

CHEST

**CRITICAL CARE** 

# Effect of Aerosolized Colistin as Adjunctive Treatment on the Outcomes of Microbiologically Documented Ventilator-Associated Pneumonia Caused by Colistin-Only Susceptible Gram-Negative Bacteria

Mario Tumbarello, MD; Gennaro De Pascale, MD; Enrico Maria Trecarichi, MD, PhD; Salvatore De Martino, MD; Giuseppe Bello, MD; Riccardo Maviglia, MD; Teresa Spanu, MD; and Massimo Antonelli, MD

*Background:* The increasing frequency of ventilator-associated pneumonia (VAP) caused by colistinonly susceptible (COS) gram-negative bacteria (GNB) is of great concern. Adjunctive aerosolized (AS) colistin can reportedly increase alveolar levels of the drug without increasing systemic toxicity. Good clinical results have been obtained in patients with cystic fibrosis, but conflicting data have been reported in patients with VAP.

*Methods:* We conducted a retrospective, 1:1 matched case-control study to evaluate the efficacy and safety of AS plus IV colistin vs IV colistin alone in 208 patients in the ICU with VAP caused by COS Acinetobacter baumannii, Pseudomonas aeruginosa, or Klebsiella pneumoniae.

**Results:** Compared with the IV colistin cohort, the AS-IV colistin cohort had a higher clinical cure rate (69.2% vs 54.8%, P = .03) and required fewer days of mechanical ventilation after VAP onset (8 days vs 12 days, P = .001). In the 166 patients with posttreatment cultures, eradication of the causative organism was also more common in the AS-IV colistin group (63.4% vs 50%, P = .08). No between-cohort differences were observed in all-cause ICU mortality, length of ICU stay after VAP onset, or rates of acute kidney injury (AKI) during colistin therapy. Independent predictors of clinical cure were trauma-related ICU admission (P = .01) and combined AS-IV colistin therapy (P = .009). Higher mean Simplified Acute Physiology Score II (P = .002) and Sequential Organ Failure Assessment (P = .05) scores, septic shock (P < .001), and AKI onset during colistin treatment (P = .04) were independently associated with clinical failure.

Conclusions: Our results suggest that AS colistin might be a beneficial adjunct to IV colistin in the management of VAP caused by COS GNB. CHEST 2013; 144(6):1768–1775

**Abbreviations:** AKI = acute kidney injury; AS = aerosolized; COS = colistin-only susceptible; GNB = gram-negative bacteria; ICU-LOS = length of ICU stay; MDR = multidrug-resistant; MIC = minimum inhibitory concentration; MV = mechanical ventilation; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; VAP = ventilator-associated pneumonia

**D**espite active preventive efforts,<sup>1,2</sup> ventilatorassociated pneumonia (VAP) remains the most frequent infectious complication of intensive care, affecting 10% to 20% of patients receiving mechanical ventilation (MV).<sup>3</sup> Reported mortality rates vary from 10% to >70%, depending on the underlying conditions and the pathogenicity of the infecting organisms.<sup>4-11</sup> Recent years have witnessed a steady

increase in the proportion of VAP cases caused by multidrug-resistant (MDR) gram-negative bacteria (GNB)—Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae in particular. The polymyxins are one of the few drug classes that are <u>still active</u> against these organisms.<sup>12,13</sup> Widely abandoned in the 1980s because of toxicity issues, they have been recalled into active service as a last-resort

1768

treatment of MDR GNB infections.<sup>12,14</sup> The best-known polymyxin, colistin (colistimethate sodium), displays good activity against carbapenem-resistant strains of *A baumannii*, *P aeruginosa*, and *K pneumoniae*,<sup>15</sup> but its polycationic/hydrophilic structure limits its penetration of lung tissue, and its efficacy in VAP remains controversial.<sup>16,17</sup>

Nebulization has been proposed to achieve bactericidal concentrations of antimicrobials (especially colistin and aminoglycosides) at the alveolar level in patients with MDR GNB VAP.<sup>18</sup> Inhaled antimicrobial aerosols produce high drug levels in the lungs without increasing the risks of systemic toxicity and the emergence of MDR gut microflora.<sup>19</sup> The efficacy of this approach has been demonstrated in cystic fibrosis,<sup>20</sup> but its value in the treatment of GNB VAP is less certain. The studies that have explored the possibility are generally quite small, and they have produced conflicting results.<sup>21-28</sup> We analyzed a large homogeneous cohort of patients with VAP caused by colistinonly susceptible (COS) A baumannii, P aeruginosa, or *K* pneumoniae to assess the efficacy and safety of aerosolized (AS) and IV colistin therapy compared with IV colistin alone.

## MATERIALS AND METHODS

#### Setting, Study Design, and Data Sources

A retrospective matched-cohort analysis was conducted in the 18-bed general ICU of a 1,400-bed teaching hospital in Rome, Italy. The protocol was approved by the Catholic University's Ethics Committee (approval number: P/237/CE/2012). Informed patient consent was not required given the study's retrospective, observational nature. Data were collected via manual review of hospital charts and computerized interrogation of the ICU and Microbiology Laboratory databases.

#### Population

Eligibility criteria were as follows: (1) age  $\geq$  18 years; (2) ICU admission between January 1, 2005, and December 31, 2012; (3) VAP with onset after  $\geq$  48 h of MV and associated with a new persistent infiltrate on chest radiograph, fever > 38°C with no other identified cause, a WBC count of < 4,000 or > 12,000 cells/µL,

Manuscript received April 27, 2013; revision accepted August 1, 2013.

Affiliations: From the Institute of Infectious Diseases (Drs Tumbarello and Trecarichi), the Department of Intensive Care and Anesthesiology (Drs De Pascale, De Martino, Bello, and Maviglia and Prof Antonelli), and the Institute of Microbiology (Prof Spanu), Università Cattolica del Sacro Cuore, Rome, Italy. Funding/Support: This study was partially supported by a grant from the Università Cattolica del Sacro Cuore, Linea D1 2012. Correspondence to: Mario Tumbarello, MD, Istituto Malattie Infettive, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00168 Roma, Italy; e-mail: tumbarello@rm.unicatt.it

© 2013 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details. DOI: 10.1378/chest.13-1018

journal.publications.chestnet.org

and purulent tracheal secretions<sup>29</sup>; (4) quantitative BAL fluid cultures growing a single COS strain of *A baumannii*, *P aeruginosa*, or *K pneumoniae*; and (5) IV colistin therapy lasting  $\geq$  72 h.

Patients who also received AS colistin (AS-IV colistin group) were matched (1:1) with those treated with IV colistin alone (IV colistin group). Matching was based on age (within 10 years) and illness severity as defined by Simplified Acute Physiology Score (SAPS) II at ICU admission (within 5 points) and by Sequential Organ Failure Assessment (SOFA) scores (within 2 points) the day IV colistin was started.<sup>30,31</sup> When multiple control candidates met the core matching criteria, the choice was based on ICU admission dates. Investigators were blinded to case outcomes during matching.

#### Microbiology Studies

Respiratory specimens for culture were obtained blindly with telescopic catheters (Combicath; Prodimed) or, in 23 cases, with bronchoscopic guidance. Respiratory specimens were quantitatively cultured on blood, chocolate, and MacConkey agars. Diagnostic quantitative culture threshold was 10<sup>4</sup> colony forming units/mL. Blood cultures (three or more sets per patient) were inoculated into Lytic/10 Anaerobic/F and Plus Aerobic/F bottles and incubated in the Bactec 9240 system (Becton, Dickinson and Company).

Isolates were identified with the Vitek 2 system (bioMérieux, Inc) (2005-June 2009) or matrix-assisted laser desorption ionizationtime-of-flight mass spectrometry (Bruker Corporation) (July 2009-2012). Minimum inhibitory concentrations (MICs) were determined with the Vitek 2 ( $\beta$ -lactam inhibitor combinations, oxyiminocephalosporins, carbapenems, aztreonam, quinolones, aminoglycosides), the E-test (bioMérieux, Inc) with cation-adjusted Mueller-Hinton agar (colistin), or Sensititre broth microdilution (Thermo Fisher Scientific) (tigecycline). Colistin MICs for Enterobacteriaceae isolates were classified using European Committee on Antimicrobial Susceptibility Testing <u>breakpoints</u> (susceptible,  $\underline{MIC \leq 2}$  mg/L; resistant, MIC > 2 mg/L).32 US Food and Drug Administration breakpoints were used for tigecycline MICs (susceptible  $\leq 2 \text{ mg/L}$ ; resistant,  $\geq 8 \text{ mg/L}$ ).<sup>33</sup> Other MICs were interpreted according to Clinical and Laboratory Standards Institute breakpoints.<sup>34</sup> Isolates classified as COS displayed full susceptibility to colistin and nonsusceptibility to all other antimicrobials tested.

## Treatment Regimens

IV colistimethate sodium was administered every 8 to 12 h at daily per-kilogram doses of approximately 100,000 International Units (a dose of 75,000 International Units in patients with creatinine clearance rates < 50 mL/min and those on continuous renal replacement therapy). When administered, AS colistin (colistimethate sodium) therapy was always started with IV colistin and discontinued when the latter was stopped. It was administered three times a day via jet or ultrasonic nebulizers (total daily dose, 3 million International Units).

#### Definitions and Outcomes

VAP onset coincided with the collection date of the index BAL culture. The following intervals (number of days) were recorded: time at risk (from ICU admission to pneumonia onset), length of ICU stay (ICU-LOS) (total, from ICU admission to ICU discharge or death, and post-VAP, from pneumonia onset to ICU discharge or death), and duration of MV before and after pneumonia onset. Septic shock was defined according to American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee criteria.<sup>35</sup> AKI was defined as a greater than twofold increase in serum creatinine or a  $\geq$  50% decrease in the glomerular filtration rate or oliguria (output < 0.5 mL/kg/h) for  $\geq$  12 h.<sup>36</sup>

The primary outcome was clinical cure, defined as the resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all chest radiograph abnormalities when colistin was discontinued. To determine whether these criteria were met, data were reviewed independently by two infectious disease specialists (G. D. P. and E. M. T.), who were blinded to patients' group origin. When judgments were discordant (about 3% of patients), the reviewers reassessed the data and reached a consensus decision. Secondary outcomes were: (1) all-cause ICU mortality, (2) microbiologic cure (disappearance of the infecting bacterium from posttreatment respiratory samples), (3) post-VAP MV duration, (4) post-VAP ICU-LOS, and (5) rates of AKI onset during colistin therapy.

## Statistical Analysis

Continuous variables were expressed as medians (interquartile ranges) and differences analyzed with Student *t* test or the Mann-Whitney *U* test (for normally and nonnormally distributed variables, respectively). Group percentages were calculated for categorical variables and differences assessed with the  $\chi^2$  or the two-tailed Fisher exact test. ORs and 95% CIs were calculated to evaluate the strength of associations. Variables associated with the primary outcome in univariate analysis ( $P \leq .2$ ) were included in a logistic regression model and a backward stepwise approach used to identify independent predictors of clinical cure. Variables with *P* values  $\leq .05$  were retained in the final model. Two-tailed *P* values  $\leq .05$  were considered significant. All analyses were performed using the Intercooled Stata program, version 11 (StatCorp LP).

## RESULTS

# Population Characteristics and VAP Incidence

During the 8-year study period, 5,812 adults were admitted to the ICU, and >95% received MV. Two hundred eighty-eight of the patients receiving MV(5%)developed monomicrobial VAP caused by COS GNB and were treated with IV colistin. Forty-two percent (n = 121) of these also received AS colistin, and 104 met all the criteria for enrollment in the AS-IV colistin cohort. Their characteristics and those of the age-, SAPS II-, and SOFA score-matched cohort treated with IV colistin alone are shown in Table 1. Most patients in both cohorts were in the ICU for medical reasons. There were no significant between-cohort differences in comorbidity rates, presenting features of VAP, initial inadequate antibiotic therapy, or the dose or duration of IV colistin therapy. The AS-IV colistin cohort had a significantly higher proportion of men and of A baumannii infections and a significantly lower proportion of K pneumoniae infections. AS colistin use increased over time, but the proportion of patients in the two cohorts was constant over the years (Fig 1).

# Outcomes

As shown in Table 1, the two cohorts were not significantly different in terms of AKI incidence rates, total or post-VAP ICU-LOS, or all-cause ICU mortality. Clinical cures were significantly more common among patients treated with AS-IV colistin (69.2% vs 54.8% of those in the IV cohort, P = .03) (Table 1). In 42 cases, bacteriologic outcomes were not documented, but analysis of the remaining 166 patients revealed a microbiologic cure rate in the AS-IV colistin cohort of 52 of 82 (63.4%) vs 42 of 84 (50%) in the IV cohort (P = .08). The most striking difference involved the median duration of post-VAP MV, which was shorter in the AS-IV colistin cohort (8 vs 12 days in the IV cohort, P = .001) (Fig 2, Table 1).

# Predictors of Clinical Cure

As shown in Table 2, univariate analysis of 208 patients revealed significant association between clinical cures and male sex, younger age, trauma-related ICU admissions, longer ICU-LOSs, and AS-IV colistin treatment regimens. Patients in the clinical failure subgroup had higher mean SAPS II and SOFA scores and higher rates of bacteremia and septic shock at VAP onset. This subgroup was also characterized by higher rates of medical ICU admissions; patients admitted with cancer, diabetes, chronic renal failure, and/or immunosuppression; and patients on hemodialysis at VAP onset. These patients were also more likely to have *K pneumoniae* VAP and to develop AKI during colistin therapy. In logistic regression analysis (Table 3), trauma-related admissions (P = .01) and AS-IV colistin therapy (P = .009) were independent predictors of clinical cures, whereas higher mean SAPS II (P = .002) and SOFA (P = .05) scores, septic shock at VAP onset (P < .001), and AKI onset during colistin therapy (P = .04) were associated with treatment failure.

# DISCUSSION

This large, retrospective, matched-cohort study of patients with VAP caused by COS GNB showed that AS-IV colistin therapy can significantly shorten the duration of MV after pneumonia onset and increase clinical cure rates, as compared with IV colistin monotherapy alone. Indeed, adjunctive AS colistin was an independent predictor of clinical cure. However, the significance of its favorable impact on microbiologic cure rates was only borderline, and it had <u>no appre-</u> ciable effects on all-cause ICU mortality or ICU LOS.

The significantly reduced duration of post-VAP MV in the AS-IV colistin cohort is a novel finding, which deserves further investigation. Smaller studies that have compared post-VAP MV times found no significant differences between patients treated with AS-IV colistin and those receiving IV colistin alone.<sup>23,37</sup> In our population, the reduced MV time did not translate into shorter post-VAP ICU stays (probably more dependent on factors other than the VAP), but it is

	Treatment		
Variable	AS-IV Colistin $(n = 104)$	IV Colistin $(n = 104)$	P Value
Patient characteristics on ICU admission			
Male sex	74 (71.1)	58 (55.8)	.02
Age, median (IQR), y	64 (48.5-76.5)	66 (49-77)	.78
Comorbidities on admission			
Diabetes mellitus	21 (20.2)	19 (18.3)	.72
Chronic renal failure	7 (6.7)	14 (13.5)	.11
Cancer	11 (10.6)	16 (15.4)	.30
Cardiovascular diseases	41 (39.4)	42 (40.4)	.89
COPD	21 (20.2)	28 (27.2)	.24
Immunosuppression <sup>b</sup>	25 (24)	22 (21.2)	.62
Type of ICU admission			
Medical	65 (62.5)	71 (68.3)	.38
Surgical	14 (13.5)	13 (12.59)	.84
Trauma-related	25(24)	20 (19.2)	.40
SAPS II on ICU admission, median (IQR)	45.5 (34-56)	46.5 (33-55)	.90
Total days in ICU, median (IQR)	24.5 (13.5-44)	26 (16.5-39)	.73
Characteristics of VAP			
Late onset <sup>c</sup>	85 (81.7)	84 (80.7)	.85
CPIS at onset, mean $\pm$ SD	$7.8 \pm 1.2$	$7.9 \pm 1.3$	.87
SOFA score at onset, median (IQR)	7 (6-12)	8 (5-11)	.75
Causative organisms			
Acinetobacter baumannii	72 (69.2)	56 (53.8)	.02
Pseudomonas aeruginosa	24 (23.1)	28 (26.9)	.52
Klebsiella pneumoniae	8 (7.7)	20 (19.2)	.01
Presenting features			
ARDS	12 (11.5)	11 (10.5)	.82
Septic shock	46 (44.2)	46 (44.2)	1.00
Concomitant bacteremia	24 (23.1)	29 (27.9)	.43
CRRT at VAP onset	23 (22.1)	18 (17.3)	.38
Treatment of VAP			
Inadequate initial antibiotic therapy	91 (87.5)	87 (83.6)	.43
Duration of colistin treatment, median (IQR), d	7 (5-14)	10 (5.5-15)	.12
Daily dose of IV colistin, mean $\pm$ SD, IU	$(7.0 \pm 2.6) \times 10^{6}$	$(7.3 \pm 2.4) \times 10^{6}$	.29
Outcomes			
Clinical cure	72 (69.2)	57 (54.8)	.03
Microbiologic cure <sup>d</sup>	52 (63.4)	42 (50)	.08
Days of MV after pneumonia onset, median (IQR)	8 (6-14.5)	12 (8-21)	.001
Days in ICU after pneumonia onset, median (IOR)	12 (7-22.5)	14 (8-22)	.69
Death in ICU	45 (43.3)	48 (46.1)	.67
AKI during colistin therapy	26 (25)	23 (22)	.62

## Table 1-Demographic and Clinical Characteristics of the 208 Patients With VAP Included in the Study

Data are presented as No. (%) unless otherwise stated. AKI = acute kidney injury; AS-IV = aerosolized plus IV; CPIS = Clinical Pulmonary Infection Score; CRRT = continuous renal replacement therapy; IQR = interquartile range; IU = International Units; MV = mechanical ventilation; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; VAP = ventilator-associated pneumonia.

<sup>a</sup>Cohorts were matched 1:1 according to age, SAPS II, and SOFA scores; if more than one match was possible, the decision was based on admission dates.

<sup>b</sup>Defined as neutropenia (neutrophils count < 500/ $\mu$ L), steroid therapy for at least 10 d, chemotherapy during the last 30 d, or therapy with immunosuppressive drugs.

°Onset after at least 96 h of MV.

<sup>d</sup>Data available for 166 patients only: 82 AS-IV colistin and 84 IV colistin.

consistent with the higher clinical cure rate documented in our AS-IV colistin cohort.

Adjunctive AS colistin significantly improved the clinical outcomes of VAP in four previous studies, all relatively small. Three found higher clinical response rates when IV antimicrobial regimens were supplemented with AS colistin in patients with VAP caused by MDR GNB<sup>24,25,38</sup>; however, very few isolates in these studies were COS, so the IV regimens usually

included colistin plus other drugs displaying in vitro activity against the organism. The fourth study (more similar to our own) retrospectively analyzed 121 patients with VAP due to MDR *A baumannii*, *P aeruginosa*, or *K pneumoniae*, but a higher percentage of the isolates were COS (56%), and > 80% of the IV regimens consisted of colistin alone. As in our population, cure rates were higher in the 78 patients who also received AS colistin, but the adjunctive therapy had



FIGURE 1. Temporal distribution of patients treated with IV colistin (IV cohort) and those who received IV and AS colistin (AS-IV cohort) in the study period. AS = aerosolized.

no significant effect on all-cause hospital or ICU mortality.<sup>37</sup> The fact that adjunctive <u>AS colistin improves</u> <u>cure rates without</u> affecting <u>survival</u> supports the view that <u>VAP</u> has <u>less impact</u> on overall ICU <u>mortality</u> than previously <u>believed</u> and that <u>survival</u> may be more closely <u>associated</u> with <u>other factors</u> (eg, age, comorbidities, illness severity at ICU admission, coexisting



FIGURE 2. Box and whisker plots showing days of MV after onset of VAP in patients treated with IV colistin (IV cohort) and those who received IV and AS colistin (AS-IV cohort). MV duration was significantly shorter in the latter cohort (P < .001). Boxes represent interquartile ranges (lower border, 25th percentile; upper border, 75th percentile) and median (50th percentile) (horizontal line within the box); whiskers indicate minimum and maximum values. MV = mechanical ventilation; VAP = ventilator-associated pneumonia. See Figure 1 legend for expansion of other abbreviation.

1772

infections).<sup>10</sup> In the randomized trial conducted by Rattanaumpawan et al,<sup>39</sup> AS-IV colistin also failed to improve overall and VAP-attributable mortality rates at 28 days but had no effect on clinical cure rates (51% vs 53.1% in control subjects). As in other studies, fewer than one-third of the GNB isolates analyzed by this group were COS. Furthermore, as the authors themselves admit, their sample (roughly one-half the size of our own) was too small to detect improvements in cure rates of < 25%.<sup>39</sup> The VAP cases examined by Kofteridis et al<sup>23</sup> were, like our own, all caused by COS A baumannii, P aeruginosa, or K pneumoniae. Again, adjunctive AS colistin had no significant effects on crude or VAP-attributable mortality. Its failure to significantly improve clinical or bacteriological outcomes is clearly related to power limitations. Indeed, the AS-IV colistin group in this study (even smaller than that analyzed by Rattanaumpawan et al<sup>39</sup>) presented an appreciably higher rate of clinical cures (54%) vs 32.5% in the IV group), which fell just short of significance (P = .05).<sup>23,39</sup>

Unlike these investigators,<sup>23</sup> Rattanaumpawan et al<sup>39</sup> found a significant association between adjunctive AS colistin and microbiologic cure rates (60.9% vs 38.2%, P = 0.03). Even higher rates (83%) have been reported by others,<sup>24</sup> and in one study AS colistin was the sole independent predictor of microbiologic eradication.<sup>28</sup> These findings are not incompatible with ours: the microbiologic cure rate in our AS-IV colistin cohort was also higher than that of the IV control

	Outcomes		Univariate Analysis	
Variable	Clinical Cure $(n = 129)$	Clinical Failure $(n = 79)$	P Value	OR (95% CI)
Patient characteristics on ICU admission				
Male sex	89 (69)	43 (54.4)	.03	1.86 (1.00-3.46)
Age, median (IQR), y	62 (45-75)	69 (58-77)	.004	
Comorbidities on admission				
Diabetes mellitus	18 (14)	22 (27.9)	.01	0.42 (0.20-0.90)
Chronic renal failure	8 (6.2)	13 (16.5)	.02	0.34 (0.11-0.93)
Cancer	10 (7.8)	17 (21.5)	.004	0.31 (0.12-0.76)
Cardiovascular diseases	47 (36.4)	36 (45.6)	.19	0.68 (0.37-1.26)
COPD	26 (20.3)	23 (29.1)	.15	0.62 (0.31-1.25)
Immunosuppression <sup>a</sup>	22 (17.1)	25 (31.7)	.01	0.44 (0.22-0-91)
Type of ICU admission				
Medical	74 (57.4)	62 (78.5)	.002	0.37 (0.18-0.73)
Surgical	18 (13.9)	9 (11.49	.59	1.26 (0.50-3.37)
Trauma-related	37 (28.7)	8 (10.1)	.002	3.57 (1.51-9.39)
SAPS II on ICU admission, median (IQR)	40 (32-50)	52 (42-60)	<.001	
Total days in ICU, median (IQR)	30 (18-43)	21 (13-35)	.008	
Characteristics of VAP				
Late onset <sup>b</sup>	106 (82.1)	63 (79.7)	.66	1.17 (0.53-2.51)
Days of MV before VAP onset, median (IQR)	5 (3-12)	4 (3-13)	.28	
CPIS score, mean $\pm$ SD	$7.9 \pm 1.1$	$8.1 \pm 1.4$	.42	
SOFA score at pneumonia onset, median (IQR)	7 (5-9)	10 (7-13)	<.001	
Causative organisms	· · ·			
Acinetobacter baumannii	83 (64.3)	45 (56.9)	.28	1.36 (0.73-2.51)
Pseudomonas aeruginosa	32 (24.8)	20 (25.3)	.93	0.97 (0.48-1.97)
Klebsiella pneumoniae	13 (10.1)	15 (18.9)	.07	0.47 (0.19-1.15)
Presenting features		× ,		· · · · · · · · · · · · · · · · · · ·
ARDS	13 (10.1)	10 (12.6)	.56	0.77 (0.29-2.08)
Septic shock	36 (27.9)	56 (70.9)	<.001	0.16 (0.08-0.31)
Concomitant bacteremia	26 (20.2)	27 (34.2)	.02	0.49 (0.25-0.96)
CRRT at VAP onset	15 (11.6)	26 (32.9)	<.001	0.27 (0.12-0.58)
Days of MV after VAP onset, median (IOR)	10 (7-18)	10 (7-21)	.84	· · · · · ·
Treatment of VAP		× /		
Inadequate initial antibiotic therapy	110 (85.2)	68 (86.1)	.88	0.93 (0.38-2.22)
Adjunctive AS colistin	72 (55.8)	32 (40.5)	.03	1.86 (1.01-3.41)
Duration of colistin therapy, d	10 (5-15)	7 (5-13)	.07	
Daily dose of IV colistin, mean $\pm$ SD, IU	$(7.3 \pm 2.5) \times 10^{6}$	$(6.1 \pm 2.8) \times 10^{6}$	.09	
AKI during colistin therapy	21 (16.3)	28 (35.4)	.02	0.35 (0.17-0.72)

## Table 2-Univariate Analysis of Factors Associated With Clinical Cure

Data are presented as No. (%) unless otherwise stated. See Table 1 legend for expansion of abbreviations.

<sup>a</sup>Defined as neutropenia (neutrophils count  $\leq$  500/µL), steroid therapy for at least 10 d, chemotherapy during the last 30 d, or therapy with immunosuppressive drugs.

<sup>b</sup>Onset after at least 96 h of MV.

subjects, but the difference was not significant (possibly because this variable was assessable in only 80% of our population).

Correlation between colistin therapy and AKI onset is very difficult to assess in a retrospective study. However, the overall rate of AKI onset during colistin therapy in our population (23.5%) is consistent with previous reports,<sup>22</sup> as is the lack of significant difference between the rates of the IV and AS-IV colistin groups.<sup>23,38</sup> Other limitations of our study must also be considered, including its retrospective single-center nature and the moderate overrepresentation in our population of VAP cases caused by *A baumannii*. Finally, the AS colistin was administered in approximately 60% of the cases via conventional ventilator jet nebulizers, which offer no control over particle size, so the amount of the drug delivered to the lungs cannot be accurately estimated.<sup>40</sup>

## CONCLUSIONS

To our knowledge, this is the second matched-cohort study involving direct comparison of AS-IV colistin and IV colistin regimens for treating VAP caused by COS GNB. Our findings tend to conflict with those of two earlier studies,<sup>23,38</sup> both conducted in populations substantially smaller than (and in one case microbiologically different from) our own. Our data indicate that in critically ill patients with VAP caused

Table 3—Multivariate Analysis of Factors Associated With Clinical Cure in Patients With VAP Caused by Colistin-Only Susceptible Gram-Negative Bacteria

Variable	P Value	OR (95% CI)
Trauma-related ICU admission	.01	3.41 (1.27-9.14)
AS-IV colistin treatment	.009	2.58 (1.27-5.23)
SAPS II on admission	.002	0.96 (0.94-0.98)
SOFA score at VAP onset	.05	0.89 (0.80-0.99)
Septic shock at VAP onset	<.001	0.22 (0.11-0.47)
AKI onset during colistin treatment	.04	0.42 (0.19-0.95)

See Table 1 legend for expansion of abbreviations.

by COS GNB, AS-IV colistin (as compared with IV colistin alone) can significantly improve clinical cure rates and reduce the need for MV without increasing the risk of AKI. As the frequency of VAP caused by MDR GNB continues to rise, colistin will be playing an increasingly critical role in the ICU. Optimizing its use to enhance efficacy without increasing adverse renal effects is an important goal. Given the conflicting data published thus far, large (multicenter), randomized controlled trials are urgently needed to further clarify the benefits and risks of adjunctive AS colistin in patients with pulmonary infections caused by COS GNB.

# Acknowledgments

**Author contributions:** Dr Tumbarello takes responsibility for the content of the manuscript, including the data and analysis. *Dr Tumbarello:* contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafted the submitted article or revised it critically for important intellectual content; and provided final approval of the version to be published.

*Dr De Pascale:* contributed to conception and design, acquisition of data, or analysis and interpretation of data and drafted the submitted article or revised it critically for important intellectual content.

*Dr Trecarichi:* contributed to conception and design, acquisition of data, or analysis and interpretation of data and drafted the submitted article or revised it critically for important intellectual content.

*Dr De Martino:* contributed to conception and design, acquisition of data, or analysis and interpretation of data and critically revised the submitted article.

*Dr Bello:* contributed to conception and design, acquisition of data, or analysis and interpretation of data and critically revised the submitted article.

*Dr Maviglia*: contributed to conception and design, acquisition of data, or analysis and interpretation of data and critically revised the submitted article.

*Prof Spanu:* contributed to conception and design, acquisition of data, or analysis and interpretation of data and critically revised the submitted article.

*Prof Antonelli*: contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafted the submitted article or revised it critically for important intellectual content; and provided final approval of the version to be published.

**Financial/nonfinancial disclosures:** The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

**Role of sponsors:** The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

#### References

- Torres A, Ewig S, Lode H, Carlet J; European HAP working group. Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med.* 2009; 35(1):9-29.
- Hayashi Y, Morisawa K, Klompas M, et al. Toward improved surveillance: the impact of ventilator-associated complications on length of stay and antibiotic use in patients in intensive care units. *Clin Infect Dis.* 2013;56(4):471-477.
- 3. van der Kooi TI, de Boer AS, Manniën J, et al. Incidence and risk factors of device-associated infections and associated mortality at the intensive care in the Dutch surveillance system. *Intensive Care Med.* 2007;33(2):271-278.
- Koulenti D, Lisboa T, Brun-Buisson C, et al; EU-VAP/CAP Study Group. Spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European intensive care units. *Crit Care Med.* 2009; 37(8):2360-2368.
- Kollef KE, Schramm GE, Wills AR, Reichley RM, Micek ST, Kollef MH. Predictors of 30-day mortality and hospital costs in patients with ventilator-associated pneumonia attributed to potentially antibiotic-resistant gram-negative bacteria. *Chest.* 2008;134(2):281-287.
- Lanspa MJ, Brown SM. Asking the right questions: the relationship between incident ventilator-associated pneumonia and mortality. *Crit Care*. 2012;16(2):123.
- Tseng CC, Liu SF, Wang CC, et al. Impact of clinical severity index, infective pathogens, and initial empiric antibiotic use on hospital mortality in patients with ventilator-associated pneumonia. Am J Infect Control. 2012;40(7):648-652.
- Timsit JF, Zahar JR, Chevret S. Attributable mortality of ventilator-associated pneumonia. *Curr Opin Crit Care*. 2011; 17(5):464-471.
- Tumbarello M, De Pascale G, Trecarichi EM, et al. Clinical outcomes of *Pseudomonas aeruginosa* pneumonia in intensive care unit patients. *Intensive Care Med.* 2013;39(4):682-692.
- Nguile-Makao M, Zahar JR, Français A, et al. Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. *Intensive Care Med.* 2010;36(5):781-789.
- Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med. 2002;165(7):867-903.
- Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(1):1-12.
- Sandiumenge A, Lisboa T, Gomez F, Hernandez P, Canadell L, Rello J. Effect of antibiotic diversity on ventilator-associated pneumonia caused by ESKAPE organisms. *Chest.* 2011; 140(3):643-651.
- Nation RL, Li J. Colistin in the 21st century. Curr Opin Infect Dis. 2009;22(6):535-543.
- Michalopoulos AS, Karatza DC. Multidrug-resistant Gramnegative infections: the use of colistin. *Expert Rev Anti Infect Ther*. 2010;8(9):1009-1017.
- Imberti R, Cusato M, Villani P, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically Ill patients after IV colistin methanesulfonate administration. *Chest.* 2010;138(6):1333-1339.
- Florescu DF, Qiu F, McCartan MA, Mindru C, Fey PD, Kalil AC. What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression. *Clin Infect Dis.* 2012;54(5): 670-680.
- Wood GC. Aerosolized antibiotics for treating hospitalacquired and ventilator-associated pneumonia. *Expert Rev Anti Infect Ther.* 2011;9(11):993-1000.

- Palmer LB. Aerosolized antibiotics in critically ill ventilated patients. *Curr Opin Crit Care*. 2009;15(5):413-418.
- Beringer P. The clinical use of colistin in patients with cystic fibrosis. Curr Opin Pulm Med. 2001;7(6):434-440.
- Luyt CE, Combes A, Nieszkowska A, Trouillet JL, Chastre J. Aerosolized antibiotics to treat ventilator-associated pneumonia. *Curr Opin Infect Dis*. 2009;22(2):154-158.
- Yahav D, Farbman L, Leibovici L, Paul M. Colistin: new lessons on an old antibiotic. *Clin Microbiol Infect*. 2012;18(1):18-29.
- 23. Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. *Clin Infect Dis.* 2010;51(11):1238-1244.
- Michalopoulos A, Fotakis D, Virtzili S, et al. Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant gram-negative bacteria: a prospective study. *Respir Med.* 2008;102(3):407-412.
- Lin CC, Liu TC, Kuo CF, Liu CP, Lee CM. Aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* pneumonia: experience in a tertiary care hospital in northern Taiwan. J Microbiol Immunol Infect. 2010; 43(4):323-331.
- 26. Kalin G, Alp E, Coskun R, Demiraslan H, Gündogan K, Doganay M. Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia: do we really need this treatment? *J Infect Chemother*. 2012;18(6):872-877.
- Arnold HM, Sawyer AM, Kollef MH. Use of adjunctive aerosolized antimicrobial therapy in the treatment of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* ventilator-associated pneumonia. *Respir Care*. 2012;57(8):1226-1233.
- Kuo SC, Lee YT, Yang SP, et al. Eradication of multidrugresistant Acinetobacter baumannii from the respiratory tract with inhaled colistin methanesulfonate: a matched case-control study. Clin Microbiol Infect. 2012;18(9):870-876.
- 29. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388-416.
- Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270(24):2957-2963.

- Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286(14):1754-1758.
- Clinical breakpoints. The European Committee on Antimicrobial Susceptibility Testing website. http://www.eucast.org/ clinical\_breakpoints. Accessed February 28, 2013.
- 33. Sader HS, Farrell DJ, Jones RN. Tigecycline activity tested against multidrug-resistant Enterobacteriaceae and Acinetobacter spp. isolated in US medical centers (2005-2009). *Diagn Microbiol Infect Dis*. 2011;69(2):223-227.
- 34. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; 22nd Informational Supplement. CLSI M100–S22. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
- 35. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* 2013;39(2):165-228.
- 36. Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med.* 2009;35(10): 1692-1702.
- 37. Korbila IP, Michalopoulos A, Rafailidis PI, Nikita D, Samonis G, Falagas ME. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. *Clin Microbiol Infect*. 2010;16(8):1230-1236.
- Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant gram-negative bacteria in patients without cystic fibrosis. *Crit Care*. 2005;9(1):R53-R59.
- Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwinai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by gramnegative bacteria. J Antimicrob Chemother. 2010;65(12): 2645-2649.
- Dhand R, Sohal H. Pulmonary drug delivery system for inhalation therapy in mechanically ventilated patients. *Expert Rev Med Devices*. 2008;5(1):9-18.