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Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: A prospective study ☆

Argyris Michalopoulos[a,*], Dimitrios Fotakis[a], Simona Virtzili[a], Christodoulos Vletsas[a], Sylvia Raftopoulou[a], Zefi Mastora[a], Matthew E. Falagas[b,c]

[a]*Intensive Care Unit, "Henry Dunant" Hospital, Athens, Greece*
[b]*Tufts University School of Medicine, Boston, MA, USA*
[c]*Infectious Diseases Clinic, Department of Medicine, "Henry Dunant" Hospital, Athens, Greece*

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Summary
Background: Ventilator-associated pneumonia (VAP) remains the leading cause of death in patients with intensive care unit (ICU) acquired infections associated with an attributable mortality around 30%. Increasing antimicrobial resistance in patients with VAP challenges intensivists to search for alternative therapeutic options. There is scarcity of data in the literature concerning the administration of aerosolized colistin in critically ill patients with VAP due to multidrug-resistant (MDR) Gram-negative pathogens.
Methods: To assess the safety and effectiveness of aerosolized colistin as an adjunctive to the intravenous antimicrobial therapy for the treatment of VAP due to MDR Gram-negative pathogens, we prospectively examined all patients, who received inhaled colistin.
Results: Sixty critically ill patients with a mean APACHE II score 16.7, received aerosolized colistin for the treatment of VAP due to MDR pathogens [*Acinetobacter baumannii* (37/60 cases), *Pseudomonas aeruginosa* (12/60 cases) and *Klebsiella pneumoniae* strains (11/60 cases)]. Half of the isolated pathogens were susceptible only to colistin. Mean (±SD) daily dosage of aerosolized colistin was 2.2 (±0.7) million international units (IU). All patients received 2946 inhalations of colistin and the mean duration of administration was 16.4 days. Fifty-seven patients received concomitant intravenous treatment with colistin or other antimicrobial agents. Bacteriological and clinical response of VAP was observed in

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*Corresponding author. Tel.: +30 2106972353; fax: +30 2106972354.
E-mail address: amichalopoulos@hol.gr (A. Michalopoulos).

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50/60 (83.3%) patients. No adverse effects related to inhaled colistin were recorded. All cause hospital mortality was 25% while mortality attributable to VAP was 16.7%.
Conclusions: Aerosolized colistin may be considered as adjunctive to intravenous treatment in patients with VAP due to MDR Gram-negative bacteria susceptible to colistin in critically ill patients. Although colistin is safe and effective, the best route of administration remains unclear. In addition, controlled comparative studies are needed to establish its effectiveness and safety.

Introduction

Ventilator-associated pneumonia (VAP) remains the most common infectious complication in the intensive care unit (ICU) setting. Its prevalence varies from 6 to 52 cases per 100 patients depending on the population studied, the type of ICU, and the diagnostic criteria used.[1] ICU patients who develop VAP are often at greater risk for infection with a wide spectrum of multidrug-resistant (MDR) Gram-negative bacterial pathogens, such as *Pseudomonas aeruginosa*, extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* strains, and *Acinetobacter baumannii*. During the last decade, antimicrobial resistance in Gram-negative bacteria in ICU patients has been an increasing problem all over the world. Multidrug resistance among these pathogens is especially worrisome, as the possible antimicrobial options are limited.

Recently, there is interest in using polymyxins and especially colistin (colistimethate sodium) for the treatment of infections caused by MDR Gram-negative micro-organisms.[2,3] VAP due to MDR Gram-negative bacteria is one of the most serious complications that occur in mechanically ventilated patients in the ICU setting. It is associated with increased mortality (up to 65%), morbidity, and hospital costs.[2] Aerosolized colistin has been used mainly in patients with cystic fibrosis.[4] There are few reports, including our limited initial published experience, indicating that aerosolized colistin may be a beneficial and safe additional therapeutic intervention for the management of VAP.[5,6] However, the number of patients included was very small. In this study, we present data from our recent experience with aerosolized colistin for the treatment of VAP due to MDR Gram-negative bacteria in 60 critically ill ICU patients.

Methods

Design of the study-patient population

We prospectively enrolled to this study all patients who received nebulized colistimethate sodium (Colomycin, Forest Laboratories®, Kent, UK or Colistin, Norma®, Athens, Greece) for the treatment of VAP due to MDR Gram-negative bacteria from 15/September/2005 to 15/June/2006 in the 38-bed general ICU at "Henry Dunant" Hospital, a 450-bed tertiary care center in Athens, Greece. Colistin therapy was initiated in all patients when VAP was documented and the responsible Gram-negative pathogen was MDR but sensitive to this antimicrobial agent. The daily dosage of aerosolized colistin was 3 million international units (IU) divided into 3 doses, while the daily dosage of intravenous colistin was 9 million IU divided into 3 doses in patients with normal renal function. In the elderly patients (age above 80 years), in patients with body weight less than 50 kg, and in those with acute or chronic renal failure (serum creatinine above 2 mg/dl) the daily dosage of aerosolized colistin was 1.5 million IU divided into 3 doses. Colistimethate sodium (also called colistin sulfamethate, colistin methanesulfonate, or colistin sulfonyl methate) was used in all patients because it is better tolerated and it is associated with less bronchoconstriction compared with colistin sulfate.[5,7,8] One milligram of the colistimethate formulations used is approximately equal to 12,500 IU of colistin. Colistimethate was prepared for nebulization by dilution of one million IU of colistin in 4 mL of sterile normal saline 0.9%. In patients with mechanical ventilatory support aerosolized colistin was delivered by means of the Siemens Servo Ventilator 300, and in the non-ventilated patients (after discontinuation of the mechanical ventilation) by the same way the inhaled β_2-agonists are given. During aerosolized treatment all patients with VAP were closely monitored for possible respiratory adverse reactions, such as chest tightness, bronchoconstriction, cough or apnea. Patients' lung mechanics were closely monitored during colistin nebulization. All the procedures used were in accordance with the recommendations found in the Helsinki Declaration of 1975. The study was approved by the Institutional Review Board (IRB) of the hospital. Patient consent was granted.

Data collection-entry

Data for several variables including demographics, cause of ICU admission, APACHE II score on ICU admission, the responsible pathogens as well as the results of laboratory and imaging tests including chest X-rays, and/or computed tomography scans of thorax were recorded in all patients receiving aerosolized colistin for VAP. Renal function tests (serum creatinine and urea), liver function tests (serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-gloutamyl transpeptidase, and bilirubin), creatine phosphokinase (CPK), and arterial blood gases taken every hour during the course of aerosolized colistin treatment (before and after) were also recorded. The dosage of aerosolized colistin, the duration of this treatment and any adverse-effect related to this administration as well as data regarding the bacteriological and clinical response of VAP, the duration of mechanical ventilation, the ICU length of stay and patients' outcome were also recorded in all patients.

Definitions

Definition of VAP

Pneumonia was considered to be ventilator associated (VAP) when its onset occurred 48 h after the initiation of mechanical ventilation and was judged not to have been incubating before the initiation of mechanical ventilation. Diagnosis of VAP required the presence of fever ($T > 38.5\,^{\circ}C$) or hypothermia ($T < 36\,^{\circ}C$), leukocytosis (WBC $> 12{,}000/mm^3$) or leukopenia (WBC $< 4000/mm^3$) and new or progressive infiltrates on chest radiograph. The diagnosis of VAP had to be confirmed by positive cultures of bronchial secretions or bronchoalveolar lavage (BAL) with isolation of MDR Gram-negative bacterium. The diagnostic threshold of bronchoscopic BAL for the identification of the VAP responsible bacteria was 10^4 cfu/mL. Bacteriologic sampling was performed in all patients on the day VAP was suspected (day 0), before instituting new antimicrobials.

Definition of multidrug resistance

Gram-negative bacteria were defined as MDR if there was resistance to all or most of the 6 antipseudomonal classes of antimicrobial agents, i.e. antipseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones, and aminoglycosides) for *P. aeruginosa* and *K. pneumoniae*, and in addition, resistance to sulbactam and tetracycline for *A. baumannii* (no in vitro susceptibility testing for tigecycline was performed). For this study, intermediate susceptibility was considered as resistance.

Definition of outcome

The definition of positive outcome (cure or improvement) of pneumonia was based on clinical (defeversense, resolution or partial resolution of presenting symptoms and signs of pneumonia, decrease of suctioning requirements), radiological (decrease or disappearance of the presenting findings on the chest X-ray) and laboratory findings (improvement of arterial blood gases, and normalization of white blood cell count, C-reactive protein, and procalcitonin).

Outcome parameters

The primary endpoint of the study was all-cause in-hospital mortality. Secondary endpoints included the clinical and bacteriological outcome of the infection (VAP) and the occurrence of adverse events during colistin treatment, and were defined as follows: clinical cure was defined as resolution of presenting symptoms and signs of infection by the end of colistin treatment; clinical improvement was defined as partial resolution of presenting symptoms and signs of infection; clinical failure (unresponsiveness) was defined as persistence or worsening of presenting symptoms and/or signs of infection during colistin administration; undetermined was recorded when clinical assessment was not possible; recurrence of infection was defined as the occurrence of a new episode of infection at least 72 h after clinical resolution of a preceding episode. The evaluation of clinical response was made on the basis of the resolution of clinical signs and symptoms, including fever, leukocytosis and improvement of chest X-rays (for pneumonia). Bacteriological outcome of the infection was defined as follows: eradication of the pathogen was defined as no growth of the pathogen in the final culture of specimens during the whole hospitalization; *persistence of the pathogen* was defined as persistent growth of the responsible pathogen regardless of the clinical outcome of the infection; recurrence (re-growth) of the pathogen was defined as re-isolation of the same pathogen regardless of the clinical outcome of the infection; colonization was defined as persistence or re-growth of the pathogen without symptoms and signs of infection; undetermined was recorded when microbiological assessment was not possible. Assessment of effectiveness was made at the end of colistin treatment.

Safety parameters

All adverse effects related to inhaled colistin such as bronchoconstriction, cough, apnea, or chest tightness, and arterial hypoxemia were recorded in every patient. In addition, safety was assessed on the basis of laboratory test results for renal function (changes from baseline in serum urea and creatinine levels) during colistin administration. Normal renal function was defined as a serum creatinine level of $\leqslant 1.2$ mg/dL. Acute renal failure was defined as a rise of 2 mg/dL in the serum creatinine level of patients with previously normal renal function. In patients with a history of renal insufficiency, acute or chronic renal failure was defined as at least a doubling of the baseline serum creatinine level (defined as the creatinine level at the initiation of colistin treatment). Organ function was evaluated daily according to the Sequential Organ Failure Assessment (SOFA) score. For each of the 6 organ systems included in the SOFA score (respiratory, cardiovascular, neurological, renal, hematological and hepatic), organ failure was defined as a score of $\geqslant 3$.[9] Prognostic factors possibly associated with adverse outcome (death) were examined during the evolution of the infection until the end of colistin treatment. We also recorded any consequent nosocomial-acquired infection, the development of resistance against colistin, as well as the selection of fungi following administration of colistin.

Results

Sixty adult critically ill patients received aerosolized colistin as adjunctive treatment for the management of VAP due to MDR Gram-negative bacteria. The patients were 40 males and 20 females and had a mean [$\pm$standard deviation ($\pm$SD)] age 59.4 ($\pm$18.3) years. Patients had a mean ($\pm$SD) Acute Physiological and Chronic Health Evaluation II (APACHE II) score on the day of ICU admission of 16.7 ($\pm$5.1). The episodes of VAP were developed between the 3rd and 38th day of mechanical ventilation (mean 11th day). Fifty-seven out of 60 patients received concomitant intravenous treatment with colistin and other antimicrobial agents (usually meropenem). The selection of the second antibiotic basically was based on the susceptibility test and MICs. The remaining 3 patients received inhaled colistin plus

meropenem because of pre-existing renal failure. The antibiotics administered intravenously in this group of patients with VAP due to multi-resistant Gram-negative bacteria are presented in Table 2. The mean first day of aerosolized colistin administration was the 11th day of mechanical ventilation.

The responsible pathogens of VAP were *A. baumannii* (37/60 cases), *P. aeruginosa* (12/60 cases) and *K. pneumoniae* strains (11/60 cases). Tables 1 and 2 describe the demographic and clinical features of patients, the responsible pathogens, as well as the outcome of the infection and of the patients. Half of the isolated pathogens were susceptible only to colistin. Mean ($\pm$SD) daily dosage of aerosolized colistin was 2.2 ($\pm$0.7) million IU, ranging from 1.5 to 3 million IU (divided into 3 doses). Totally, all patients received 2946 inhalations of colistin and the mean duration of administration was 16.4 ($\pm$10.9) days (ranged from 5 to 49 days). Bacteriological and clinical response of VAP associated with improvement of chest X-ray and arterial blood gases, and normalization of white blood cell count, C-reactive protein, and procalcitonin was observed in 50 out of 60 patients (83.3%). Clinical response of VAP due to MDR Gram-negative pathogen sensitive only to colistin is shown in Table 3.

No adverse effects related to inhaled colistin (bronchoconstriction, cough, apnea, or chest tightness) were recorded. Arterial blood gases and lung mechanics did not alter during colistin inhalation in all patients. However, 12 patients with history of chronic obstructive pulmonary disease (COPD) received concurrent treatment with inhaled β_2-agonist. Mean ($\pm$SD) total mechanical ventilatory support was 27.4 ($\pm$18.5) days. Mean ($\pm$SD) ICU stay was 32.5 ($\pm$19.7) days. Colistin-associated side effects, such as paresthesias, vertigo, or muscle weakness were not observed. No other complication possibly related to colistin administration was recorded. In the subgroup of patients ($n = 57$) who received a combination of antibiotics including colistin administered both intravenously and inhaled and had a normal renal function prior to ICU admission, 9 (15.7%) patients developed acute renal failure. However, the majority of these patients developed renal failure associated with multiple organ failure.

All cause hospital mortality was 15/60 (25%). Patients with VAP due to MDR Gram-negative bacteria associated with poor prognosis died from septic shock and multiple organ failure. Out of 50 patients with bacteriological and clinical response of VAP, 3 patients developed later on during ICU stay candidemia, one developed a second episode of VAP due to *Stenotrophomonas maltophilia* and another one wound infection and finally died. Attributable mortality in patients with VAR due to MDR Gram-negative bacteria was 10/60 (16.6%). Patients with good outcome of VAP were discharged from the ICU and the hospital.

Table 1 Demographics, clinical data, responsible pathogens, bacteriological and clinical outcome of VAP and outcome of critically ill patients who received aerosolized colistin.

Variables	Value
No. of studied patients	60
Age (years)	59.4 ($\pm$18.3)
Gender (males)	40/60 (66.7%)
Apache II on ICU admission	16.7 ($\pm$5.1)
Duration of mechanical ventilation (days)	27.4 ($\pm$18.5)
ICU length of stay (days)	32.5 ($\pm$19.7)
Pathogens	
Acinetobacter baumannii	37
Pseudomonas aeruginosa	12
Klebsiella pneumoniae	11
Microbiological eradication	50/60 (83.3%)
Cure or improvement of VAP	50/60 (83.3%)
Acinetobacter baumannii	31/37 (83.8%)
Pseudomonas aeruginosa	10/12 (83.3%)
Klebsiella pneumoniae	9/11 (81.8%)
Discharge from hospital	45/60 (75%)

Discussion

The main finding of this study is that aerosolized colistin may be an effective and safe adjunctive treatment of VAP due to MDR Gram-negative bacteria in critically ill adult patients in the ICU setting. This finding has clinical interest because VAP remains a serious and common infectious complication in patients with prolonged ventilatory support and is clearly associated with increased morbidity, mortality and total hospital costs. However, since randomized-controlled trials are missing, the best route of colistin's administration remains unclear.

Colistin (or polymyxin E) is an old antibiotic discovered from different species of *Bacillus polymyxa* in the decade of 1940s and was extensively used parenterally for more two decades. Subsequently, polymyxins were gradually withdrawn from clinical practice for many years owing to reports of nephrotoxicity and neurotoxicity.[10,11] Two different forms of colistin are available for clinical use; colistin sulfate orally for bowel decontamination and topically as a powder for the treatment of bacterial skin infections, and colistimethate sodium for parenteral and aerosol therapy. Colistimethate sodium is a basically a pro-drug of colistin.[12,13]

Colistin has rapid concentration-dependent bactericidal activity against Gram-negative pathogens and exhibits considerable post-antibiotic effect. It has excellent antimicrobial activity against most of the Gram-negative microorganisms, including *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae*. The re-introduction of polymyxins in clinical practice during the last years was the result of the increased resistance rates among Gram-negative bacteria, especially in the ICU setting, and the absence of new and effective alternative therapeutic options.[14] There have been several recent studies showing that intravenous colistin is an effective and safe antimicrobial agent in the treatment of most types of Gram-negative infections, including hospital-acquired pneumonia and VAP due to MDR Gram-negative pathogens.[3,15]

There are many reports in the literature concerning the effectiveness of aerosolized colistin in preventing relapses of lung infections,[16] the eradication of *P. aeruginosa* from the respiratory tract,[17] and the treatment of respiratory

Table 2 Antibiotics administered intravenously in 60 critically ill patients with VAP due to multi-resistant Gram-negative bacteria who received aerosolized colistin.

Antibiotics (i.v.)	No. of patients[a]	Cure of VAP[a]	Microbiological eradication[a]	Death[a]	Attributable mortality[a]
Meropenem+colistin	31	25 (80.6)	25 (80.6)	9 (29)	6 (19.3)
Piperacillin/tazo+colistin	11	9 (81.8)	9 (81.8)	3 (27.3)	2 (18.2)
Ampicillin/ sulbactam+colistin	6	5 (83.3)	5 (83.3)	2 (33.3)	2 (33.3)
Imipenem+colistin	4	3 (75)	3 (75)	1 (25)	0
Gentamicin+colistin	3	3 (100)	3 (100)	0 (0)	0
Meropenem	3	3 (100)	3 (100)	0 (0)	0
Third-generation cephalosporin+colistin	1	1 (100)	1 (100)	0 (0)	0
Cefepime+colistin	1	1 (100)	1 (100)	0 (0)	0

[a]If the entry is n (p), n is the number and p is the percentage.

Table 3 Patients with VAP due to multidrug-resistant Gram-negative pathogens sensitive only to colistin ($n = 30$).

Pathogen of VAP	Patients[a]	Clinical response of VAP[a]	In-hospital death[a]
Acinetobacter baumannii	19/37 (51.3)	14/19 (73.7)	5/19 (26.3)
Pseudomonas aeruginosa	6/12 (50.0)	4/6 (66.7)	2/6 (33.3)
Klebsiella pneumoniae	5/11 (45.4)	3/5 (60.0)	2/5 (40.0)

[a]If the entry is n (p), n is the number and p is the percentage.

tract infections due to *P. aeruginosa* strains[18] in patients with cystic fibrosis. In addition, aerosolized colistin has been used successfully for prophylaxis and treatment of pneumonia caused by *P. aeruginosa* in patients with human immunodeficiency virus (HIV) infection.[19,20]

In patients without history of cystic fibrosis or HIV infection, aerosolized colistin was used recently as supplementary therapy to the conventional intravenous antibiotic treatment for the treatment of nosocomial or ICU-acquired pneumonia caused by MDR Gram-negative microorganisms with good results.[5,6]

The dosage of aerosolized colistin recommended in the UK is 500,000 IU every 12 h for patients with body weight $\leqslant$40 kg and 1 million IU every 12 h for patients with body weight $>$40 kg. For recurrent pulmonary infections, the dosage can be increased to 2 million IU every 8 h. Dosage adjustments are recommended for patients with mild-to-moderate renal dysfunction.[21]

As far as the possible adverse effects (bronchospasm, chest tightness, and apnea due to neuromuscular blockade) of aerosolized colistimethate, no complication from the respiratory system occurred in our patients. However, it should be noted that 12 out of 60 studied patients who had history of COPD received concurrent treatment with inhaled β_2-agonist. This finding is in agreement with the report of Hamer[22] that none of the patients described in his report experienced any adverse effects from the respiratory system related to aerosolized colistin. Similarly, the study by Kwa et al.[6] reported that only 1 out of 21 patients receiving aerosolized colistin suffered from bronchospasm likely associated with this treatment. In addition, a recent study showing that inhaled colistin can cause bronchospasm particularly in patients with history of bronchial asthma (preexisting bronchial hyperreactivity).[23] However, treatment with inhaled β_2-agonists before the initiation of aerosolized colistin could prevent the development of such adverse effects from the respiratory system. It should be emphasized that aerosolized colistin should be administered immediately after its preparation because of the molecule instability.

Our study is not without limitations. It is not a comparative study; specifically we did not have a control group of patients with VAP due to MDR Gram-negative pathogens receiving treatment with only intravenous antimicrobial agents. The open-label, non-controlled design of this study has the potential to limit the possibility to draw definite conclusions about efficacy of this treatment approach. However, the observed clinical outcomes (survival and clinical response of infection) are better compared with historical controls with comparable severity of disease as it is evident from the distribution of the APACHE II score of our patients.[2] Although firm conclusions cannot be made, the good outcome of our critically ill patients who received aerosolized colistin as an adjunctive treatment, despite the severity of their infection and their high APACHE II scores, is promising.

Conclusion

The data from this case series including a relatively large number of patients suggest that aerosolized colistin may be

considered as adjunctive to intravenous treatment in patients with VAP due to MDR Gram-negative bacteria. Despite this encouraging finding, the best route of colistin's administration remains unclear. Subsequently, randomized controlled trials studying the possible benefits and risks related to the use of aerosolized colistin in addition to the intravenous antimicrobial treatment, in patients with VAP due to MDR Gram-negative bacteria are urgently needed. Meanwhile, strict use of colistin is required to prevent the rapid development of emergence and dissemination of pandrug-resistant Gram-negative bacteria (development of resistance against colistin), and selection of fungi.

Key messages

1. Aerosolized colistin may be considered as adjunctive to intravenous treatment in patients with VAP due to MDR Gram-negative bacteria susceptible to colistin.
2. Although aerosolized colistin appears to be safe, its exact role in the treatment of VAP due to MDR Gram-negative bacteria in critically ill patients remains unclear due to the scarcity of comparative studies examining different routes of administration of colistin.
3. The co-administration of aerosolized colistin was associated with good results in 60 adult patients with VAP.
4. Randomized controlled trials examining the possible benefits and risks related to the use of aerosolized colistin in addition to the intravenous antimicrobial treatment, in patients with VAP due to MDR Gram-negative bacteria are urgently needed.
5. Strict use of colistin is required to prevent the rapid development of emergence and dissemination of pandrug-resistant Gram-negative bacteria (development of resistance against colistin), and selection of fungi.

Competing interests

The authors declare that they have no competing interests.

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