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Colistin and rifampicin in the treatment of nosocomial infections from multiresistant *Acinetobacter baumannii*

Said Motaouakkil [a,*], Boubaker Charra [a], Abdelhamid Hachimi [a], Hicham Nejmi [a], Abdellatif Benslama [a], Naima Elmdaghri [b], Habiba Belabbes [b], Mohamed Benbachir [b]

[a] *Medical Intensive Care Unit, Ibn Rochd University Hosptial, Casablanca, Morocco*
[b] *Laboratory of Microbiology, Ibn Rochd University Hospital, Casablanca, Morocco*

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Summary *Introduction:* The increased incidence of nosocomial infections by multidrug resistant *Acinetobacter baumannii* creates demand on the application of some combinations of older antimicrobials on that species. We conducted the present observational study to evaluate the efficacy of intravenous and aerosolized colistin combined with rifampicin in the treatment of critically patients with nosocomial infections caused by multiresistant *A. baumannii*.
Patients and methods: Critically ill patients with nosocomial infections caused by *A. baumannii* resistant to all antibiotics except colistin in a medical intensive care unit. Diagnosis of infection was based on clinical data and isolation of bacteria. The bacterial susceptibilities to colistin were tested. Clinical response to colistin + rifampicin was evaluated.
Results: Twenty-six patients (43.58 ± 18.29 years, Acute Physiology and Chronic Health Evaluation II Score (APACHE II): 6.35 ± 2.99), of whom 16 cases of nosocomial pneumonia treated by aerosolized colistin (1×10^6 IU three times/day) associated with intravenous rifampicin (10 mg/kg every 12 h), nine cases of bacteraemia treated by intravenous colistin (2×10^6 IU three times/day) associated with intravenous rifampicin (10 mg/kg every 12 h) in which three cases associated with ventilator associated pneumonia and one case of nosocomial meningitis treated by intrathecal use of colistin associated with intravenous rifampicin. The clinical evolution was favourable for all ill patients. Concerning side effects, we have noticed a moderate hepatic cytolysis in three patients.

* Corresponding author. Medical Intensive Care Unit, CHU Ibn Rochd, Casablanca 20000, Morocco. Tel.: +212 22 22 8817.
E-mail address: smotaouakkil@yahoo.fr (S. Motaouakkil).

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Conclusion: This is the first clinical report of colistin combined with rifampicin for treatment of *A. baumannii* infection. Despite the lack of a control group and the limited number of patients, the results seem to be encouraging.

Introduction

Over the last 15 years, *A. baumannii* has emerged as an important nosocomial pathogen, and hospital outbreaks caused by this organism have increased worldwide.[1–5] Its extraordinary ability to acquire resistance to almost all groups of commercially available antibiotics is a clinical problem of great concern. In fact, most *A. baumannii* strains isolated in hospitals today are highly resistant to modern non-carbapenem β lactams, amino glycosides, and fluoroquinolones.[6,7] Imipenem used to be considered the ''gold standard'' therapy for severe infections, but many countries have reported growing resistance to carbapenem.[3,4,8,9] The in vitro activity of colistin was increased significantly in the presence of rifampicin, and this combination has been proposed for administration in vivo.[10,11] However, no data are available on the clinical report but the preliminary results obtained in the mouse pneumonia model by Montero et al. are interesting.[12] We describe the clinical outcome of 26 patients infected with multiresistant *A. baumannii* who were treated with colistin—rifampicin, as well as the adverse events of this combination.

Patients and methods

We report an opened monocentric and observational study, spread over 1 year (2004), realized in the Medical Intensive Care Unit in the Ibn Rochd University Hospital at Casablanca (Morocco). 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. More specifically, the clinical prerequisites for the diagnosis of ventilator associated pneumonia (VAP) were as follows: the presence of at least two of fever ($>38.3\ ^{\circ}C$), leukocytosis or leucopenia, purulent bronchial secretions, and a new or persistent infiltrate on chest radiography. All the strains of *A. baumannii* were resistant to all antibiotics apart from colistin. The polymicrobism was the criterion of exclusion. The treatment of 16 cases of VAP consisted of aerosolized colistin (1×10^6 IU three times/day) associated with intravenous rifampicin (10 mg/kg every 12 h) during 15 days. Nine cases of bacteraemia were treated by intravenous colistin at a dose of 2×10^6 IU three times/day associated with intravenous rifampicin (10 mg/kg every 12 h) combined with intravenous rifampicin (10 mg/kg every 12 h). One case of nosocomial meningitis following drain of ventriculostomy was treated by colistin intrathecally at a dose of 5 mg for the first day and 10 mg/day during 21 days. Susceptibility testing was done using the disk diffusion method. The break points for susceptibility were those recommended by the National Committee for Clinical Laboratory Standards. Rifampicin was not tested but its association with colistin was founded on theoretical bases.[11] The definition of a positive outcome of VAP was based on clinical (fever defervescence, resolution or partial resolution of presenting symptoms and signs of pneumonia, decrease in suctioning requirements), radiological (decrease or disappearance of presenting findings on chest x-ray) and laboratory findings (improvement in arterial blood gases, or normalisation of white blood cell count and C reactive protein).

Results

Twenty-six critically ill patients (17 males) with multiresistant *A. baumannii* infection, mean age 43.58 ± 18.29 years, in the Medical Intensive Care unit in the university Hospital in Casablanca (Morocco) were studied. Data on the 26 patients are presented in Table 1. All were receiving mechanical ventilation (mean length of ventilation 29 ± 5.5 days). The APACHE II was 6.35 ± 2.99 and SAPS II was 14.42 ± 5.22. The colistin and rifampicin were introduced when culture results became available for all the patients who had not responded to the initial empiric regimen. During 2004 in our hospital, 420 strains of *A. baumannii* were isolated (blood, bronchial samples, urinary, cerebrospinal fluid) in which 130 strains were multidrug-resistant (30.95%).

The evolution was favourable for all patients with sterilization of bronchial secretions by the 10th day. Blood cultures were negatives after 72 h, as well as CSF (one case of nosocomial meningitis). The duration of treatment was 15 days for VAP and bacteraemia. It lasted 21 days for nosocomial meningitis. In bacteriologic foreground, the

Table 1 Critically ill patients treated with colistin and rifampicin: clinical characteristics and outcome

Patient	Age (years)	Sex	Underlying disease	APACHE II	SAPS II	Infection	Antibiotic adverse events	Evolution
1	17	M	PPD poisoning	8	13	VAP	None	Favourable
2	80	F	Pulmonary embolism	6	17	VAP	None	Favourable
3	27	M	Trauma	7	16	VAP	None	Favourable
4	43	F	AHS	10	19	VAP	Cytolysis[a]	Favourable
5	46	M	AIS	4	10	VAP	None	Favourable
6	24	F	OP poisoning	7	19	VAP	None	Favourable
7	44	M	Trauma	3	7	VAP	None	Favourable
8	26	M	Epileptic coma	3	5	VAP	Cytolysis[a]	Favourable
9	76	M	AIS	6	16	VAP	None	Favourable
10	44	F	AHS	8	17	VAP	None	Favourable
11	50	M	Cerebral abscess	15	22	VAP	None	Favourable
12	59	M	AHS	11	21	VAP	None	Favourable
13	70	M	AIS	7	18	VAP	None	Favourable
14	34	F	GBS	2	7	VAP,BSI	None	Favourable
15	29	F	Trauma	6	10	VAP,BSI	None	Favourable
16	40	M	Tetanus	9	17	VAP,BSI	None	Favourable
17	33	F	Trauma	2	6	BSI	None	Favourable
18	41	M	Cardiac failure	7	18	BSI	None	Favourable
19	16	M	Trauma	4	13	BSI	None	Favourable
20	30	F	GBS	3	9	BSI	Cytolysis[a]	Favourable
21	45	M	Tetanus	3	7	BSI	None	Favourable
22	48	M	Leptospirosis	5	16	BSI	None	Favourable
23	30	F	Asthma	8	23	BSI	None	Favourable
24	75	M	Trauma	7	16	BSI	None	Favourable
25	70	M	AIS	7	18	BSI	None	Favourable
26	36	M	Trauma	7	15	NM	None	Favourable

F, female; M, male; PPD, paraphenylene diamine; VAP, ventilator associated pneumonia; AHS, acute haemorrhagic stroke; AIS, acute ischemic stroke; OP, organophosphorus; GBS, Guillain Barre syndrome; BSI, bloodstream infection; NM, nosocomial meningitis.

[a] The hepatic cytolysis is moderate (<5 times the normal).

broncho-alveolar lavage realized at 3rd day, 6th day, 10th day, and 15th day, sterilisation was obtained on the tenth day, whereas blood culture was negative after 72 h. Sterilization of cerebrospinal fluid (CSF) was obtained after 48 h of treatment. No deterioration of kidney function was noticed. However, three patients presented a moderate hepatic cytolysis (<5 times the normal), which had not required withdrawal of rifampicin.

Discussion

The emergence and further persistence of imipenem resistance among *A. baumannii* strains responsible for the outbreak in our unit presented a serious therapeutic challenge. However good results were obtained using local intrathecal colistin for treatment of catheter-associated ventriculitis. Furthermore a successful intravenous colistin has been reported in a case of meningitis[13] and in a variety of nosocomial infections.[14] Clinical experience with colistin is still limited[15,16] and relatively little is known on its efficiency in treating severe infections, especially in comparison with other antibiotics. Recently, several studies regarding the use of this antibiotic in the therapy of pneumonia were published.[12]

Pneumonia is the most serious nosocomial infection due to multiresistant *A. baumannii*.[3,17,18] Effective mouse models of pneumonia due to this micro-organism have been described.[19,20] Michalopoulos et al.[21] reported that colistin should be considered as a treatment option for critically ill patients in intensive care units with infections caused by multiresistant *P. aeruginosa* and *A. baumannii*. We have observed previously that rifampicin is active in vitro against *A. baumannii*, and this led us to investigate the potential therapeutic role of this antimicrobial agent in combination with polymixin B, ampicillin—sulbactam and colistin.[11,22] The in vitro activity of colistin is increased significantly in the presence of rifampicin and this combination has been proposed for administration in

vivo.[10,11] Our results join those which are recently published.[21] In a group of patients with VAP, colistin was used in nebulized form. The idea of using colistin in nebulized form for the management of pneumonia due to gram-negative bacteria is not new. In 1963, Pino et al.[23] used aerosolized colistin in patients with pulmonary infection. A few years later, Marschke and Sarauw[24] reported two cases of pneumonia due to *P. aeruginosa* strains in patients with underlying bronchiectasis and chronic bronchitis, in which polymixin B was given by inhalation. Actually, Michalopoulos[25] concluded that aerolized colistin should be a beneficial adjunctive treatment in the management of nosocomial pneumonia due to multidrug-resistant gram-negative bacteria. In our series, the evolution was favourable for all patients with VAP who received colistin in nebulized form. However, our study is not without limitations. It is a small case series. In addition, there is no control group of patients receiving treatment by intravenous route only.

Treatment with aerolized colistin may further be complicated by bronchoconstriction and chest tightness. However, treatment with inhaled β_2 agonists before the initiation of treatment with aerolized colistin could prevent the development of bronchoconstriction.[26] In our series, these adverse effects have not been noticed. Among patients who received intravenous colistin no one presented a deterioration of kidney function during the period of treatment. However, toxicity, particularly nephro-toxicity, is an important concern with colistin. In the study conducted by Koch-Weser et al.[27] impairment in kidney function—usually reversible at the end of treatment—was observed in 20.2% of 288 patients. Recent data indicate that colistin-related toxicity mainly nephrotoxicity, may be less prominent than previously thought.[28] Notably, in two studies conducted exclusively among patients in intensive care units who received 3×10^6 IU of colistin administrated intravenously every 8 h, the incidences of nephrotoxicity were 18.6% and 14.3%, respectively.[21,28] However colistin has already been reported as an adequate alternative in sporadic cases of nosocomial infections by multidrug resistant *A. baumannii*.[11]

Conclusion

This is the first clinical report of colistin combined with rifampicin for treatment of *A. baumannii* infection. Despite the lack of a control group and the limited number of patients, results seem to be encouraging.

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