Colistin efficacy in the treatment of multidrug-resistant and extremely drug-resistant gram-negative bacterial infections*

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Background/aim: Colistin is used as a salvage therapy for multidrug-resistant and extremely drug-resistant gram-negative bacterial infections. Our aim was to evaluate colistin efficiency and toxicity in the treatment of these resistant gram-negative bacterial infections.

Materials and methods: This is a retrospective study carried out in a tertiary care hospital during 2011–2013. Study data were collected from the medical records and consultations of the infectious diseases clinic.

Results: The study group included 158 patients with nosocomial infections and 136 (86.1%) of them were hospitalized in the ICU. Respiratory tract infections were the most commonly observed ones (n = 103, 65.2%). The most frequently isolated microorganism was *Acinetobacter baumannii* (72.2%). A total of 98 (62.0%) patients had clinical cure. There was no statistically significant difference between monotherapy (n = 3/6, 50.0%) and combination therapies (n = 95/152, 62.5%) according to clinical response. Underlying ultimately fatal disease, previous renal disease, and total parenteral nutrition were independent risk factors for poor clinical response. Nephrotoxicity developed in 80 (50.6%) patients and clinical cure was statistically unrelated with nephrotoxicity.

Conclusion: Colistin may be used as an effective agent for multidrug-resistant and extremely drug-resistant gram-negative bacterial infections with close monitoring of renal functions, especially for older and critically ill patients.

Key words: Colistin, efficacy, extreme drug-resistance, gram-negative bacteria, multidrug-resistance, nephrotoxicity

1. Introduction

The polymyxin group of polypeptide antibiotics is among the first antibiotics, discovered in the 1940s, with significant activity against gram-negative bacteria. Both polymyxin E (colistin) and polymyxin B were used clinically. Following reports on nephrotoxicity and neurotoxicity in the 1970s, other antibiotics were used instead of them. In the last decade, this group was reconsidered as a therapeutic option for multidrug-resistant/extremely drug-resistant gram-negative (MDR/XDR-GN) bacterial infections and particularly for the carbapenem-resistant *Acinetobacter* species (1,2).

After its reintroduction in medical practice in the last 5 years, studies focused on the effectiveness and the side effects of colistin, especially nephrotoxicity. Nephrotoxicity after intravenous colistin treatment was observed at rates of 6%–58% in recent studies. Rates of 10%–27% and 58% were found in patients with basal normal and abnormal renal functions, respectively (3,4).

The difference in the nephrotoxicity rates was explained by various definitions of acute kidney injury. Some studies used RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease), while some used the threshold of failure or creatinine level of more than 2 mg/dL. Risk factors for nephrotoxicity were older age, preexisting renal insufficiency, hypoalbuminemia, hyperbilirubinemia, and concomitant use of nonsteroidal antiinflammatory drugs, calcineurin inhibitors, or other nephrotoxic agents like vancomycin (1,5,6).

In this study, the efficiency against nosocomial MDR/XDR-GN bacterial infections and risk of nephrotoxicity with intravenous colistin treatment were investigated.

2. Materials and methods

2.1. Study design

This retrospective study includes the records of patients treated with intravenous colistin between January 2011 and February 2013 in Celal Bayar University Hospital in

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Manisa, Turkey, a tertiary care hospital with 585 beds. Patients older than 18 who had been treated for nosocomial MDR/XDR-GN bacterial infections with intravenous colistin for at least 72 h were included.

The patients were treated with colistin (Colimycin, Koçak Farma, Turkey; each vial contained 150 mg of colistin base activity). We administered a daily IV colistin dosage of 2.5–5 mg/kg (base activity), divided into two or three doses in patients with normal renal function. The total daily dosage was modified for renal impairment according to the manufacturer's instructions. A loading dose for colistin had not been recommended at the time the study was conducted, so a loading dose was not given to the study patients.

2.2. Data collection
Study data were collected with a standardized form from the medical records and consultations of the infectious diseases clinic.

The variables of the patients including age, sex, hospitalization wards, underlying disease determined according to the classification of McCabe and Jackson (7), duration of hospital and intensive care unit (ICU) stay, type of infection, recent surgical or other invasive procedures, presence of risk factors, empiric antibiotic therapy, duration and dosage of colistin treatment, and outcome were recorded.

Risk factors affecting clinical response during hospitalization were defined as the following conditions: surgery (within 2 weeks prior to the infection episode), total parenteral nutrition, mechanical ventilation (during the infection diagnosis period), previous antibiotic therapy (within 2 weeks prior to infection), hemodialysis (during the hospital stay), and corticosteroid therapy (prednisone at 20 mg daily for at least 2 weeks or 30 mg daily for at least 1 week before the infection episode).

2.3. Definitions
According to the McCabe and Jackson classification, patients were categorized as 0, no underlying disease; 1, nonfatal underlying disease; 2, ultimately fatal underlying disease; and 3, rapidly fatal disease.

Renal side effects of colistin were evaluated according to the RIFLE classification system (8). This system uses three severity categories (risk, injury, and failure) and two outcome categories (complete loss of kidney function and end-stage kidney disease).

Nosocomial infections were diagnosed according to CDC definitions (9).

Isolated bacteria were identified by the API 20NE system. Antimicrobial resistance of isolates was studied by disk diffusion test and interpreted according to the criteria suggested by the Clinical Laboratory Standards Institute.

Isolates nonsusceptible to ≥1 agent in ≥3 antimicrobial categories were accepted as multidrug-resistant (MDR)

bacteria. Those nonsusceptible to ≥1 agent in all but ≤2 antimicrobial categories were accepted as extremely drug-resistant (XDR) bacteria. Antibiotic categories were evaluated according to the isolated bacteria (10).

Clinical cure was defined as the resolving of signs and symptoms of infections and laboratory findings, and eradication of the isolated microorganisms in subsequent cultures from the original infection site was determined as microbiological cure. Therapeutic failure was defined as persistence or worsening of signs and symptoms of infection after colistin therapy.

2.4. Statistical analysis
The results were analyzed using SPSS 15.0 for Windows. Categorical variables were analyzed using chi-square or Fisher exact tests. The association between factors and cure was analyzed using a logistic regression model. The odds ratios (ORs) with 95% confidence intervals were presented. All P-values were 2-tailed and P < 0.05 was considered as statistically significant.

3. Results
3.1. Study population
In the study period, 158 patients fulfilled the inclusion criteria. The study group included 111 (70.3%) male and 47 (29.7%) female patients with a mean age of 58.2 years (range: 18–92). Among these, 136 patients (86.1%) were hospitalized in the ICU with a mean duration of 36.80 ± 26.75 days.

According to the McCabe and Jackson classification, 29 (18.4%) patients had no underlying diseases, while they were nonfatal for 71 (44.9%), ultimately fatal for 55 (34.8%), and rapidly fatal for 3 (1.9%) patients.

The most common predisposing conditions were as follows: diabetes mellitus (n = 35, 22.2%), cardiac disease (n = 38, 24.1%), chronic pulmonary disease (n = 41, 25.9%), and solid malignancy (n = 29, 18.3%). The presence of other conditions, including hematological malignancy, neurological disorders, connective tissue disease, and chronic liver disease, was infrequent.

3.2. Infections
All infections were nosocomial. There were 103 cases of respiratory tract infections (65.2%), 21 cases of blood stream infections (13.3%), 12 surgical infections (7.6%), 9 cases of urinary infections (5.7%), and 13 infections of other sites (8.2%). Among the respiratory tract infections, 76 (48.1%) infections were ventilator-associated pneumonia.

There were 130 (72.2%) cases of *Acinetobacter baumannii*, 40 (22.2%) of *Pseudomonas aeruginosa*, 9 (5.0%) of *Klebsiella pneumoniae*, and 1 (0.6%) of *E. coli* isolated. In 22 (13.9%) cases both *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolations were determined.

According to the susceptibility results, isolated strains were grouped as MDR and XDR and these results are shown in Table 1.

3.3. Colistin treatment and outcome

The mean duration of colistin administration was 16.4 ± 11.96 days (median: 14.5). The median duration of hospitalization prior to colistin treatment was 18.47 ± 13.32 days (range: 3–67 days).

Six patients (3.8%) were administrated only colistin. Dual and triple combination therapies were given to 64 (40.5%) and 88 (55.7%) patients, respectively. Clinical cure was determined in 98 (62.0%) and microbiological cure was determined in 55 (34.8%) patients. Monotherapy and dual and triple therapy were statistically compared with microbiological and clinical cure and no significance was determined (respectively, P = 0.560, P = 0.826). The most commonly added antibiotic group was carbapenem (n = 79, 32.9%). The other groups were beta-lactams other than carbapenems (n = 62, 25.8%), aminoglycosides (n = 52, 21.7%), quinolones (n = 28, 11.7%), and tigecycline (n = 19, 7.9%). There was no significance when carbapenem-involving combinations (n = 79) were compared with other combinations according to microbiological and clinical cure rates (P = 0.168, P = 0.437, chi-square test).

In the carbapenem-involving combination group, microbiological cure was 29.1% (n = 23) and clinical cure was 58.2% (n = 46), while cure rates in the other antibiotic group were 39.7% (n = 29) and 64.4% (n = 47), respectively.

Univariate analyses were performed to determine the factors for clinical response in patients with colistin treatment. Factors significantly associated with poor clinical response were older age (≥65 years), total parenteral nutrition, hospitalization in the ICU, underlying ultimately fatal disease, previous renal disease, hemodialysis, and previous antibiotic usage. The characteristics of patients and the relationships of risk factors with clinical response are shown in Table 2 and microbiological and clinical cure rates of colistin therapy are summarized in Table 3.

Statistically significant variables were also analyzed with a logistic regression model. Underlying ultimately fatal diseases, underlying renal diseases, and total parenteral nutrition were determined as independent risk factors for poor clinical response with colistin treatment of MDR/XDR-GN infections by this multivariate analysis. Results are shown in Table 4.

3.4. Adverse reactions

According to the RIFLE classification, nephrotoxicity developed in 80 (50.6%) patients during colistin treatment. Among them, 14 (17.5%), 20 (25.0%), and 46 (57.5%) patients developed renal impairment within risk, injury, and failure categories, respectively. Nephrotoxicity developed after 11.23 ± 11.10 days (median: 9).

In these patients, renal function tests returned to baseline levels in 21 (26.25%) patients with colistin dose reduction and in 35 (43.75%) patients with the discontinuation of the therapy.

When risk factors related to nephrotoxicity during colistin therapy were evaluated with univariate analyses, only older age (≥65 years) was found to be statistically significant (P = 0.003, Fisher exact test). Usage of other nephrotoxic drugs, underlying renal disease, and colistin dosage were not found as significant risk factors. The relationship between colistin nephrotoxicity and clinical response was not found to be significant (P = 0.130, Fisher exact test). Results are shown in Table 2.

We could not evaluate the neurologic adverse reactions of 136 patients hospitalized in ICU because of unconsciousness and sedated condition. No neurotoxicity was determined in the remainder of patients.

4. Discussion

The effectiveness of colistin for treating MDR/XDR-GN bacterial infections was shown in several studies and most of them were carried out in ICUs. The clinical response reported in these studies varied between 45% and 88% (11–16). There was a wide range of clinical outcomes,

Table 1. Susceptibility of the isolated organisms.

Susceptibility	XDR n (%)[a]	MDR n (%)[a]	Total
Acinetobacter baumannii	120 (92.3)	10 (7.7)	130
Pseudomonas aeruginosa	27 (67.5)	13 (32.5)	40
Klebsiella pneumoniae	9 (100.0)	-	9
E. coli	-	1 (100.0)	1
Total	156 (86.6)	24 (13.4)	180

[a]Row percentage.

Table 2. The characteristics of patients and the relationships of risk factors with clinical response.

		n	Cure (%)[a]	P-value
Sex	Male	111	71 (64.0)	0.440[b]
	Female	47	27 (57.4)	
Age	<65	90	64 (71.1)	0.007[b]
	≥65	68	34 (50.0)	
Hospitalization in ICU*		136	80 (58.8)	0.039[b]
Underlying ultimately fatal disease		55	23 (41.8)	0.000[b]
Nephrotoxicity due to colistin		80	45 (56.2)	0.130[b]
Previous renal disease		27	6 (22.2)	0.000[b]
Previous antibiotic usage		56	28 (50.0)	0.021[b]
Central venous catheter		76	43 (56.6)	0.174[b]
Mechanical ventilation		116	69 (59.5)	0.274[b]
Total parenteral nutrition		76	38 (50.0)	0.003[b]
Steroid usage		10	7 (70.0)	0.591[c]
Hemodialysis		16	6 (37.5)	0.033[b]

*ICU: Intensive care unit.
[a]Row percentage, [b]Chi-square test, [c]Fisher exact test.

Table 3. Microbiological and clinical cure of colistin therapy.

Therapy	n	Microbiological cure (%)[a]	Clinical cure (%)[a]
Monotherapy	6	3 (50.0%)	3 (50.0%)
Dual therapy	64	24 (37.5%)	41 (64.1%)
Triple therapy	88	28 (31.8%)	54 (61.4%)
Total	158	55 (34.8%)	98 (62.0%)
P-value[b]		0.560	0.826

[a]Row percentage, [b]Chi-square test.

Table 4. Related factors in patients who did not respond to colistin.

Risk factor	OR (95% CI)	P-value
Ultimately fatal disease	6.5 (1.6–26.1)	<0.0001
Underlying renal disease	9.1 (1.9–41.9)	<0.0001
Total parenteral nutrition	4.5 (1.9–10.3)	0.003

Variables included in the model: Dependent variable: Cure (yes: 0, no: 1); Age (ref, <65 years: 0); Ultimately fatal disease (ref, no: 0); Hospitalization in ICU (ref, no: 0); Underlying renal disease (ref, no: 0); Hemodialysis (ref, no: 0); Total parenteral nutrition (ref, no: 0); Previous antibiotic usage (ref, no: 0). OR: Odds ratio; CI: Confidence interval.

which might be related to different clinical characteristics of patients. The clinical response rate in our study was 62%, similar to the literature (12–17). Our study sample (n = 158) was larger than most of the previous ones and included critically ill patients who had been hospitalized (86.1%) in the ICU.

The risk factors for clinical outcome were reported as bacteremia, acute respiratory distress syndrome, and high APACHE II score in previous studies (17–20). In our study, multivariate analyses showed that underlying ultimately fatal disease, previous renal diseases, and total parenteral nutrition were important independent risk factors for worse clinical response.

There were a number of in vitro studies that demonstrated a synergistic activity when colistin was combined with rifampicin or amikacin. In animal studies, comparisons of colistin monotherapy with combinations with rifampicin, carbenicillin, piperacillin, and imipenem for treatment of *P. aeruginosa*, *A. baumannii*, or *Escherichia coli* infections were evaluated and decreased mortality rates were determined with these combinations (21).

Although the data are promising for in vitro and animal studies, there is no clinical proof of an advantage for colistin combination therapy and future clinical studies are necessary (21–24). In a recent study from Turkey, colistin-carbapenem, colistin-sulbactam, and colistin with other antibiotic combinations were investigated for XDR *Acinetobacter* blood stream infections and significance was not found according to 14-day survival and clinical or microbiological outcome (25).

In our study, colistin was administered as monotherapy in six patients (3.8%) and with different antibiotic groups for the remainder. We determined no difference in terms of effectiveness between monotherapy and combination colistin therapies, probably due to the low power value of the statistical comparison (power value = 8.8%) (26). A small number of patients with colistin monotherapy might be a limitation of our study, and we think that clinical studies with larger numbers of patients given both monotherapy and combination colistin therapies are mandatory.

Rates of nephrotoxicity in recent studies have ranged from 6% to 55% and this great difference can be explained by various definitions of acute kidney injury. Risk factors for nephrotoxicity found in different studies included older age, preexisting renal insufficiency, hypoalbuminemia, hyperbilirubinemia, and concomitant use of nonsteroidal antiinflammatory drugs, calcineurin inhibitors, or other nephrotoxic agents like vancomycin (1,5,6).

We determined nephrotoxicity in 80 (50.6%) patients during colistin treatment and older age was the statistically significant risk factor associated with nephrotoxicity. The usage of other nephrotoxic drugs, underlying renal disease, and colistin dosage were not found as important risk factors for induction of renal injury.

The mechanism for colistin-related nephrotoxicity is unknown as there are rare studies about the pharmacokinetics and pharmacodynamics of the drug. It is dose-dependent and usually reversible following discontinuation of therapy, so it is thought to be caused by acute tubular necrosis (ATN) like aminoglycoside- and amphotericin-related nephropathies (5,27). Cheng et al. (14), determined nephrotoxicity in 14% of their 115 patients on colistin. After the discontinuation of colistin, the reversibility of toxicity was shown. In our study, renal function tests returned to baseline levels with discontinuation of colistin in 35 (43.75%) patients and dose reduction in 21 (26.25%) patients.

The other adverse effect, neurotoxicity (0%–7%), is less common than nephrotoxicity. Clinical manifestations of neurotoxicity are dizziness, muscle weakness, paresthesias, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, ataxia, and neuromuscular blockade (28,29). Neurotoxicity was evaluated in only conscious and nonsedated patients in our study and was not determined in any of them.

In conclusion, the effect of nephrotoxicity on the clinical response of colistin for MDR/XDR-GN bacterial infections was not determined in our study. We suggest that colistin may be a valuable therapeutic option for MDR/XDR-GN bacterial infections with close monitorization of renal functions, especially for older and critically ill patients.

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