% significance level, and results were not tested multivariately. The possibility of β error was not thoroughly discussed, and a large and clinically relevant absolute mortality difference cannot be excluded. To what extent total colistin dose or specific administration route added to this effect remains to be determined. All together, however, results look promising and should prompt further research in this direction.

I agree with the authors ultimately: More randomized controlled trials are needed, but as a start, retrospective studies with presentation of confidence intervals instead of *P*-values, larger sample sizes, and better-controlled dosing schemes would make comparison and pooling of data possible.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgements section.

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Clinical Infectious Diseases 2011;52(12):1472–1473

1058-4838/2011/5212-0016$14.00
DOI: 10.1093/cid/cir248

resistant gram-negative infections for which polymyxins are sometimes the only active antimicrobial agents [3]. We have considered all of the questions raised.

Indeed, patients in the aerosolized (AS)—intravenous (IV) group received higher total colistin doses. This was part of the design of the study. However, no difference in clinical success and/or mortality has been observed between the groups (one of the major objectives) [2]. We agree that patients in the IV group had renal dysfunction more often. However, this did not result in worse outcomes (another objective of the study).

Regarding the Kaplan-Meier curves and number of deaths, the numbers in Table 2 are in full accordance with the number of deaths in the curves. The horizontal steps in the curves are step functions, where each step down indicates presence of an event (death in this study). Thus, each death represents a downward step in the curve. When we try to extract the number of events from the curves, it is crucial to keep in mind that two or more events can coexist at a specific time, so the drop can be twice as large or more.

The Analysis [illegible] has been performed, and absolute numbers, *P* values, and confidence intervals are available. We did not include this information in the article in order to keep the numbers brief and avoid confusion.

We agree that the small sample size of the study population permits beta error vulnerability. Indeed, we have described the sample size as the major limitation of the study [2]. The author, based on this potential bias and on the results of the multivariate analysis, thinks that the odds ratio reveals a strong effect regarding the clinical cure rate in favor of AS-IV colistin. This is one side of the coin. We should keep in mind that studies with small-to-moderate sample sizes employing logistic regression to study the association of exposure variables (in the present case, AS-IV or IV

Reply to van Leeuwen

To The Editor—We appreciate the comments provided by D.H.J. van Leeuwen [1] regarding our article [2]. We understand the concern for multidrug-

colistin) and outcome (clinical cure) may overestimate the effect measure [4]. Thus, the presented "nearly significant" odds ratio could be an overestimation due to the small sample size rather a true effect of the AS-IV colistin in this outcome measure.

Considering complementary information deriving from *P* value and confidence intervals [5], we do not believe that retrospective studies should present confidence intervals instead of *P* values.

Overall, we had to comply with statistical rules. Hence, since differences did not reach significant levels, we reported no difference in outcomes between the two groups. Additionally, the study population could not be bigger considering practical difficulties in conducting such studies [6].

Finally, the author comes to the same conclusion as we did regarding the need for further randomized control trials.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgements section.

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Clinical Infectious Diseases 2011;52(12):1473–1474

1058-4838/2011/5212-0017$14.00
DOI: 10.1093/cid/cir251

MAJOR ARTICLE

Aerosolized plus Intravenous Colistin versus Intravenous Colistin Alone for the Treatment of Ventilator-Associated Pneumonia: A Matched Case-Control Study

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(See the editorial commentary by Paterson and Rogers, on pages 1245–1247.)

Objectives. The incidence of ventilator-associated pneumonia (VAP) due to multidrug-resistant (MDR) organisms is increasing. Intravenous (IV) colistin or aerosolized (AS) plus IV colistin have been recently used to treat these life-threatening infections. The purpose of this study was to compare the efficacy and safety of AS plus IV colistin versus IV colistin alone for patients with MDR VAP due to gram-negative bacteria.

Methods. A retrospective matched case-control study was performed at the Intensive Care Unit of the University Hospital of Heraklion, Greece, from January 2005 through December 2008. Forty-three patients with VAP due gram-negative MDR pathogens received AS plus IV colistin and were matched on the basis of age and Acute Physiology and Chronic Health Evaluation II score with 43 control patients who had received IV colistin alone.

Results. Demographic characteristics, clinical status, and gram-negative isolated pathogens were similar between the 2 treatment groups. *Acinetobacter baumannii* (66 cases [77%]) was the most common pathogen, followed by *Klebsiella pneumoniae* (12 cases [14%]) and *Pseudomonas aeruginosa* (8 cases [9.3%]). No colistin-resistant strains were isolated from patients in either group. No significant differences between the 2 groups were observed regarding eradication of pathogens ($P = .679$), clinical cure ($P = .10$), and mortality ($P = .289$). Eight patients (19%) in each treatment group developed reversible renal dysfunction. No AS colistin–related adverse events were recorded.

Conclusions. Addition of AS colistin to IV colistin did not provide additional therapeutic benefit to patients with MDR VAP due to gram-negative bacteria.

Ventilator-associated pneumonia (VAP) is a serious and common complication for patients in the intensive care unit (ICU) with considerable morbidity and mortality [1–4]. The growing epidemic of infections in the ICU caused by multidrug-resistant (MDR) pathogens [5, 6] has led clinicians to reconsider prescribing polymyxin antimicrobials (polymyxin B and colistin [polymyxin E])—drugs that were removed from use in the past because of their neuro- and nephrotoxicity [7, 8].

There is limited information on the pharmacokinetics of colistin after intravenous (IV) administration, and its effectiveness for treatment of pneumonia has been questioned because of its inadequate penetration in the lung parenchyma [9]. However, there are several reports of successful treatment of pneumonia with IV colistin [8–10].

Because inhaled antibiotics deliver high drug concentrations at the site of infection with ignorable systemic absorption and toxicity, aerosolized (AS) colistin appears to be a suitable option for the treatment of patients with ventilator-associated pneumonia (VAP) due to MDR pathogens. AS colistin has shown its value in preventing and treating infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis [11–14]. However, there are limited data on the efficacy and safety profile of inhaled colistin in patients with VAP [11, 15–18].

Received 2 March 2010; accepted 27 May 2010; electronically published 25 October 2010.

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Clinical Infectious Diseases 2010;51(11):1238–1244

1058-4838/2010/5111-0003$15.00
DOI: 10.1086/657242

Table 1. Demographic and Clinical Characteristics of Study Patients

Characteristic	IV colistin (n = 43)	AS-IV colistin (n = 43)	P
Age, mean years ± SD	62.35 ± 14.92	62.00 ± 15.14	.890
Sex, male/female	30/13	28/15	.645
Mean APACHE II score ± SD	17.74 ± 7.61	16.95 ± 6.59	.852
Reason for admission			
Acute respiratory failure	16 (37)	12 (28)	.357
Shock	7 (16)	5 (12)	.532
Postoperative resuscitation	3 (7)	8 (19)	.106
Multiple trauma	5 (12)	3 (7)	.713
Underlying disease			
Diabetes mellitus	5 (12)	4 (9)	.725
Chronic obstructive pulmonary disease	12 (28)	7 (16)	.194
Malignancy	9 (21)	3 (7)	.117
Renal failure	5 (12)	1 (2)	.202
Prior receipt of antibiotic therapy	40 (93)	38 (88)	.458
Immunosuppressive therapy	10 (23)	5 (12)	.115
Prior blood transfusion	12 (28)	15 (35)	.486
Presence of fever	38 (88)	34 (79)	.243
Septic shock	3 (7)	4 (9)	.693
Microorganism			
Acinetobacter baumannii	31 (72)	35 (81)	
Klebsiella pneumoniae	7 (16)	5 (12)	.584
Pseudomonas aeruginosa	5 (12)	3 (7)	
Duration of ICU stay, median days (range)	18 (3–78)	20.5 (3–93)	.676
Duration of MV, median days (range)	16.5 (5–62)	15 (3–97)	.840
Duration of colistin therapy, median days (range)	10 (4–36)	13 (5–56)	.080

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE II, Acute Physiology and Chronic Health Evaluation; AS, aerosolized; ICU, intensive care unit; IV, intravenous; MV, mechanical ventilation; SD, standard deviation.

The purpose of this study was to compare the efficacy and safety of AS plus IV colistin versus only IV colistin in patients with MDR VAP due to gram-negative bacteria.

PATIENTS AND METHODS

Setting and Study Design

Patient population. This retrospective case-control matching study (ratio, 1:1) was performed at the intensive care unit (ICU) of the University Hospital of Heraklion (Crete, Greece), an 11-bed medical-surgical unit. All patients with culture-documented monomicrobial VAP due to *Acinetobacter baumanii, Pseudomonas aeruginosa,* or *Klebsiella pneumoniae* that was susceptible only to colistin during the period January 2005–December 2008 were potentially eligible for the study.

Eligible case patients had received ⩾6 doses of AS therapy and ⩾3 days of IV therapy (the AS-IV colistin group) [15]. Control patients had to have had received IV colistin for ⩾3 days without AS colistin therapy (the IV colistin group). Control patients were chosen according to the following matching criteria: age (±5 years) and Acute Physiology and Chronic Health Evaluation (APACHE) II score (±4 points) on the day of the introduction of colistin therapy. If >2 control patients were available, the date of ICU admission was used as an additional matching criterion. The additional matching criterion was necessary for the equal distribution of patients in the 2 treatment groups during the 2 study periods. Thus, 11 patients were distributed in each arm during the first 2 years, and 32 patients were distributed in each arm during the last 2 years of the study. In selecting control patients, the investigators were not aware of the outcome of the treatment.

Data from all case patients were reviewed independently by 2 infectious disease specialists (G.S. and D.P.K.) to check the clinical outcomes in case and control patients. In the event of a discrepancy, the 2 reviewers assessed the records again and reached a consensus decision. The response to treatment was assessed at the time of discharge from the ICU or at the end of antimicrobial therapy. The 2 investigators were not aware of the patient's therapy.

Definitions. Pneumonia was considered to be ventilator-associated if the onset occurred after the patient was intubated for ⩾48 h and the infection was judged not to have been incubating before the initiation of mechanical ventilation [8].

Table 2. Clinical and Bacteriological Outcomes, Mortality, and Adverse Events in Both Treatment Groups

Outcome	No. (%) of patients		P
	IV colistin group (n = 43)	AS-IV colistin group (n = 43)	
Clinical outcome			
Clinical cure	14 (32.5)	23 (54)	.05
Clinical improvement	12 (28)	9 (21)	.451
Clinical failure	14 (32.5)	7 (16)	.126
Recurrence	3 (7)	4 (9)	>.99
Bacteriological outcome[a]			
Eradication	17 (50)	19 (45)	.679
Persistent	12 (35)	10 (24)	.272
Recurrence	2 (6)	5 (12)	.450
Colonization	3 (9)	8 (19)	.208
Mortality			
All-cause	18 (42)	10 (23)	.066
VAP-related	11 (26)	7 (16)	.289
Adverse events			
Nephrotoxicity	8 (19)	8 (19)	>.99
Neurotoxicity	0	0	

NOTE. AS, aerosolized; IV, intravenous; VAP, ventilator-associated pneumonia

[a] Bacteriological outcome was evaluated in 34 patients in the IV colistin group and in 42 patients in the AS-IV colistin group.

Pneumonia was diagnosed on the basis of a radiographic finding of a new and progressive pulmonary infiltrate and at least 2 of the following clinical criteria: body temperature, >38°C or <35.5°C; leukocytosis (leukocyte count, >12,000 cells/mm^3) or leukopenia (leukocyte count, <4000 cells/mm^3); and clinical evidence suggestive of pneumonia, such as purulent bronchial secretions and a decrease in oxygenation [19].

Microbiological diagnosis of VAP was established by positive cultures of bronchial secretions or bronchoalveolar lavage with isolation of an MDR gram-negative bacterium with a concentration of $\geqslant 10^4$ CFU/mL [18]. Bacteriologic sampling was performed for all patients on the day that VAP was suspected (day 0), before new antimicrobials were started. The severity of the clinical condition was assessed according to the APACHE II score [20]. The response to treatment was assessed at the time of discharge from the ICU or at the end of antimicrobial therapy, especially if the patient remained hospitalized for a non VAP-related disease.

The primary end point of the study was the clinical outcome of VAP. As secondary end points, we evaluated microbiological outcome, VAP-related mortality, all-cause mortality, and the occurrence of adverse events during colistin treatment.

Clinical outcome was classified as clinical cure (ie, resolution of presenting symptoms and signs of infection by the end of colistin treatment), clinical improvement (ie, partial resolution of presenting symptoms and signs of infection), clinical failure (ie, persistence or worsening of presenting symptoms and/or signs of infection during colistin administration), and recurrence of infection (ie, occurrence of a new episode of infection at least 72 h after clinical resolution of a preceding episode). Clinical success was defined as clinical cure or clinical improvement.

Microbiological outcome was rated as eradication of the pathogen (ie, no growth of the pathogen in the final culture of specimens during the entire hospitalization), persistence of the pathogen (ie, persistent growth of the responsible pathogen regardless of the clinical outcome of the infection), recurrence (regrowth) of the pathogen (ie, reisolation of the same pathogen regardless of the clinical outcome of the infection), or colonization (ie, persistence or regrowth of the pathogen without symptoms and signs of infection).

VAP-related mortality was defined as death that occurred during the treatment period when the signs of pneumonia remained and as death due to septic shock.

In patients with normal renal function, nephrotoxicity was defined as a serum creatinine value >2 mg/dL; as a reduction in the calculated creatinine clearance of 50%, compared with the value at the start of treatment; or as a decline in renal function that prompted renal replacement therapy. In patients with preexisting renal dysfunction, nephrotoxicity was defined as an increase of >50% of the baseline creatinine level or as a reduction in the calculated creatinine clearance of 50% relative to the value at therapy initiation. All adverse effects related to AS colistin use, such as bronchoconstriction, cough, apnea, or chest tightness, and arterial hypoxemia were recorded.

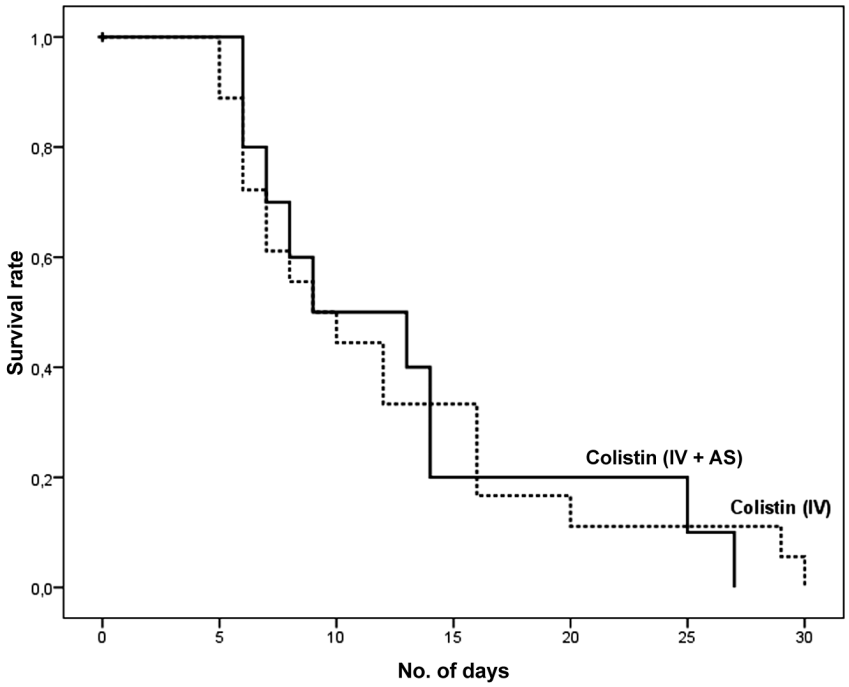

Figure 1. All-cause mortality in the 2 treatment groups. AS, aerosolized; IV, intravenous.

The following variables were also recorded demographic characteristics; cause of ICU admission; duration of ICU stay; comorbidities, including chronic lung disease, malignancy, diabetes mellitus, and renal failure; antineoplastic therapy; use of systemic corticosteroids and antibiotics 1 week prior to and/or during the infectious episode; previous surgery; length and dosage of colistin treatment; simultaneous use of other antimicrobials; causative bacteria; source of diagnostic culture; antimicrobial susceptibility; the results of laboratory and imaging tests; treatment-associated adverse events; clinical and microbiological outcome; and VAP-associated and overall mortality.

Microbiological Testing

Susceptibility testing of gram-negative microorganisms was performed using an automated broth microdilution method (Organon Teknika Corp). The breakpoints used were those defined by the Clinical and Laboratory Standards Institute [21]. Susceptibility to colistin was also tested using the Etest methodology (susceptibility, $\leqslant$2 mg/L; resistance, $\geqslant$4 mg/L) and the disk diffusion method with a 10-μg colistin sulfate disk. Gram-negative microorganisms were defined as MDR susceptible only to colistin if they were resistant to all of the 6 antipseudomonal classes of antimicrobial agents (antipseudomonal penicillins, cephalosporins, carbapenems, monobactams, fluoroquinolones, and aminoglycosides) for *P. aeruginosa* and *K. pneumoniae,* and in addition, resistance to ampicillin-sulbactam and tetracycline for *A. baumanii.*

Treatment Regimen

The daily dose of AS colistin was 2 million international units (IU) divided into 2 doses, whereas the daily dose of IV colistin was 9 million IU divided into 3 doses in patients with normal renal function.

Data Management and Statistics

Data were collected on forms and were computerized and analyzed using SPSS software, version 16.0 (SPSS). Variables for the matched case-control pairs were compared by Wilcoxon matched pairs test. The χ^2 or Fisher exact test was used to assess differences in categorical variables, as appropriate. Differences in continuous variables were assessed by the Student *t* test or nonparametric Mann-Whitney *U* test. Kaplan–Meier curves were used to assess differences between the IV group and the IV plus AS group and overall mortality. The log-rank test was used to determine the level of statistical significance when comparing survival curves. Multivariate logistic regression analysis was used to assess the independent effect of therapy on each of the 2 outcomes (clinical cure and microorganism eradication). *P* values are 2-tailed, and *P* values $<.05$ were considered to be statistically significant.

RESULTS

During the 4-year study period, 151 patients with MDR-gram negative VAP treated with colistin were identified. Ninety-five patients were available as control patients, and there were 56

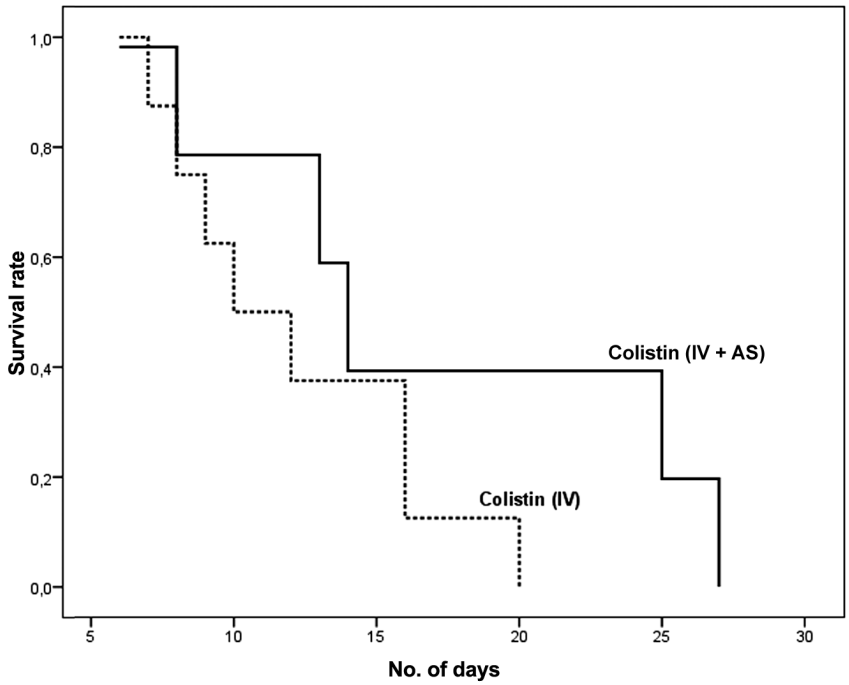

Figure 2. Ventilator-associated pneumonia–related mortality in the 2 treatment groups. AS, aerosolized; IV, intravenous.

potentially eligible case patients who had received simultaneous AS and IV colistin treatment.

Among them, we evaluated 43 case patients with MDR VAP due to gram-negative bacteria who received simultaneous AS and IV colistin and 43 corresponding control subjects who received IV colistin alone matched for age and APACHE II score on the day of introduction of colistin for VAP; their baseline characteristics are shown in Table 1. The median duration of hospitalization in the ICU was similar for both groups: 18 days (range, 3–75 days) for the IV colistin group and 20.5 days (range, 3–93 days) for the AS-IV colistin group ($P = .676$).

The pathogens responsible for VAP were *A. baumannii* (66 cases [77%]), *K. pneumoniae* (12 cases [14%]), and *P. aeruginosa* (8 cases [9.3%]). One patient in the IV colistin group had concurrent *A. baumannii* bacteremia, whereas in the AS-IV colistin group, 2 patients had *A. baumannii* bacteremia and 1 had *K. pneumoniae* bacteremia No colistin-resistant strains were isolated from patients in either group.

A separate analysis of VAP cases due to *A. baumannii,* which was the most common pathogen in both arms, was performed to exclude a potential effect of other pathogens on outcome. No significant differences between the 2 arms in terms of clinical and microbiological outcome or mortality were found.

The median duration of therapy was comparable between the 2 treatment groups: 10 days (range, 4–36 days) for the IV colistin group and 13 days (range, 5–56 days) for the AS-IV colistin group ($P = .840$).

The clinical and bacteriological outcomes for the 2 treatment groups are summarized in Table 2. No significant differences were found in bacteriological outcome between the 2 treatment groups. Eradication of the causative microorganism was achieved in 17 (50%) of 34 patients in the IV colistin group and in 19 (45%) of 42 patients in the AS-IV colistin group.

The patients in AS-IV colistin group had a marginally better rate of clinical cure than did patients in IV colistin group (23 [54%] of 43 patients vs 14 [32.5%] of 43 patients; $P = .05$). However, we found no statistically significant difference in terms of clinical success (26 [60%] of 43 patients in the IV colistin group vs 33 (74%) of 43 patients in AS-IV colistin group; $P = .10$).

To investigate the role of simultaneous AS and IV colistin treatment as an independent predictor of clinical cure, a logistic regression model was used, with adjustments for renal failure, presence of diabetes mellitus, malignancy, prior immunosuppressive treatment, and prior antibiotic or corticosteroid use. No statistically significant better clinical cure rate was observed in association with AS-IV colistin treatment (odds ratio, 2.375; 95% confidence interval, 0.901–6.258; $P = .080$).

Overall, the mortality rate in the ICU was 42% (18 of 43 patients) in the IV colistin, compared with and 24% (10 of 43 patients) in the AS-IV colistin group ($P = .066$). The VAP-related mortality rates were 26% (11 of 43 patients) and 16% (7 of 43 patients), respectively ($P = .289$). Kaplan-Meier curves revealed no statistically significant differences in either all-cause mortality ($P = .888$, by log-rank test) or VAP-related mortality ($P = .268$, by log-rank test) (Figures 1 and 2).

Eight patients (19%) in each treatment group presented with renal dysfunction. One patient in the IV colistin group had preexisting mild chronic renal disease. In all 16 patients, the dose of colistin was reduced; none of the patients required renal replacement therapy or discontinuation of colistin treatment. No adverse events, such as bronchoconstriction, apnea, or chest tightness, were associated with AS colistin therapy. In addition, neurotoxic adverse effects were not observed in any patient in either treatment group.

DISCUSSION

The main finding of the present study was that the addition of AS to IV colistin did not provide any additional therapeutic benefit to patients with MDR VAP due to gram-negative bacteria. In addition, adverse events associated with systemic and AS use of colistin, such as nephrotoxicity, neurotoxicity, and direct toxicity on airways, were not observed.

VAP is the most frequent nosocomial infection in the ICU; it affects up to 27% of patients undergoing mechanical ventilation and is associated with considerable morbidity and mortality [8, 22]. The increasing rate of VAP due to gram-negative MDR strains resistant to almost all available antimicrobials has led to the reintroduction of polymyxin antimicrobials (polymyxin B and colistin), which were discontinued from use because of their nephrotoxicity and neurotoxicity [8, 9].

However, the efficacy of colistin for treatment of pneumonia has been questioned because of its inadequate penetration into lung parenchyma [9]. AS colistin appears to be a suitable option for the treatment of patients with VAP, because it achieves higher pulmonary concentrations with ignorable systemic absorption and toxicity [9, 23]. Indeed, sputum and lung tissue antibiotic levels achieved after inhalation are higher than those obtained after IV administration [24, 25]. In addition, topical antibiotics may reduce sputum volume and sputum bacterial growth in patients undergoing ventilation who are at risk of developing VAP [24]. However, there has been extensive experience with administration of AS colistin only for patients with cystic fibrosis [9, 24].

By contrast, AS colistin as adjunctive to IV antimicrobials for the treatment of VAP caused by MDR gram-negative pathogens has been evaluated only in a few studies [11, 15–18, 26]. These reports have shown encouraging results, with a high favorable clinical response and microbiological eradication (>80%) and mortality rates ranging from 12.5% to 46.7%. However, all of these studies included a small number of patients, and with the exception of the study by Korbila et al [18], they did not include a control arm [8, 11, 15–17, 26].

Furthermore, AS colistin as monotherapy has been used only in a case series of 5 patients with nosocomial pneumonia. A favorable clinical outcome was observed in 4 of these patients, suggesting that AS-only colistin therapy may be effective in certain cases [27]. Finally, despite these encouraging data, current guidelines do not recommend AS colistin treatment.

The results of the present case-control study are in contrast with results of previous case studies, because the addition of AS colistin did not offer any benefit. Furthermore, our results partially contrast with the results of a recent comparative cohort study by Korbila et al [18]. That study revealed a statistical significant difference in favor of combination treatment regarding disease resolution. However, Korbila and colleagues did not find improvements in the mortality rate between the 2 study groups, as was also shown by the data from our study.

The microbiological results showed that AS therapy had no impact on bacterial growth. It should be noted that 45% of the patients in our study had confirmed pathogen eradication, a percentage considerably lower than that previously reported with inhaled colistin [11, 15, 17, 26] but comparable with data from reports including patients who received only IV colistin [10].

In terms of clinical outcome, there was a marginal benefit of combined AS-IV colistin therapy for clinical cure ($P = .05$). However, although several clinical factors that could affect patient's outcome appears to be present in higher percentages among patients who received IV colistin alone, a multivariate analysis including potential confounding factors showed no difference between the 2 treatment groups. Moreover, clinical success of VAP infection did not reveal any significant difference and was in accordance with previous reports for both IV [9] and AS colistin use [11, 15, 17, 26].

Both VAP-related mortality and the all-cause mortality rates did not differ between the 2 groups, and the mortality rates were in agreement with those reported in the literature [10, 11, 15, 17, 18, 26].

With regard to adverse events, the incidence of nephrotoxicity—the major limiting factor in the use of colistin in the past—was found to be lower in recent studies than in studies from the 1960s and early 1970s [10, 11, 16, 17, 26]. In the present study, renal dysfunction was observed in 19% of the patients, which is comparable to the rate in previous reports [10, 11, 15, 17]. None of the patients discontinued colistin treatment or required renal replacement therapy because of renal dysfunction. It is noteworthy that the renal dysfunction rate was similar in the 2 treatment groups, suggesting that the addition of AS colistin does not cause systemic adverse events. Neurotoxicity and neuromuscular blockade, which were frequently reported in early studies from the 1960s, was been observed among the patients in our study. Furthermore, no major toxicity of colistin administered via the respiratory tract (bronchospasm, chest tightness, or apnea) was noted, a finding in agreement with other studies [11,15, 16, 26], with the exception of the study by Kwa et al [17], which reported that 1 AS colistin recipient experienced bronchospasm.

There are some drawbacks regarding the AS use of antimicrobials. Although, in normal lungs, AS antimicrobials have shown good penetration, little is known about the penetration of these agents into infected tissues from the airway lumen [28]. Another concern is the impending emergence of resistant strains due to the use of inhaled antibiotics [29]. In the present study, no colistin-resistant pathogens were isolated after the AS treatment.

This report has several limitations. First, this is a single-center, retrospective study with a relatively small number of patients and is thus vulnerable to β error. Second, relatively few *P. aeruginosa* and *K. pneumoniae* organisms were isolated. Therefore, our results provide limited information and cannot be generalizable with regard to these 2 pathogens. Finally, we did not monitor the volume of respiratory secretions, which is a marker of airway inflammation [25]. However, to our knowledge, this is the first matched case-control study to have tried to address the role of AS in addition to IV colistin in patients with VAP. Also, to our knowledge, this study and the study by Korbila et al [18] are the only studies to have directly compared AS-IV colistin with IV colistin for the treatment of VAP.

In conclusion, the present study has revealed that the addition of AS colistin did not add any clinical, microbiological, or survival benefit for patients with VAP caused by gram-negative MDR pathogens susceptible only to colistin. Because of the differences between the present findings and those of other investigators, randomized, controlled trials are needed to examine the efficacy and safety of AS colistin therapy in addition to IV treatment in patients with VAP.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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