Original Article

Intravenous colistin in the treatment of multidrug-resistant gram-negative organism in tertiary hospital, Jazan, KSA

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Abstract

Background: It was considered that the resistance of drugs such as carbapenems and cephalosporins against severe or high risk gram-negative bacteria became a tremendous confront. This might be attributed to the little amount of these drugs to be used against the multi-resistant bacteria (MRB). Therefore, Colistin, Fosfomycin, Temocillin, and Rifampicin are antibiotics that have been used as multidrug-resistant bacterial infections in the treatment of some species of bacteria such as Acinetobacter, Pseudomonas species, and Enterobacteriaceae. **Aim:** the present study is aimed to assess the integrity and efficiency of colistin for treating of the multidrug-resistant bacteria (MDR) especially gram-negative one among critical and non-critical patients in tertiary hospital in Jazan city. Ninety four patients who met the selection criteria and received colistimethate sodium (colistin) in the period between Februarys 2017 and March 2018 were recruited and their charts were reviewed retrospectively. Patients' information, medical conditions, and laboratory data were extracted. All patients received IV colistin, and the majority of the patients showed in their culture reports multidrug-resistant bacteria such as Pseudomonas aeruginosa and Acinetobacter baumannii. Patients who had normal renal function received from 2.5 to 5.0 mg of colistin/kg, which was divided in two or three doses intravenously, for duration ranging between 10 and 14 days.**Results and conclusion :** Approximately half of patients (48.93%) were fully recovered, while 19% of them were partially responded to colistin treatment. In the current study it was showed that IV colistin treatment against the multidrug-resistant bacteria (gram-negative bacteria) was strongly related to mild nephrotoxicity in addition to with a proper response as shown only in three of our patients

Keywords: Colistimethate sodium, intravenous colistin, multidrug resistant gram negative bacteria (MDR), nephrotoxicity

Introduction

Colistin is a polypeptide antibiotic that belonging to the group of Polymyxins (discovered in 1947), and consisted of different five chemical compounds that were known as polymyxins A, B, C, D, and E. Colistin is known as the polymyxin (E) that has been only used for the clinical purpose in addition to the polymyxin B.[1]

Matthew *et al.*[1] reported that colistin was synthesized from specific strains of gram-positive bacteria that known as *Bacillus polymyxa*, under subspecies of *Colistinus Koyama*. However, colistin was discovered in 1949, it was started to be used in

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Japan and in Europe in 1950 and was used in 1959 in the form of colistimethate sodium in the United States for definite therapeutics.[1] In 1980, the incidence of nephrotoxicity was highly increased that led to decreasing use of IV colistin and polymyxin (B) in most areas around the world. Additionally, IV colistin and polymyxin (B) were used for treating of lung infections under limited and restricted conditions because of MDR gram-negative bacteria in cystic fibrosis cases of patients.[2] On the other hand, colistin has been used recently in different area around the world such as Europe, North America, and Asia because of appearance of MDR species such as *Acinetobacter*, *Pseudomonas*, and *Stenotrophomas*. Also, colistin has been utilized in the Kingdom of Saudi Arabia because of appearance and detonation of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[3]

Colistin is a polypeptide compound that has the ability to interact with the outer membrane of bacteria through displacing calcium and magnesium bacterial ions of the phospholipids that led to damaging of bacterial cell wall and finally death of the bacteria. Colistimethate sodium (CMS) had low toxicity than colistin so has been used for parenteral.[4] It was reported previously that the maintain use of colistin led to nephrotoxicity that might be attributed to the kidney is the primary passage for drug excretion. Therefore, nephrotoxicity was found to be intramuscular administrated as reported by previous literature.[5,6] Patients who had chronic renal disease showed 36% incidence of nephrotoxicity,[5,7] while by the time the rate of nephrotoxicity incidence decreased to be 10% that might attribute to more than reason; good monitoring of the intensive care unit (ICU), or purified preparation of the colistin, or avoid interference with any drugs that leading to nephrotoxic such as vancomycin and NSAIDs as reported in previous study from 2000 to 2007.[4] Although there are other risk factors that led to nephrotoxicity such as decreasing of albumin level, using of anti-inflammatory drug, elder age, and lack efficiency of kidney.[4] Other risk factors might appear after using of colistin such as seizures, visual disturbances, weakness of the muscle, and ataxia, all of previous diseases might be related to interaction of colistin with neurons hence it contain a large amount of lipid.[8] Resistance is inevitable, therefore *Acinetobacter baumannii* has been used for resistance this adverse impact of colistin through completing the lost part (lipid a component) of phospholipids.[6]

Li *et al*.[9] used Colistimethate sodium (colistin) in treating multidrug-resistant gram- negative infections in a tertiary hospital in Philippines. Colistin was given in combination with carbapenem (96.4%) for 12 days and 61.2% of patients showed clinical success and overall mortality rate was high (41.6%). Nephrotoxicity was a common adverse effect. Avila *et al*.[10] showed that the nephrotoxicity described in drug-safety studies for therapeutics could be prevented by monitoring colistin plasma data. Almutairy *et al*.[11] measured the incidence of nephrotoxicity' risk factors associated with colistin dose and reported a highly significant incidence of colistin-associated acute kidney injury (AKI) among patients who received intravenous (IV) colistin for >72 h. They added that daily colistin dose, serum albumin level, severity of illness, and BMI are independent predictors of nephrotoxicity.

The present study is aimed to assess the integrity and efficiency of colistin for treating of the multidrug-resistant bacteria (MDR) especially gram negative one among critical and non-critical patients at tertiary hospital in Jazan city. Additionally, to determine whether adverse effects occurred and evaluate the clinical outcomes when colistin was used.

Methodology

This was a retrospective study that reviewed all patient charts during the period from February 2017 to March 2018 who received IV colistin. We used CMS at tertiary hospital in Jazan city for injection purpose by using 150 mg colistin base/vial). It was reported through the database of the pharmacy that 94 of patients met the eligibility criteria had order recorded for colistin. Those patients were admitted in critical (ICU, CCU) or non-critical area (ambulatory and medical ward) in a tertiary hospital. The children (less than 15 years) and patients who had cystic fibrosis were excluded from the study.

Medical records for all patients were followed up for 5 weeks. Charts of all patients were checked by the investigator, after that all data for each individual were concluded as the following: culture results, susceptibility organisms, colistin dose, duration of therapy, demographic information, underlying medical conditions, and adverse events. All of microbiological data were collected; it included the isolation of the causative organism from the infection site, and undergoing tests to check its susceptibility to different types of antibiotics among them colistin were tested. The sensitivity of these organisms was depending on the size or dimension of the inhibition zone (11 mm or more) by using diffusion disk (10 μg colistinsulphate disk). A routine microbiological method has been used for the identification of all causative organisms and the resistant strains such as *P. aeurginosa* and *A. baumannii* at the laboratory of microbiology at tertiary hospital.

Serum creatinine was recorded for all patients were obtained. Increasing of a peak serum creatinine level up to 50% to be higher than the standard level that was used during treatment or kidney failure that needs an urgent therapy for replacement, all of this was identified as nephrotoxicity.

Other adverse events also were documented in patient chart sand progress note, and were followed up for assessing the outcomes according to clinical criteria till the end of treatment. These clinical criteria included some of clinical symptoms such as leukocytosis, fever, and improving of a proper diagnostic investigations. Patients' outcomes were classified into two groups: favorable and unfavorable according to all collected data (microbiological and/or clinical). At the end of the treatments, if the outcome symptoms had a complete resolution it was identifies as a favorable response, while occurrence of death during treatments or worsening of outcomes symptoms was known as unfavorable response. Ethical approval was obtained prior to starting data collection by the board of ethics review,

Jazan University, Jazan, KSA. A written consent was obtained from all patient before data collection and they informed that participation was entirely voluntary. The study was approved from the ethics committee of Jazan university. Application no. 5104/702/1439.

Results

Half (51%) the patients were young in age (20–40 years), 62% (59 patients) were males while the remaining 37% (35 patients) were females. 83 patients were admitted in critical area while 6 patients in CCU, 4 patients in general ward and only one patient was in ambulatory care.

The underlying conditions were diabetes mellitus (22.34%), cardiovascular disease (10.6%), chronic medical condition (24.46%), traumatic surgical condition (29.78%), brain surgery (8.5%), burns (13.83), sepsis and septic shock (52.12%). [Table 1]

The patients were received two or three doses from 2.5 to 5.0 mg of IV colistin/kg, while these doses have been differentiated and adjusted per day if a kidney failure occurred. Eighty five percent of those patients who received colistimethate sodium were on ventilator as they were critically ill. Majority of patient received colistin after their culture reports that showed MDR Gram negative bacteria which were susceptible to colistin such as *P. aeurginosa* and *A. baumannii*.

Sixty patients (63.8%) where infected with *A. baumannii*, seven patients (7.44%) infected with *Pseudomonas*, while 27 patients (28.76%) showed no growth in their culture reports but they were very severely ill [Figure 1].

Most of the patients (89%) received intravenous colistin in combination with carbapenems namely intravenous Meropenem (1 gevery 8 h) although some strains showed resistance to carbapenems.

Colistin was initiated empirically in some patient (35.11%) who showed clinical failure with other broad spectrum antibiotics or susceptibility reporting were still pending, while 61 patients (64.89%) receiving colistimethate sodium after their culture reports shown MDR Gram-negative strain [Figure 2].

All patients received colistin via intravenous route with the dose expressed as colistin base (2.5–5 mg/kg/day) and calculated according to their body weight and creatinine clearance. The vial contains 1 million IU or 2 million IU were available in the pharmacy department. The highest dose was 12 million IU per day and the duration of colistin ranged between 3 days and 14 days. Two patients only received colistin for more than 2 weeks.

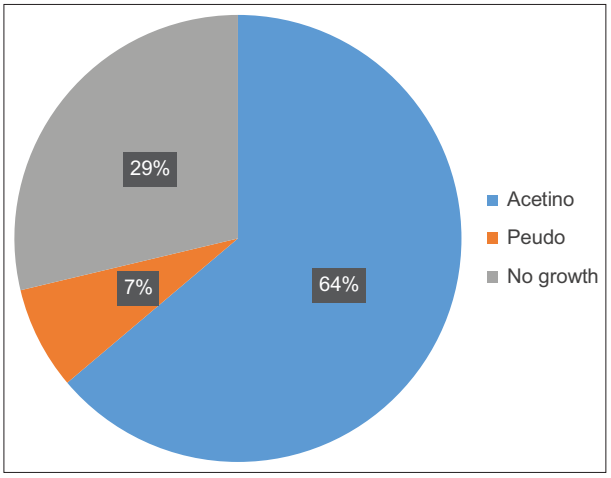

Figure 1: Identification of isolated organisms

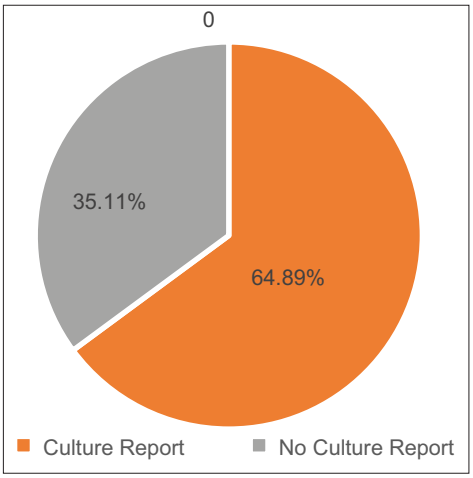

Figure 2: Presence of culture reports

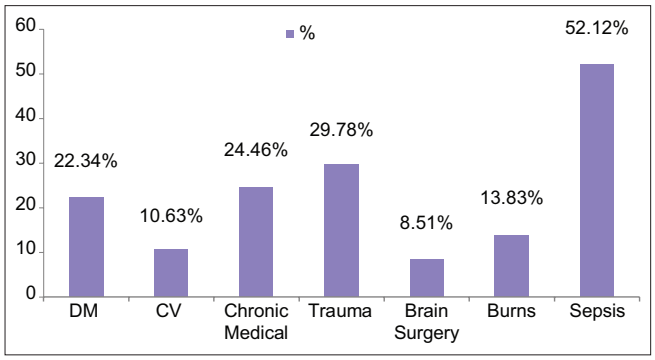

Figure 3: Medical condition of patients using colistin

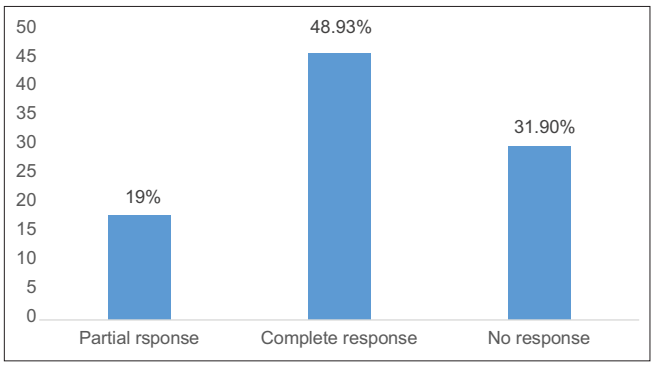

Figure 4: Treatment outcomes

Table 1: Baseline characteristics of the patients

Variable		Patients response to colistin			
		Partial response (n=30)	Complete response (n=34)	No response (n=30)	*P*
Sex, *n* (%)	Male	16 (53.3)	29 (85.3)	14 (46.7)	0.003*
	Female	14 (46.7)	5 (14.7)	16 (53.3)	
Age, *n* (%)	<20	0	1 (2.9)	0	
	20-40	16 (53.3)	27 (79.4)	6 (20.0)	0.0001*
	41-59	5 (16.7)	6 (17.6)	10 (33.3)	
	>60	9 (30.0)	0	14 (46.7)	
Weight, *n* (%)	<50	1 (3.3)	0	5 (16.7)	
	50	29 (96.7)	34 (100.0)	25 (83.3)	0.017*
	>50	0	0	0	
Site of care, *n* (%)	ICU	27 (90.0)	34 (100.0)	22 (73.3)	
	CCU/CTM	2 (6.7)	0	4 (13.3)	0.069
	Ambulatory	0	0	1 (3.3)	
	General ward	1 (3.3)	0	3 (10.0)	
Mechanical ventilation, *n* (%)		29 (96.7)	26 (76.5)	30 (100.0)	0.002*

*Statistically significant

Table 2: Indications for using colistin, *n* (%)

Variable	Patients response to colistin		
	Partial response (*n*=30)	Complete response (*n*=34)	No response (*n*=30)
DM with underlying cause, *n* (%)	9 (30)	4 (11.8)	8 (26.7)
Cardiovascular disease, *n* (%)	3 (10)	0 (0)	7 (23.3)
Cancer, *n* (%)	6 (20)	2 (5.9)	15 (50)
COPD, *n* (%)	8 (26.7)	15 (44.1)	5 (16.7)
Recent CV surgery, *n* (%)	0 (0)	8 (23.5)	0 (0)
Recent abdominal surgery, *n* (%)	5 (16.7)	7 (20.6)	1 (3.3)
Other condition, *n* (%)	19 (63.3)	14 (41.2)	16 (53.3)

DM=diabetes mellitus; COPD=chronic obstructive pulmonary disease; CV=cardiovascular. *Statistically significant

Table 3: Microbiological and administration data

Variable		Patients response to colistin			*P*
		Partial response (*n*=30)	Complete response (*n*=34)	No response (*n*=30)	
Culture, *n* (%)	Yes	17 (56.7)	24 (70.6)	20 (66.7)	0.492
	No	13 (43.3)	10 (29.4)	10 (33.3)	
Organism Susceptibility, *n* (%)	Acinetobacter baumannii	17 (56.7)	25 (73.5)	18 (60)	0.615
	CRE	0 (0)	0 (0)	0 (0)	
	Pseudomonas aeruginosa	2 (6.7)	2 (5.9)	3 (10)	
	Klebsiella penumoniae	0 (0)	0 (0)	0 (0)	
	Other	11 (36.7)	7 (20.6)	9 (30)	
Duration of administration (days), *n* (%)	1-5	4 (13.3)	0 (0)	9 (30)	0.002*
	6-10	12 (40)	7 (20.6)	10 (33.3)	
	11-15	14 (46.7)	25 (73.5)	11 (36.7)	
	16-20	0 (0)	2 (5.9)	0 (0)	
Dose of colistin (mg\kg\day), *n* (%)	4 MIU	16 (53.3)	2 (5.9)	21 (70)	0.0001*
	8 MIU	6 (20)	5 (14.7)	6 (20)	
	12 MIU	8 (26.7)	27 (79.4)	3 (10)	
	16 MIU	0 (0)	0 (0)	0 (0)	
Had another antibiotic along with colistin, *n* (%)	Yes	28 (93.3)	34 (100)	27 (90)	0.19
	No	2 (6.7)	0 (0)	3 (10)	

*Statistically significant

Conditions which were treated with colistin included: diabetes mellitus (22.34%), cardiovascular disease (10.6%), chronic medical condition (24.46%), traumatic surgical condition (29.78%), brain surgery (8.5%), burns (13.83), sepsis and septic shock (52.12%) [Figure 3 and Table 2].

The treatment outcomes are shown in Figure 4. Forty six patients (48.9%) showed complete response and good recovery, while 18 (18%) patients showed partial response as manifested by reduction of outcomes symptoms of infections. The unfavorable response was observed in thirty (31.9%) who were critically

Table 4: Multivariate logistic regression of presence (versus absence) of a favorable response

Variable	*P*	Odd ratio	Confidence interval (95%)
Sex	0.710	0.79	(0.23-2.69)
Age	0.013*	2.40	(1.21-4.81)
Weight (kg)	0.039*	0.08	(0.01-0.88)
Dose of Colistin (mg\kg\day)	0.059	0.62	(0.23-1.03)
Duration	0.252	0.49	(0.27-1.41)

*Statistically significant

ill patients. However, patients who died within 2–3 days of treatment cannot really be considered as treatment failure.[Table 3 and 4].

The adverse effects of colistin were assessed by daily reviewing the patients' charts. Nephrotoxicity was observed in 3 (6.38%) cases treated with colistin; however, those patients had predisposing factors contributing to their renal deterioration plus they were critically ill. Two of three patients had diabetes or cardiovascular diseases with sepsis; the third one had diabetes and cardiovascular disease.

Discussion

The duration of treatment by intravenous colistin was varied it ranged between 3 and 14 days. There were 13 patients (13.83%) used intravenous colistin for less than 5 days, 29 patients received it for up to 10 days, while 50 patients (53.19%) received it for 2 weeks. Only two patients received colistin up to 20 days after they exhibited remarkable improvement.

The majority of patients who were treated for MDR Gram-negative organisms were co-administered one other active antibiotic usually meropenem.[12] The current study showed a good clinical response and resolution of signs and symptoms of presenting illness in patients after using of colistin for treating of MDR *Gram-negative bacteria (P. aeurginosa* and *A. baumannii*). 68.6% of patients who received colistin showed a good clinical outcome against resistant infections in critical and non-critical area.

The study included seven patients who were infected by MBL-producing *Pseudomonas aeurginosa* which were susceptible to colistin and the patients showed full response when receiving the IV colistin in combination with IV meropenem. Similar outcomes were observed from other studies, they reported that 67% of the patients who were infected by MDR *Peudomonas aeruginosa* strain showed good clinical response: complete or partial resolution.[12]

One study performed by Markou, Nikolaos[13] showed a good response in 73% of patients admitted in ICU and survival at 30 days was 57.7% when for treating patient who had sepsis that caused by Gram-negative bacteria because of colistin. Other studies[14,15] have also reported a good therapeutic response that ranged between 52% and 75%, for treating of the infections that caused by MDR after receiving colistin. So, it was concluded that the toxicity was depending on the dose amount.[16] One study[17] found the incidence of nephrotoxicity of polymyxins less common.

In the present study, 6.3% patients developed nephrotoxicity compared to 30% patients receiving colistin in study carried in Thailand.[18] In our study, most of patients who had a nephrotoxicity had also other factors other than colistin. On the other hand, some patients after the signs and symptoms of infection had resolved after using the antibiotics showed a renal function enhancement. Some patients showed muscle weakness which was reversible after discontinuation of drug. No drug reaction or allergies were observed in our patients.

We can summarize the most important key point in our study:

- A good clinical outcome against resistant infections in critical and non-critical area after using of colistin for treating of MDR *Gram-negative bacteria (P. aeurginosa* and *A. baumannii*).
- The risk of nephrotoxicity was low among the patients compared to other studies.
- No drug reaction or allergies were observed in our patients.

In conclusion, colistin was found reasonably effective in MDR bacterial infections in patients at critical settings, and favorably safe.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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