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Safety and efficacy of colistin compared with imipenem in the treatment of ventilator-associated pneumonia: a matched case–control study

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Abstract *Objective:* Our study aimed to determine the efficacy and safety of colistin in the treatment of ventilator-associated pneumonia (VAP) caused by pan-drug-resistant *Pseudomonas aeruginosa* or *Acinetobacter baumanii. Design:* Pairwise, retrospective exposed–unexposed study. *Setting:* Combined medical and surgical intensive care unit of Habib Bourguiba University Hospital (Sfax, Tunisia). *Patients:* Sixty patients with VAP caused by pan-drug-resistant *A. baumanii* or *P. aeruginosa* matched to 60 controls with VAP caused by *A. baumanii* or *P. aeruginosa* susceptible to imipenem. All patients had normal renal function at the onset of antibiotic therapy. *Interventions:* Case patients were treated by colistin intravenously and control patients were treated by imipenem intravenously. *Measurements and results:* Baseline characteristics were similar between the colistin and imipenem groups. The mean duration of antibiotic therapy for VAP was 9.5 ± 3.8 days (range 5–22 days) with colistin and 8.9 ± 2.8 days (range 5–20 days) with imipenem ($p = 0.32$). A favorable clinical response to antibiotic therapy for VAP occurred in 45 patients (75%) in the colistin group and in 43 patients (71.7%) in the imipenem group ($p = 0.68$). The time to resolution of infectious parameters after the initiation of antibiotic therapy was not statistically different between the two groups. During the antibiotic course, none of the patients in either group developed renal failure. *Conclusions:* We conclude that colistin can be a safe and effective option in the treatments of VAP caused by pan-drug-resistant *P. aeruginosa* or *A. baumanii*.

Keywords Colistin · Ventilator-associated pneumonia · Nephrotoxicity · Imipenem

Introduction

Pan-drug-resistant (PDR) gram-negative bacteria are an important problem worldwide, especially in the intensive care unit (ICU) [1, 2]. Multiple drug resistance makes difficult the choice of the empiric antimicrobial molecule and is responsible for delayed adapted antimicrobial treatment [3]. In the recently published literature, *Pseudomonas aeruginosa* and *Acinetobacter baumanii* are the two most widely described microorganisms to be resistant to the most of available antibiotics [4]. For this reason, colistin has been recently considered as a last therapeutic option for the treatment of patients with infections caused by these microorganisms [4].

Colistin is an old antibiotic which was used until the early 1980s to treat infections caused by gram-negative rods. When gentamicin and second- and third-generation cephalosporins became available, colistin was dropped, mainly because of its neuro- and nephrotoxicity [5–8]. The increasing prevalence of PDR gram-negative organisms,

especially in ICUs, prompted interest in colistin. Thus, it was used as a salvage therapy in patients with serious infections and showed an acceptable efficacy [9–20]. However, its effectiveness for treatment of ventilator-associated pneumonia (VAP) has been reported in only few controlled studies [16, 19], and little is known about its penetration into the pulmonary parenchyma.

In our hospital, *P. aeruginosa* and *A. baumanii* cause more than one third of nosocomial infections [21]. The emergence of PDR strains corresponding to a resistance to most of commercially available antibiotics including piperacillin, ceftazidime, imipenem, amikacin, and fluoroquinolones prompted us to use colistin in the treatment of serious nosocomial infections in the ICU [20].

Our study set out to ascertain the efficacy and safety of colistin in the treatment of VAP caused by PDR *P. aeruginosa* or *A. baumanii* in patients with normal renal function at the onset of the colistin course, compared with imipenem in the treatment of VAP caused by susceptible *P. aeruginosa* or *A. baumanii* in patients with normal renal function at the onset of the imipenem course.

Methods

Setting

The study was conducted in the combined medical and surgical ICU of Habib Bourguiba University Hospital. Our ICU is a 22-bed unit in a 510-bed tertiary-care teaching center that serves as first-line medical center for an urban population of one million inhabitants and as a referral center for a larger population from south Tunisia.

Study design

We performed a pairwise, retrospective case–control study with 1:1 matching. The study period for cases extended from 1 July 2003 to 30 June 2005, during which time 1,208 patients were admitted to the ICU.

Eligible patients were those who developed VAP caused by PDR *A. baumanii* or *P. aeruginosa*, who were treated by colistin intravenously, and who had normal renal function at the onset of colistin therapy (colistin group).

Control patients had to have developed VAP caused by *A. baumanii* or *P. aeruginosa* susceptible to imipenem, have been treated by imipenem intravenously, and have had normal renal function at the onset of imipenem therapy (imipenem group).

A list of potential controls was obtained from a database including all patients who had developed VAP over a 4-year period (from 2000–2003). Controls were chosen according to the following matching criteria: age ($\pm$ 5 years), Simplified Acute Physiology Score (SAPS) II ($\pm$ 6 points) calculated within 24 h of ICU admission [22], and PaO_2/FiO_2 at the onset of antibiotic therapy for VAP ($\pm$ 20 points).

On admission, the following variables were recorded: age, gender, SAPS II, date of admission, shock, PaO_2/FiO_2, serum urea nitrogen and creatinine concentration. On the day of introduction of colistin or imipenem, the following variables were recorded: fever, leukocyte count, chest X-ray findings, PaO_2/FiO_2, serum urea nitrogen and creatinine concentration. Patients were followed up daily until the end of the treatment for outcome (favorable or unfavorable, based on the evolution of fever, leukocyte count and chest X-ray infiltrates) and adverse events, mainly acute renal failure (based on daily serum urea nitrogen and creatinine sampling) and the presence of muscular weakness. When patients were discharged from hospital, the following variables were recorded: date of discharge from ICU and from hospital and outcome.

The diagnosis of pneumonia was based on: (1) temperature $\leq 36°C$ or $\geq 38.5°C$, (2) leukocytes count $\leq 1{,}500$ or $\geq 10{,}000$ leukocytes/mm^3, (3) new or progressive infiltrate on the chest radiograph, (4) presence of at least one microorganism at a concentration of at least 10^6 cfu/ml on the endotracheal aspirates samples [23]. Acute renal failure (ARF) was defined by a serum creatinine concentration of more than 150 μmol/l, and/or a blood urea nitrogen concentration of more than 10 mmol/l.

The course of VAP was assessed daily. VAP was considered to have favorable outcome if there was remission of sepsis-related symptoms (fever, leukocytosis or leukopenia) with PaO_2/FIO_2 ratio higher than 187 (25 kPa) [24] and radiological resolution (decrease or disappearance of presenting findings on chest X-ray). VAP was considered to have unfavorable outcome if there was no remission of sepsis-related symptoms and/or no radiological resolution.

Microbiological testing

All causative micro-organisms were identified using routine microbiological methods. Susceptibility testing was done using the disk diffusion method (The breakpoints were those defined by the National Committee for Clinical Laboratory Standards [25, 26].) Susceptibility to colistin was tested by means of the disk diffusion method using a 10-μg colistin disk; isolates were considered sensitive if the inhibition zone was ≥ 11 mm. Intermediate sensitivity of isolated gram-negative pathogens to antimicrobial agents was considered resistance. Pan-drug resistance was defined as resistance of the isolate to antipseudomonal penicillins, cephalosporins, carbapenems, quinolones, and aminoglycosides. An isolate was defined as colistin-only sensitive if it was resistant to all antipseudomonal agents except colistin.

Treatment regimen

In the colistin group, patients were treated with colistin sulfomethate sodium (Bellon; Rhône-Poulenc Rorer) administered intravenously. The dosage was 6 million units (≈ 100,000 U/kg) of colistin daily, divided into three doses. In the imipenem group, patients were treated with imipenem (imipenem/cilastatin; MSD) administered intravenously. The dosage was 2 g of imipenem daily, divided into four doses. In this study, all patients received colistin or imipenem on an empirical basis, which made the initial antibiotic treatment appropriate in all cases.

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as mean values (SD). Percentages were compared using the chi-square test and means with the *t*-test. The Wilcoxon matched pairs test was used to compare the matching criteria (age, SAPS II, and PaO_2/FiO_2). Kaplan–Meier curves were used to assess differences between the colistin group and the imipenem group in (1) resolution of infectious parameters after the initiation of antibiotic therapy and (2) mortality at 28 days after the onset of colistin or imipenem therapy for VAP. Curves were compared using the log-rank test. A p value ≤ 0.05 in a two-tailed test was considered to indicate statistical significance.

Results

During the study period, 1,208 patients were admitted to the unit. One thousand and seventy six of them (89.1%) received mechanical ventilation and 123 (11.4%) developed VAP. In 78 (63.4%) of these patients the VAP caused by PDR *A. baumanii* or *P. aeruginosa* and was treated with colistin. Of these 78 patients potentially eligible as cases, 12 were excluded because of renal failure at the onset of colistin therapy. Of the 66 remaining case patients enrolled in the study, matching was possible for only 60 (90.9%).

All patients were matched for age, SAPS II, and PaO_2/FiO_2 at the onset of antibiotic therapy for VAP. Overall success of matching was achieved in 100% of the variables used (Table 1). Baseline characteristics of the study population are shown in Table 2.

In the colistin group, 51.7% of cases of VAP were caused by *A. baumanii* and 48.4% by *P. aeruginosa*. In all patients in this group, *A. baumanii* and *P. aeruginosa* were PDR and were susceptible only to colistin. In the imipenem group, 61.7% of cases of VAP were caused by *A. baumanii* and 38.3% by *P. aeruginosa*. In all patients in this group, *A. baumanii* and *P. aeruginosa* were resistant to penicillins and third-generation cephalosporins and susceptible to imipenem.

The mean ICU stay before the initiation of antibiotic therapy for the VAP was 13 ± 10 days (range 5–43 days) in the colistin group and 11 ± 9 days (range 5–38 days) and the imipenem group ($p = 0.24$). The mean duration of antibiotic therapy for VAP was 9.5 ± 3.8 days (range 5–22 days) and 8.9 ± 2.8 days (range 5–20 days) respectively ($p = 0.32$). Eight patients in the colistin group and 9 patients in the imipenem group received antibiotics (colistin or imipenem) for less than 10 days because they died during the course of therapy. A favorable clinical response to antibiotic therapy for VAP occurred in 45 patients (75%) in the colistin group and in 43 patients (71.7%) in the imipenem group ($p = 0.68$). Figures 1 and 2 show the resolution of infectious parameters and the evolution of

Table 1 Matching criteria of the study population

	Colistin group ($n = 60$)	Imipenem group ($n = 60$)	p	Effectiveness of matching
Age (years)	43.4 ± 18.8	41.4 ± 16.7	0.60	100%
SAPS	35.2 ± 12.3	33.2 ± 10.8	0.35	100%
PaO_2/FiO_2 on day of initiation of antibiotics	213 ± 79	215 ± 81	0.87	100%

Table 2 Baseline characteristics of the study population

	Colistin group ($n = 60$)	Imipenem group ($n = 60$)	p
Reason for admission *n* (%)			
Acute respiratory failure	7 (11.7)	8 (13.3)	0.78
Coma	8 (13.3)	4 (6.6)	0.22
Multiple trauma	42 (70)	48 (80)	0.20
Postoperative resuscitation	3 (5)	0 (0)	0.24
Sex ratio (male/female)	6.5	4.45	0.45
Shock *n* (%)	18 (30)	14 (23.3)	0.40
Antibiotics *n* (%)	46 (76.7)	39 (65)	0.16
PaO_2/FiO_2 at admission	311 ± 82	313 ± 84	0.9
Urea nitrogen (mmol/l)	5.9 ± 1.9	6.4 ± 2.0	0.18
Serum creatinine (μmol/l)	79.7 ± 17.8	82.0 ± 15.4	0.46

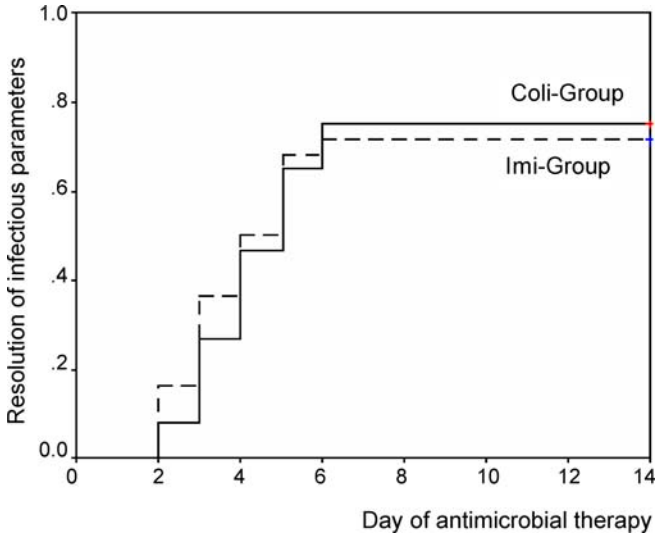

Fig. 1 Resolution of infectious parameters according to time after the initiation of antibiotic therapy (log rank = 0.09). *Coli*, colistin; *Imi*, imipenem

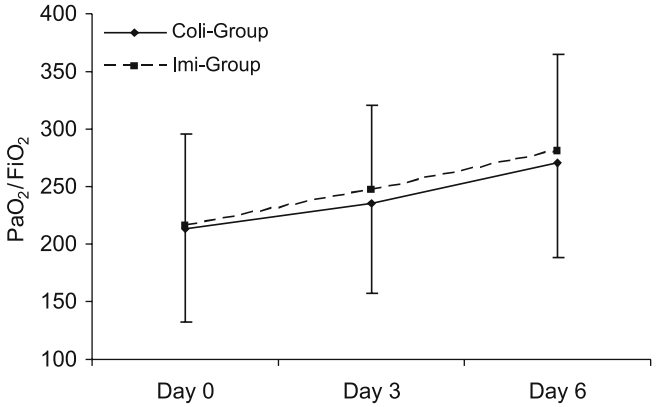

Fig. 2 Evolution of the PaO_2/FiO_2 ratio according to time after the initiation of antibiotic therapy

the PaO_2/FiO_2 ratio according to time after the initiation of antibiotic therapy in the two groups. A clinical relapse of VAP was observed in six cases in the colistin group and in five cases in the imipenem group. Of these five latter cases, three relapses of VAP were caused by *P. aeruginosa* and two by *A. baumanii*; all of them were susceptible to imipenem.

Overall, the mortality rate in the ICU was 41.7% in the colistin group and 35% in the imipenem group ($p = 0.45$) and the hospital mortality was 41.7% and 38.3% respectively ($p = 0.7$). The causes of death in the ICU are shown in Table 3. The total duration of stay in ICU was 35.5 ± 31.2 days in the colistin group and 31.2 ± 28.7 days in the imipenem group ($p = 0.43$). The mortality at 28 days after the onset of the colistin or

Table 3 Causes of death in the ICU

	Colistin group ($n = 60$)	Imipenem group ($n = 60$)	p
Septic shock *n* (%)	5 (8.3)	4 (6.7)	1
Multiple organ failure *n* (%)	2 (3.3)	6 (10)	0.27
Pulmonary embolism *n* (%)	4 (6.7)	2 (3.3)	0.67
Brain herniation *n* (%)	14 (23.3)	9 (15)	0.24
Total *n* (%)	25 (41.7)	21 (35)	0.45

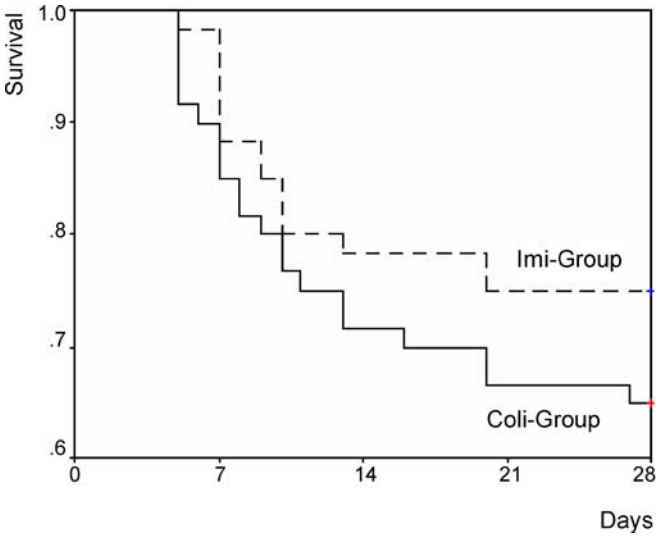

Fig. 3 The 28-days mortality in the two studied groups (log rank = 0.22)

imipenem therapy for VAP was about 35% and 25% respectively ($p = 0.22$ by log-rank test) (Fig. 3).

At the initiation of antibiotic therapy for VAP, all patients had normal renal function. Serum urea nitrogen concentration was 5.8 ± 1.9 and 6.3 ± 1.9 mmol/l and serum creatinine level was 79.6 ± 16.3 and 83.2 ± 17.4 μmol/l in the colistin group and the imipenem group respectively ($p = 0.11$ and $p = 0.25$). During the antibiotic course, none of the patients treated by colistin or imipenem developed acute renal failure. At the end of the antibiotic course serum urea nitrogen concentration was 5.8 ± 2.0 and 6.3 ± 2.3 mmol/l and serum creatinine level was 79.2 ± 18.4 and 83.5 ± 23.4 μmol/l in the colistin group and the imipenem group respectively ($p = 0.17$ and $p = 0.26$).

One patient treated with colistin developed diffuse muscular weakness during hospitalization that resolved within 1 month after ICU discharge.

Discussion

Our results shows that colistin in the treatments of VAP caused by PDR *P. aeruginosa* or *A. baumanii* is as effective as imipenem in the treatment of VAP caused by susceptible

P. aeruginosa or *A. baumanii*. In addition, they show that colistin therapy at normal doses [16] did not cause renal failure in patients with normal renal status.

The increasing rate of antibiotic resistance among gram-negative pathogens has prompted interest in the treatment with colistin as a last resort in patients with serious infections caused by multidrug-resistant gram-negative organisms. In the last years, many studies [9–20] have been published showing that colistin may be a good therapeutic option for the treatment of severe infections caused by multidrug-resistant organisms. In these reports, favorable clinical response ranged between 57% and 73%. Moreover, in the management of VAP caused by *A. baumanii* resistant to imipenem, colistin was found to be just as effective as imipenem in the management of VAP caused by *A. baumanii* susceptible to imipenem [16]. These results are confirmed by our case–control study, where we matched patients who had VAP caused by PDR *A. baumanii* or *P. aeruginosa* and who were treated by colistin intravenously, with patients who had VAP caused by *A. baumanii* or *P. aeruginosa* susceptible to imipenem and who were treated by imipenem intravenously. The matching criteria were age, SAPS II, and PaO_2/FiO_2 at the onset of antibiotic therapy for VAP. We chose this methodology to give a maximum of viability to our conclusions. Indeed, patients were similar in age, severity at admission and severity at the onset of the antibiotic therapy. We found a favorable clinical response to antibiotic therapy for VAP in 75% of patients in the colistin group and in 71.7% of those in the imipenem group ($p = 0.68$). In addition, the time to resolution of infectious parameters and the evolution of the PaO_2/FiO_2 ratio after the initiation of antibiotic therapy were similar in patients treated with colistin or with imipenem.

Colistin and polymyxin B are known for causing nephrotoxicity [5–8]. Levin et al. [9] found renal failure in 26.8% of patients with normal renal function at the initiation of colistin therapy. Markou et al. [13] found renal failure in 3 of 21 patients with normal renal function at the initiation of colistin therapy. Ouderkik et al. [14] found renal failure in 11.7% of cases treated with polymyxin B; but in all cases, amikacin and/or vancomycin were associated with the polymyxin B. In the study by Garnacho-Montero et al. [16], 23.8% of patients treated with colistin and 42.8% of patients treated with imipenem developed renal failure ($p > 0.05$), and 90.9% of patients with renal failure had developed shock on the day of the worsening of the renal function. In the remaining studies, no renal toxicity was observed in the three cases reported by Stein and Raoult [12], in the two cases reported by Jimenez-Mejias et al. [10, 11] or in the case reported by Karabinis et al. [17]. In our study, all patients had normal renal function at the onset of the antibiotic course for VAP. This inclusion criterion allowed us to exclude patients at risk of accumulation of colistin or imipenem, and then allowed us to study the effect of colistin on the kidneys independently of the situations of overdosage. To our great surprise, we found that no patient developed renal failure, either in the colistin or in the imipenem group.

To the best of our knowledge, our study is the largest and the most informative one about the treatment of VAP caused by PDR *P. aeruginosa* or *A. baumanii* in patients with normal renal function. Indeed, despite the large number of series reporting the efficacy and safety of colistin in treatment of nosocomial infections in ICU, little is known about colistin in the treatment of VAP and about its penetration into the pulmonary parenchyma.

We conclude that colistin can be an effective option in the treatments of VAP caused by PDR *P. aeruginosa* or *A. baumanii*. In addition, in patients with normal renal function, colistin is a safe option in the treatment of VAP.

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