ORIGINAL ARTICLE

Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic

A. S. Michalopoulos[1], S. Tsiodras[2], K. Rellos[1], S. Mentzelopoulos[1] and M. E. Falagas[2,3,4]

[1]Intensive Care Unit and [2]Department of Medicine, Henry Dunant Hospital; [3]Alfa HealthCare, Athens, Greece; and [4]Tufts University School of Medicine, Boston, MA, USA

ABSTRACT

A retrospective case series study was performed in a 30-bed general intensive care unit (ICU) of a tertiary care hospital to assess the effectiveness and safety of colistin in 43 critically ill patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria. Various ICU-acquired infections, mainly pneumonia and bacteraemia caused by multiresistant strains of *Pseudomonas aeruginosa* and/or *Acinetobacter baumannii*, were treated with colistin. Good clinical response (cure or improvement) was noted in 74.4% of patients. Deterioration of renal function occurred in 18.6% of patients during colistin therapy. Nephrotoxicity was elevated significantly in those patients with a history of renal failure (62.5%). All-cause mortality amounted to 27.9%. In this group of critically ill patients, an age of >50 years (OR, 5.4; 95% CI 1.3–24.9) and acute renal failure (OR, 8.2; 95% CI 2.9–23.8) were independent predictors of mortality. Colistin should be considered as a treatment option in critically ill patients with infection caused by multiresistant Gram-negative bacilli.

Keywords *Acinetobacter baumannii*, colistin, infection, nosocomial, ICU-acquired infection, *Pseudomonas aeruginosa*

INTRODUCTION

Inadequate therapy for infections acquired in the intensive care unit (ICU) is associated with increased mortality [1], but the frequent use of broad-spectrum antibiotics means that the ICU environment has become a theatre for selection of multiresistant microorganisms. Infections caused by multiresistant Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have become a serious problem worldwide [2]. Colistin, an antibiotic first discovered almost 60 years ago, has not been used greatly since the early 1980s because of its nephrotoxicity, except in patients with cystic fibrosis [3,4]. However, it has been reintroduced recently in clinical practice as a last resort for treatment of nosocomial infections caused by multiresistant bacteria [5–10]. The present study describes a retrospective analysis of colistin use in a group of critically ill ICU patients suffering from ICU-acquired infections caused by multiresistant strains of *P. aeruginosa* and *A. baumannii*. The study was designed to evaluate the effectiveness and safety of colistin, and to identify independent risk factors of mortality.

PATIENTS AND METHODS

Design and setting

The study was designed as a retrospective case series of critically ill patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria treated with intravenous colistin. It was conducted at the 30-bed general ICU of the Henry Dunant Hospital, Athens, Greece (*c*.2000 patients admitted to the ICU annually). The study was approved by the Institutional Review Board of the hospital.

Patient identification

From 1 July 2001 to 1 December 2003, colistin-treated patients were identified through the electronic databases for antibiotic use and in-vitro antimicrobial susceptibility results. All adult patients with multiresistant (except to colistin) Gram-negative bacterial infections requiring treatment with intravenous

Correspondence: M. E. Falagas, Henry Dunant Hospital, 107 Mesogion Ave, 11526, Athens, Greece
E-mail: matthew.falagas@tufts.edu

colistin were eligible for the study, including patients with chronic renal failure. Intermediate susceptibility to other antibiotics, e.g., carbapenems, was considered as resistance.

Route of colistin administration and dosage

All patients in the study received intravenous colistin sulphomethate sodium at a dose of 3 million units every 8 h for at least 48 h, with 1 mg of the colistin used being approximately equal to 12 500 IU (Forest Laboratories, Bexley, UK) or 13 333 IU (Norma, Athens, Greece). Dosage adjustments were made according to creatinine clearance in patients with renal failure. For patients with serum creatinine of up to 1.2 mg/100 mL, 1.3–1.5 mg/100 mL, 1.6–2.5 mg/100 mL, and >2.6 mg/100 mL, the unit dose of colistin was 3 million IU administered every 8, 12, 24 and 36 h, respectively. For patients receiving dialysis treatment, the dosage was adjusted to 1 million IU after each period of dialysis.

Microbiological methods

Standard media and techniques for bacterial isolation and identification were used. Antibiotic susceptibility was determined both by disk diffusion and by microdilution tests (Vitek; bioMérieux, Hazelwood, MO, USA). Using the disk diffusion method with a colistin 10 μg disk (Oxoid, Basingstoke, UK), an inhibition zone of ≥11 mm was accepted as the cut-off to determine susceptibility. Quality control was performed according to NCCLS recommendations.

Data collection

For each patient, clinical data were extracted from the medical record and entered into a database. The following information was collected: demographics, dates of admission and discharge, transfer from another institution, medical history, previous surgery, infection on ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II scores [11], previous nosocomial infections, clinical course, ICU length of stay, hospital discharge diagnoses, and outcome. Data on positive bacterial cultures, antibiotic susceptibilities, antibiotics administered, dates and sites of the first isolation of multiresistant bacteria, subsequent culture results, and the duration of colistin therapy were also collected. Side-effects related to colistin, organ dysfunctions, and the development of septic shock during the evolution of nosocomial infection leading to administration of colistin were recorded, as well as the concomitant use of other drugs that could potentially cause nephrotoxicity. Two independent investigators determined the type of infection and the outcome.

Definitions

Standard definitions were used for co-morbid conditions (e.g., diabetes mellitus, chronic obstructive pulmonary disease, etc.).

Diagnosis of pneumonia required the presence of new, persistent and otherwise unexplained pulmonary infiltrates appearing on chest radiographs. Moreover, at least two of the following criteria were also required: (i) temperature of >38°C; (ii) leukocytosis of >10 000 cells/mm^3; and (iii) purulent respiratory secretions. Pneumonia was considered to be ventilator-associated when it occurred after intubation and infection was judged not to have occurred before an artificial airway was put

in place (in patients mechanically ventilated for more than 48 h) [12]. Tracheobronchial secretions and/or bronchoalveolar lavage (BAL) specimens were used for microbiological diagnosis of pneumonia using non-quantitative culture methods.

Diagnosis of bacteraemia required either growth of a recognised pathogen from one or more blood cultures, or at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following: (a) common skin contaminant (e.g., diphtheroids, *Bacillus* sp., *Propionibacterium* sp., coagulase-negative staphylococci or micrococci) grown from two or more blood cultures drawn on separate occasions; or (b) common skin contaminant grown from at least one blood culture from a patient with an intravascular line and physician-instituted antimicrobial therapy [13]. If bacteraemia was suspected, at least two blood samples were obtained for culture from separate sites before the initiation of therapy.

Other infections, such as urinary tract infections and central venous catheter-related infections, were defined based on the guidelines issued by the Centers for Disease Control and Prevention [13]. Septic shock was defined as sepsis with prolonged hypotension (≥2 h) despite adequate fluid resuscitation, together with the presence of perfusion abnormalities such as lactic acidosis, oliguria, or acute alteration in mental status.

Outcome measures

The primary endpoint of the study was all-cause in-hospital mortality. Secondary endpoints included the clinical and bacteriological outcome of the infection 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; *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; *colonisation* 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 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 ≤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 six organ systems included in the SOFA score (respiratory, cardiovascular, neurological, renal, haematological and hepatic), organ failure was defined as a score of = 3 [14]. Prognostic factors possibly associated with adverse outcome (death) were examined during the evolution of the infection until the end of colistin treatment.

Statistical analysis

The chi-square test or Fisher's exact test for categorical variables, and the two-sample *t*-test for continuous variables, were used for univariate analysis of the association between clinical characteristics and adverse outcome (death) among infected patients. Backward stepwise logistic regression analysis was then conducted to determine independent correlates of death in infected patients. Variables with $p < 0.2$ in the univariate analysis were considered for inclusion in the multivariate analysis. Analyses were performed with SPSS v. 10.0 software (SPSS Inc., Chicago, IL, USA). Data were reported as the mean (±SD), median (range), or odds ratio (OR) with 95% confidence interval (CI), as appropriate. Significance was set at $p < 0.05$.

RESULTS

All patients ($n = 43$) who received colistin intravenously for the treatment of ICU-acquired infection caused by a Gram-negative bacterium susceptible only to colistin between 1 July 2001 and 1 December 2003 were studied. During this period, 4727 adult patients (29.5% females) of mean age 63.2 (±14.9) years were admitted to the ICU. These patients had a mean ICU stay of 3.8 days and an ICU mortality rate of 6.5%.

Table 1 shows the demographic and clinical characteristics for the 43 patients in the study. Most (86%) patients were male and aged >50 years (77%). Seven patients were referred to the ICU from other institutions. Co-morbidity related directly to the cause of ICU admission was present in 29 (67.4%) patients. The mean APACHE II score was 25.8 (±3.7), range 19–35. This group of patients had a mean ICU and hospital stay of 61.3 (±41.3) and 78.3 (±50.3) days, respectively.

All of these patients developed several nosocomial infections preceding the ICU-acquired infection caused by a multiresistant pathogen. Some patients developed more than one episode of infection for which they received treatment. The patients developed the first ICU-acquired

Table 1. Demographic and clinical characteristics for the patients studied ($n = 43$)

General features	Entire group
Male gender, *n* (%)	37 (86)
Mean age, years (SD)	56.5 (16.2)
Previous surgery, *n* (%)	6 (13.9)
Underlying disease	
Diabetes mellitus	7
Chronic obstructive pulmonary disease	4
Chronic renal dysfunction	5
Non-Hodgkin's lymphoma	1
Transfer from another institution, *n* (%)	7 (16.4)
APACHE II score on ICU admission (mean ± SD)	25.8 ± 3.7
Previous antibiotic courses during the same hospitalisation period, median (range)	4 (2–6)
Number of organ dysfunctions, median (range)	2 (0–4)
Length of stay before isolation of multiresistant pathogen (sensitive only to colistin) –associated infection, median (range) (days)	18 (3–64)
Mechanical ventilation for >48 h, *n* (%)	43 (100)
Total length of ICU stay, median (range) (days)	61 (8–181)

APACHE, Acute Physiology and Chronic Health Evaluation score.

infection at 5.4 (±0.8) days following ICU admission. Infections were polymicrobial in 28 (65.1%) patients. Thirty-eight (88.4%) patients developed pneumonia, which was ventilator-associated in 32 (84.2%) cases. Fifteen (34.9%) patients developed bacteraemia; some patients had both bacteraemia and a specific site infection, mainly pneumonia. Central venous catheter-related infection, urinary tract infection and soft tissue infection developed in 22 (51.2%), ten (23.3%) and five (11.6%) patients, respectively, while one (2.3%) patient developed a central nervous system infection. The following antibiotics were used (usually in combination) for the treatment of these infections: a third-generation cephalosporin (33 patients), a quinolone (30), clindamycin (19), an aminoglycoside (9), a glycopeptide (7), a carbapenem (7), metronidazole (4) and penicillin G (2).

During their ICU stay, all patients in the study developed an ICU-acquired infection caused by a pathogen (*A. baumannii* or *P. aeruginosa*) that was susceptible only to colistin. Table 2 displays the characteristics of these infections, most of which were pneumonia or bacteraemia. Most bacteraemias were caused by *P. aeruginosa*. The antibiotic spectrum was narrowed following microbiology results for 20 (46.5%) patients, and changed because of antibiotic resistance for all patients. All patients received intravenous colistin therapy. The mean cumulative dosage of colistin and duration of treatment were 141.2 (±75.3) million IU and 18.6 (±5.8) days, respectively. Concomitant antimicrobial therapy included a carbapenem (17 patients), piperacillin-tazobactam (10), ampicillin-sulbactam

Table 2. Characteristics of infections caused by pathogens susceptible only to colistin (*n* = 43)

Type of infection	*n*	PA	AB	Death
Pneumonia (VAP)	21	14	7	2 (1 with PA + 1 with AB infection)
Bacteraemia	11	10	1	4 (all with PA infection)
Pneumonia (VAP) and bacteraemia	3	3		2 (all with PA infection)
Pneumonia (VAP) and catheter-related infection	3	3		2 (all with PA infection)
Pneumonia and urinary tract infection	2	2		1 (with PA infection)
Pneumonia and surgical wound infection	2	2		1 (with AB infection)
Sinusitis	1	1		

VAP, ventilator-associated pneumonia; PA, *Pseudomonas aeruginosa*; AB, *Acinetobacter baumannii*.

(2), an aminoglycoside (2) and ciprofloxacin (1). Concurrently, 14 patients received a glycopeptide for the treatment of bacteraemia caused by a Gram-positive coccus. In addition, 12 patients received inotropic drugs for the treatment of septic shock. No patient received nephrotoxic agents such as cyclosporin or tacrolimus.

Clinical cure of infection was observed in 30 (69.8%) patients, and clinical improvement in two (4.7%) patients. Eleven (25.6%) patients did not respond to colistin treatment (clinical failure); all of these patients died. In addition, one of two patients with clinical improvement of the infection died following cerebral haemorrhage. None of the patients in the study had a recurrent nosocomial infection caused by the same multiresistant pathogen. Among the 32 patients with clinical cure or improvement, eradication of the pathogen was observed in 29 (67.4%) cases, and colonisation in three cases.

Colistin-associated side-effects, such as paresthesias, vertigo, muscle weakness or apnoea, were not observed. With regard to nephrotoxicity, eight (18.6%) patients had a documented diagnosis of chronic renal failure at ICU admission (serum creatinine >2 mg/dL); of these, five (62.5%) developed acute or chronic renal failure during colistin therapy. In addition, two further patients developed acute renal insufficiency in the ICU before colistin administration. During colistin treatment, eight (18.6%) of the 43 patients developed acute renal failure, including five patients with chronic renal failure, one of the two patients who developed acute renal failure before administration of colistin, and two (6%) of 33 patients who did not have renal failure at ICU admission and on initiation of colistin treatment. All of these patients died. Fig. 1 shows the distribution of serum creatinine values at the start of colistin treatment, and the maximum value during treatment and at the end of treatment.
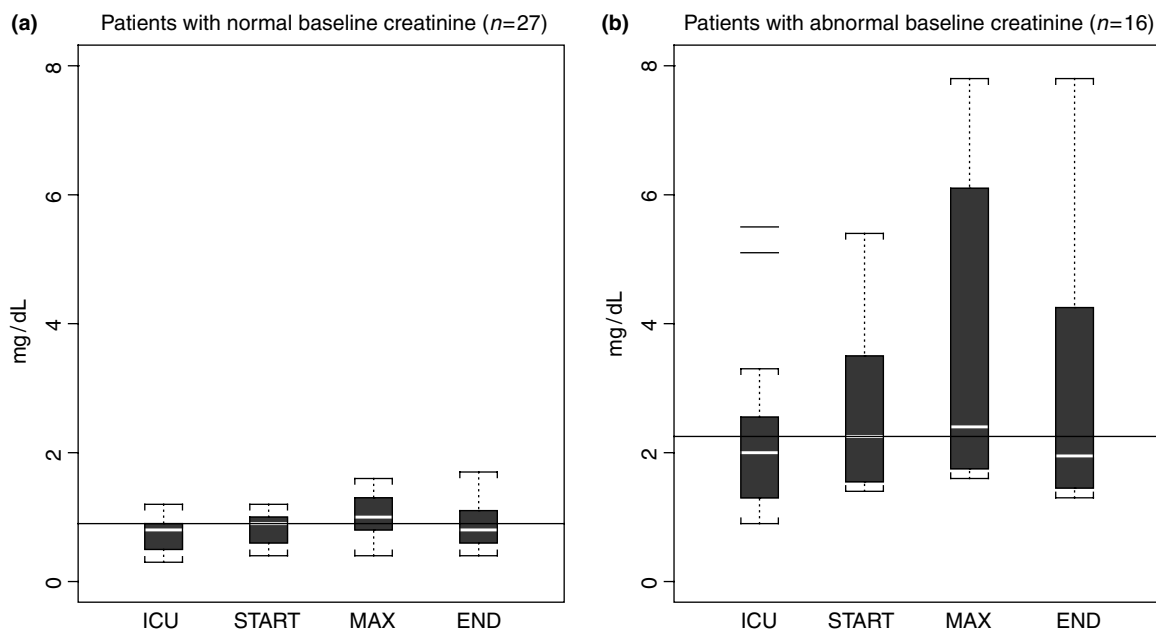

Fig. 1. Distribution of serum creatinine levels on admission to the intensive care unit (ICU), on the first day of colistin treatment (start), at the peak value (max), and at the end of colistin treatment (end) in the group of patients with normal baseline creatinine value (a), and in the group of patients with abnormal baseline creatinine value (b). The horizontal line within the boxes represents the median creatinine baseline value on the first day of colistin treatment.

Twelve (27.9%) patients died during their hospitalisation. All deaths occurred in the ICU (no patients died in the ward following ICU discharge). Most (91.7%) of these were males. In nine of the 12 patients with an adverse outcome, the multiresistant bacterium was isolated from at least two different sites, while nine patients developed septic shock, and nine patients had at least three major organ dysfunctions (12.9% in survivors). The median ICU stay of these 12 patients was 36 days (range, 8–50 days).

Table 3 shows the results of the univariate analysis for the factors associated with mortality; these factors were gender, an age of >50 years, transfer from another hospital, an APACHE II score of >30, the presence of more than one organ dysfunction, septic shock, acute renal failure, and the length of ICU stay. Multivariate analyses showed that an age of >50 years (OR, 5.4, 95% CI 1.3–24.9; $p < 0.001$) and acute renal failure developed during colistin treatment (OR, 8.2, 95% CI 2.9–23.8; $p < 0.001$) were independent predictors of mortality.

DISCUSSION

This study evaluated the effectiveness and safety of colistin in 43 critically ill patients with ICU-acquired infections caused by Gram-negative bacteria that were susceptible only to colistin. Good clinical response (cure/improvement) was observed with 74.4% of patients, and eradication of the multiresistant Gram-negative pathogen was obtained for 67.4% of the patients. Acute renal failure was developed by 18.6% of the patients during colistin treatment, but mainly by patients with a history of chronic renal failure. This may be explained by the fact that potentially nephrotoxic agents are associated with a higher toxicity

Table 3. Factors associated with adverse clinical outcome (univariate analysis)

Variable	Adverse outcome (*n* = 12)	Survivors (*n* = 31)	Odds ratio	95% CI	p
Female gender	1	5	0.4	0.1–0.7	<0.05
Age >50 years	12	17	5.3	1.8–15.3	<0.01
Transfer from another institution	3	4	1.7	1.1–7.3	<0.05
APACHE II score >30	5	3	2.2	1.4–9.9	<0.05
Presence of >1 organ dysfunction	12	23	1.2	1.1–8.0	<0.05
Septic shock	9	2	8.8	3.1–26.0	<0.01
Acute renal failure	8	0	8.1	2.6–23.9	<0.01
ICU length of stay >40 days	7	20	1.1	1.1–4.8	<0.05

ICU, Intensive care unit.

in patients with abnormal renal function, even with adjusted dosages. In addition, this group of patients often develops nosocomial infections for which other potentially nephrotoxic agents may be used, and has higher acute illness severity scores than patients with normal renal function [15]. However, renal function impairment should not be attributed solely to colistin toxicity as other factors, e.g., the development of septic shock and multi-organ failure, may also make a significant contribution. Indeed, previous studies have shown that advanced age, severe sepsis, major surgery, low cardiac output syndrome and hypovolaemia are all common conditions associated with acute renal failure in the ICU setting [16,17].

The observed mortality rate in the present study was 27.9%, which is no worse than the mortality reported in studies with comparable patient groups [18–20]. In keeping with results from other studies which investigated predictors of adverse outcome in ICU patients with infection [21], renal failure was found to be an independent predictor of death. Considering the fact that nephrotoxicity is the main adverse reaction of colistin treatment, it is interesting to note that the rate of acute renal failure in this patient population was 18.6%, which is similar to the rates reported in studies of ICU patients treated with antibiotics other than colistin [22].

Clinical experience regarding the use of colistin in severely ill patients is limited. The overall favourable response of nosocomial infections caused by *P. aeruginosa* and *A. baumannii* was 60% in a study from Brazil [8], although a major side-effect observed in that study was renal insufficiency. In another report from Spain, 21 patients with ventilator-associated pneumonia caused by bacteria susceptible only to colistin showed a cure rate of 57% following colistin treatment [7]. Both of these studies showed higher mortality rates than the present study. However, differences in mortality should be interpreted with caution because of potential differences in patient characteristics. In addition, there are differences in the potencies of commercial formulations of colistin in different countries, and this may translate into differences in efficacy and safety [23]. In a recent study from New York [9] in which polymyxin B was used, the mortality rate was 20% for patients with infections caused by multiresistant Gram-negative bacteria (much closer to the results obtained in the present study).

Ouderkirk *et al.* [9] also found that mortality was considerably higher in patients who developed renal dysfunction, which is in agreement with the present results.

Earlier reports showed a high incidence of colistin toxicity. However, some of these studies had design defects and involved inappropriate patient monitoring [5]. In contrast, the present findings agreed with other reports published recently [7–9]. Renal injury is the major adverse effect of colistin. In the largest study to date, published in 1970, frequently reversible renal impairment was found in 20% of patients receiving colistin [24]. This possibility of renal toxicity should be considered seriously, especially when colistin is used as a last resort in patients prone to renal dysfunction because of illness severity and/or sepsis.

In an era of continuously increasing rates of infections with multiresistant pathogens, further clinical studies should examine the efficacy and safety of combinations of colistin with other antibiotics, e.g., carbapenems, ceftazidime and rifampicin, which may prove synergistic *in vivo*, as has been suggested by in-vitro studies [25–27]. In addition, aerosolised colistin may prove beneficial in certain cases of pneumonia in ICU patients, as has been suggested for patients with cystic fibrosis; however, it is always necessary to be aware of the potential for development of colistin resistance [28].

The present study was not without limitations. First, the study had the inherent weaknesses of studies with retrospective design, including the need to collect data from already completed medical records. Second, the study was not designed to specifically investigate the effectiveness of colistin by providing (for example) comparative outcome data using a control group of ICU patients with infection caused by multiresistant Gram-negative bacilli and treated with a carbapenem following in-vitro susceptibility test results. Third, the study cannot provide an estimate for the possible relative contribution of colistin to renal dysfunction in patients who developed this complication. Finally, data on possible side-effects of colistin apart from nephrotoxicity were not evaluated actively. Nevertheless, several interesting points of clinical relevance emerged from the study. The results indicated that colistin can be used with satisfactory efficacy and safety in ICU patients with infections caused by bacteria which show in-vitro suscepti-

bility only to colistin. However, patients aged >50 years with rapid deterioration of renal function of any pathogenesis during colistin therapy are at high risk for death. In such cases, prophylactic and/or intensive renal replacement therapy may be indicated [29].

In conclusion, colistin appears to be relatively safe and effective in treating severely ill ICU patients with infections caused by multiresistant Gram-negative bacteria. Clinicians should be vigilant for renal function deterioration during colistin therapy as this predisposes strongly to an adverse outcome. However, further investigation is warranted to further clarify the role of colistin in the management of critically ill patients with ICU-acquired infections caused by multiresistant pathogens.

REFERENCES

1. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999; **115**: 432–474.
2. Livermore D. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa:* our worst nightmare? *Clin Infect Dis* 2002; **34**: 634–640.
3. Catchpole CR, Andrews JM, Brenwald N, Wise R. A reassessment of the in vitro activity of colistin sulfomethate sodium. *J Antimicrob Chemother* 1997; **39**: 255–260.
4. Horton J, Pankey GA. Polymyxin B, colistin and sodium colistimethate. *Med Clin North Am* 1982; **66**: 135–142.
5. Conway SP, Pond MN, Watson A, Etherington C, Robey HL, Goldman MH. Intravenous colistin sulfomethate in acute respiratory exacerbations in adult patients with cystic fibrosis. *Thorax* 1997; **52**: 987–993.
6. Beringer P. The clinical use of colistin in patients with cystic fibrosis. *Curr Opin Pulm Med* 2001; **7**: 434–440.
7. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ *et al.* Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. *Clin Infect Dis* 2003; **36**: 1111–1118.
8. Levin AS, Baron AA, Penco J *et al.* Intravenous colistin as therapy for nosocomial infections caused by multidrug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Clin Infect Dis* 1999; **28**: 1008–1011.
9. Ouderkirk JP, Nord JA, Turett GS, Kislak JW. Polymyxin B nephrotoxicity and efficacy against nosocomial infections caused by multiresistant Gram-negative bacteria. *Antimicrob Agents Chemother* 2003; **47**: 2659–2662.
10. Markou N, Apostolakos H, Koumoudiou C *et al.* Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients. *Crit Care* 2003; **7**: 78–83.
11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II. a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–829.

12. Rello J, Paiva JA, Baraibar J *et al.* International conference for the development of consensus on the diagnosis and treatment of ventilator-associated pneumonia. *Chest* 2001; **120**: 955–970.

13. Gaynes RP, Horan TC. Surveillance of nosocomial infections. Appendix A. CDC definitions of nosocomial infections. In: Mayhall, CG, ed. *Hospital epidemiology and infection control*. Baltimore: Williams & Wilkins 1996, 1–14.

14. Vincent JL, de Mendonça A, Cantraine F *et al.* Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicentric, prospective study. *Crit Care Med* 1998; **26**: 1793–1800.

15. Clermont G, Acker CG, Angus DC, Sirio CA, Pinsky MR, Johnson JP. Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal failure on ICU outcomes. *Kidney Int* 2002; **62**: 986–996.

16. Uchino S, Doig GS, Bellomo R *et al.* Diuretics and mortality in acute renal failure. *Crit Care Med* 2004; **32**: 1669–1677.

17. De Mendonca A, Vincent JL, Suter PM *et al.* Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intens Care Med* 2000; **26**: 915–921.

18. Michalopoulos AS, Geroulanos S, Mentzelopoulos SD. Determinants of candidemia and candidemia-related death in cardiothoracic intensive care unit patients. *Chest* 2003; **124**: 2244–2255.

19. Annane D, Aegerter P, Jars-Guincestre MC, Giodet B, CUB-Rea Network. Current epidemiology of septic shock: the CUB-Rea Network. *Am J Respir Crit Care Med* 2003; **168**: 165–172.

20. Bercault N, Boulain T. Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: a prospective case-control study. *Crit Care Med* 2001; **29**: 2303–2309.

21. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Effects of nosocomial candidemia on outcome in critically ill patients. *Am J Med* 2002; **15**: 480–485.

22. Giamarellou H. Therapeutic guidelines for *Pseudomonas aeruginosa* infections. *Int J Antimicrob Agents* 2000; **16**: 103–106.

23. Li J, Turnidge J, Milne R, Nation RL, Coulthard K. In vitro pharmacodynamic properties of colistin and colistin methanesulfonate against *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. *Antimicrob Agents Chemother* 2001; **45**: 781–785.

24. Koch-Weser G, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. *Ann Intern Med* 1970; **72**: 857–868.

25. Rynn C, Wooton M, Bowker KE, Holt HA, Reeves DS. In vitro assessment of colistin's antipseudomonal antimicrobial interactions with other antibiotics. *Clin Microbiol Infect* 1999; **5**: 32–36.

26. Gunderson BW, Ibrahim KH, Hovde LB, Fromm TL, Reed MD, Rotschafer JC. Synergistic activity of colistin and ceftazidime against multiantibiotic resistant *Pseudomonas aeruginosa* in an in vitro pharmacodynamic model. *Antimicrob Agents Chemother* 2003; **47**: 905–909.

27. Giamarellos-Bourboulis EJ, Sambatakou H, Galani I, Giamarellou H. In vitro interaction of colistin and rifampin on multidrug resistant *Pseudomonas aeruginosa*. *J Chemother* 2003; **15**: 235–238.

28. Denton M, Kerr K, Mooney L *et al.* Transmission of colistin resistant *Pseudomonas aeruginosa* between patients attending a pediatric cystic fibrosis center. *Pediatr Pulmonol* 2002; **34**: 257–261.

29. Drumi W. Prophylactic use of continuous renal replacement therapies in patients with normal renal function. *Am J Kidney Dis* 1996; **28**: S114–S120.