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Colistin and rifampicin in the treatment of multidrug-resistant *Acinetobacter baumannii* infections

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***Objectives*: The increased incidence of nosocomial infections by multidrug-resistant organisms has motivated the re-introduction of colistin in combination with other antimicrobials in the treatment of infections. We describe the clinical and microbiological outcomes of patients infected with multidrug-resistant *Acinetobacter baumannii* who were treated with a combination of colistin and rifampicin.**

***Patients and methods*: Critically ill patients with pneumonia and bacteraemia caused by *A. baumannii* resistant to all antibiotics except colistin in medical and surgical intensive care units were enrolled. Clinical and microbiological responses and safety were evaluated.**

***Results*: Twenty-nine patients (47 ± 14 years and APACHE II score 17.03 ± 3.68), of whom 19 were cases of nosocomial pneumonia and 10 were cases of bacteraemia, were treated with intravenous colistin sulphomethate sodium (2 million IU three times a day) in addition to intravenous rifampicin (10 mg/kg every 12 h). All *A. baumannii* isolates were susceptible to colistin. The mean duration of treatment with intravenous colistin and rifampicin was 17.7 (±10.4) days (range 7–36). Clinical and microbiological responses were observed in 22 of 29 cases (76%) and the overall infection-related mortality was 21% (6/29). Three of the 29 evaluated patients (10%) developed nephrotoxicity when treated with colistin, all of whom had previous renal failure. No cases of renal failure were observed among patients with normal baseline renal function. No neurotoxicity was noted.**

***Conclusions*: Colistin and rifampicin appears to be an effective and safe combination therapy for severe infections due to multidrug-resistant *A. baumannii*.**

Keywords: ICU, multiresistant, nephrotoxicity, bacteraemia, ventilator-associated pneumonia

Introduction

Acinetobacter baumannii is a Gram-negative coccobacillus, widespread in nature, that has emerged as an important nosocomial pathogen in recent years, and hospital outbreaks caused by this organism have increased worldwide.[1,2] Its ability to acquire resistance to almost all groups of available antibiotics is a problem of great concern. Recent reports showed that most *A. baumannii* strains isolated in hospitals, especially in intensive care units (ICUs), are highly resistant to β-lactams, aminoglycosides, fluoroquinolones and carbapenems.[3] Colistin is an old antimicrobial belonging to the polymyxins and is widely applied nowadays for the management of infections caused by multidrug-resistant Gram-negative pathogens.[4] Colistin should therefore be considered as a treatment option for critically ill patients in the ICU with infections caused by multiresistant *A. baumannii*,[5] owing to its favourable properties of rapid bacterial killing, a narrow spectrum of activity and an associated slow development of resistance.[6]

A recent study had demonstrated that the *in vitro* activity of colistin was increased significantly by the presence of rifampicin and the combination was effective in prolonging survival in an

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experimental model of infection by multidrug-resistant *A. baumannii*.[7]

We describe the clinical and microbiological outcomes of patients infected with multidrug-resistant *A. baumannii* who were treated with the colistin and rifampicin combination, as well as the adverse events seen with this combination.

Patients and methods

The study is a prospective uncontrolled case series that took place in two medical and surgical ICUs in Liguria Region in Italy between January 2006 and July 2007. We considered patients with the following inclusion criteria: critically ill patients with ventilator-associated pneumonia (VAP) or bacteraemia caused by *A. baumannii* resistant to all drugs tested (except colistin) admitted in medical and surgical ICUs. Diagnosis of infection was based on clinical findings and the isolation of bacteria, either from a normally sterile site or from quantitative cultures of bronchoalveolar lavage (BAL) according to the literature.[8] More specifically, the clinical prerequisites or the diagnosis of VAP was as follows: the presence of at least two episodes of fever ($>38.3^{\circ}$C), leucocytosis or leucopenia, purulent bronchial secretions, plus a new or persistent infiltrate on chest radiography. Polymicrobial infection was a criterion for exclusion. All the patients were treated with colistin sulphomethate sodium (Bellon; Rhône-Poulenc Rorer, France) administered intravenously at the dosage of 6 million units ($\sim$100 000 U/kg) divided into three doses associated with intravenous rifampicin (10 mg/kg every 12 h). All causative microorganisms were identified using routine microbiological methods. Susceptibility testing was performed using the agar dilution method. Disc susceptibility testing was performed and interpreted according to the guidelines published by CLSI.[9] Pan-drug resistance was defined as resistance of the isolate to anti-pseudomonal penicillins, cephalosporins, carbapenems, quinolones and aminoglycosides. VAP and bacteraemia were considered to have clinical and microbiological favourable outcomes if there was remission of sepsis-related symptoms (fever, leucocytosis or leucopenia), radiological resolution of VAP (decrease or disappearance of presenting findings on chest X-ray), and if BAL and blood cultures became negative. Renal function was monitored by daily measurement of the serum creatinine level. In patients with normal renal function (serum creatinine level, <1.2 mg/dL, or 110 μM), nephrotoxicity was defined as a serum creatinine value of >2 mg/dL (171 μM), as a reduction in the calculated creatinine clearance of 50% relative to the value at antibiotic therapy initiation. In patients with pre-existing renal dysfunction, nephrotoxicity was defined as an increase of $\geq$50% of the baseline creatinine level, as a reduction in the calculated creatinine clearance of 50% relative to the value at antibiotic therapy initiation. The study was approved by the Ethics Committee and did not require signatures of informed consent from the patients.

Results

Twenty-nine critically ill patients with multiresistant *A. baumannii* infections (age 47 $\pm$ 14 years) were studied: 19 patients had nosocomial pneumonia and 10 had bacteraemia. All the patients that matched the inclusion criteria were included in the study. Twenty-two were receiving mechanical ventilation (mean length of ventilation 24 $\pm$ 5.5 days). The APACHE II score was 17.03 $\pm$ 3.68. Data on the 29 patients are presented in Table 1. All *A. baumannii* isolates were tested against colistin and rifampicin and were susceptible. The mean duration of treatment was 17.7 ($\pm$10.4) days (range 7–36). The mean length of hospital stay was 33.2 ($\pm$15.8) days (range 12–74). The mean length of the ICU stay was 19.5 ($\pm$7.9) days (range 11–56). Clinical and microbiological favourable responses were observed in 22 of 29 cases (76%) and the overall infection-related mortality was 21% (6/29 cases). The 30 day in-hospital mortality was 31% (9/29 cases). We did not observe any cases of development of resistance to rifampicin and colistin. Three of the 29 (10%) evaluated patients developed nephrotoxicity when treated with colistin (all of them had previous renal failure). Among the treated patients, none required dialysis. No cases of renal failure were observed among patients with normal baseline renal function. No neurotoxicity was noted.

Discussion

The emerging problem of nosocomial infections by multidrug-resistant *A. baumannii* has focused clinical attention on colistin, an old antimicrobial that is active against that species.[4] The efficacy of colistin for the management of these infections may only be established by prospective double-blind, placebo-controlled trials; however, our prospective clinical experience confirmed that the combination of colistin plus rifampicin is safe and effective in the treatment of multidrug-resistant *A. baumannii* infections. To the best of our knowledge, this is the largest clinical trial of *A. baumannii* infections in critically ill patients treated with the colistin/rifampicin combination published in the literature.[10,11] The first study, by Petrosillo *et al.*,[10] evaluated the clinical outcome of carbapenem-resistant *A. baumannii*-infected patients treated with a combination of colistin (same dosage as our experience) and rifampicin in 14 mechanically ventilated critically ill patients with pneumonia due to *A. baumannii*. Of the 14 treated patients, 7 recovered from *A. baumannii* infections and 9 had microbiological clearance.[10] Another study with combination therapy of colistin plus rifampicin was that of Motaouakkil *et al.*,[11] who conducted an observational study to evaluate the efficacy of intravenous (same dosage as our experience) and aerosolized colistin combined with rifampicin in the treatment of critically ill patients with nosocomial infections caused by multiresistant *A. baumannii* in a medical ICU. The clinical outcome was favourable for all patients. Despite the limited number of treated patients, our clinical and microbiological response rate (76%) was better than that of other similar studies.[10,11] In recent years, many studies have been published showing that colistin may be a good therapeutic option for the treatment of severe infections caused by multidrug-resistant organisms.[12–14] In these reports, favourable clinical response ranged between 57% and 73%.

The main adverse effects of colistin are nephrotoxicity (acute tubular necrosis) and neurotoxicity (dizziness, weakness, facial paraesthesia, vertigo, visual disturbances, confusion, ataxia and neuromuscular blockade, which can lead to respiratory failure or apnoea).[4] In our series, no cases of renal failure were observed among patients with normal baseline renal function, as recently observed by Kallel *et al.*[14] Among patients with previous renal impairment, 10% experienced nephrotoxicity during treatment.

Table 1. Patients treated with colistin and rifampicin: clinical characteristics and outcome

Patient	Age (years)	Underlying disease	APACHE II score	Infection	Evolution	Outcome of hospital stay	Total length of hospital stay (days)	ICU stay (days)
1	34	trauma	15	VAP	favourable	discharge	46	18
2	65	cardiac failure	17	VAP	favourable	discharge	54	21
3	46	AIDS	18	VAP	favourable	death	28	28
4	56	trauma	15	VAP	failure	death	12	12
5	38	AHS	21	VAP	favourable	discharge	24	13
6	54	liver transplant	24	VAP	favourable	discharge	65	25
7	51	intestinal cancer	19	VAP	favourable	discharge	19	11
8	38	trauma	15	VAP	favourable	death	28	19
9	23	AIDS	21	VAP	favourable	discharge	25	18
10	65	AIS	17	VAP	favourable	discharge	29	17
11	46	lung cancer	19	VAP	failure	death	22	22
12	37	trauma	12	VAP	favourable	discharge	25	19
13	40	epilectic coma	20	VAP	favourable	discharge	50	21
14	72	non-Hodgkin's lymphoma	18	VAP	favourable	discharge	30	18
15	32	AML	25	VAP	failure	death	29	20
16	63	trauma	19	VAP	failure	discharge	28	21
17	33	LLA	14	VAP	favourable	discharge	21	15
18	19	poisoning	21	VAP, BSI	failure	death	19	19
19	77	AIS	17	VAP, BSI	favourable	death	30	17
20	27	epileptic coma	12	BSI	favourable	discharge	25	12
21	51	asthma	18	BSI	favourable	discharge	26	21
22	48	myocardial infarction	16	BSI	favourable	discharge	23	16
23	37	AML	12	BSI	failure	death	14	14
24	61	pulmonary embolism	13	BSI	favourable	discharge	24	16
25	57	gastric cancer	12	BSI	failure	discharge	57	21
26	48	trauma	15	BSI	favourable	discharge	49	19
27	42	cardiac failure	17	BSI	favourable	discharge	74	56
28	59	AHS	21	BSI	favourable	death	28	14
29	49	asthma	11	BSI	favourable	discharge	59	22

VAP, ventilator-associated pneumonia; AHS, acute haemorrhagic stroke; AIS, acute ischaemic stroke; BSI, bloodstream infection; AML, acute myeloid leukaemia; LLA, lymphatic leukaemia acute.

Colistin was developed several decades ago, and no studies were ever performed to characterize its pharmacokinetic profile in critically ill patients.[4] The optimal dosing regimen for critically ill patients is unknown. The synergy between colistin and rifampicin has certainly been demonstrated *in vitro* against multiresistant *A. baumannii*.[7] In our study, colistin in combination with rifampicin showed very interesting clinical and microbiological results. Although this is by no means a definitive outcome study, it is an important one, adding to the body of the literature.

Despite the lack of a control group and the limited number of patients, colistin in association with rifampicin appears to be relatively safe and effective in treating critically ill patients with infections caused by multidrug-resistant *A. baumannii*.

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Transparency declarations

None to declare.

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