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Use of Colistin in a Neonatal Intensive Care Unit: A Cohort Study of 65 Patients

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Background: The emergence of infections related to multidrug-resistant Gram-negative bacilli (MDR-GNB) reintroduced the use of colistin, an antibiotic that was previously abandoned due to adverse effects. However, because of its limited use in neonatal intensive care units, there is very little data about the effectiveness and safety of colistin in children and newborns. In this study, which will be the largest case study in the literature, we aimed to evaluate the effectiveness and safety of colistin in full-term and preterm newborns.

Material/Methods: The study included patients admitted into 2 level 3 neonatal intensive care units between January 2013 and June 2015. The medical records of patients diagnosed with sepsis, meningitis, pneumonia, and urinary tract infection based on the diagnostic culture results and treated with colistin were analyzed retrospectively. The patients whose infections were not verified were excluded from the study.

Results: The study included 65 patients (18 term, 47 preterm). The most frequently isolated pathogens were *Klebsiella pneumoniae* and *Acinetobacter baumannii* followed by *Pseudomonas aeruginosa* and *Enterobacter cloacae*. Mean colistin treatment time was 15±3.5 days. All patients treated with colistin were being treated with at least 1 other antibiotic. While a complete clinical response was achieved in 51 (72.3%) patients, 14 (21.5%) patients died during treatment. Four (7.7%) patients died during as a result of another infection. Three patients developed renal toxicity, another 3 patients had seizures, and apnea was observed in 3 patients.

Conclusions: Colistin was found to be effective and safe for treatment of MDR-GNB infections in preterms and infants with very low birth weight. Given the severity of the infection, the adverse effects of colistin were at acceptable levels.

MeSH Keywords: Acute Kidney Injury • Colistin • Gram-Negative Bacterial Infections • Infant, Newborn

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Background

Health care-associated infections (HCAI) lead to mortality and morbidity in neonatal intensive care units (NICU). The frequency of HCAI in the NICU were reported to range between 7% and 24% [1,2]. In the last 2 decades there has been a rapid increase in resistance to infections caused by multidrug-resistant Gram-negative bacilli (MDR-GNB), especially *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* and *Klebsiella pneumonia.* Since the production of antibiotics that can treat MDR-GNB infections is limited, the use of colistin has increased worldwide [3,4]. In previous years, the parenteral use of colistin has been reported to have many toxic effects, including nephrotoxicity, and although studies in recent years showed that toxic adverse effects might not be as common as previously thought, the use of colistin is limited to MDR-GNB infections that have clinical and microbiological resistance [5]. In addition, there is very little data regarding the effectiveness and safety of intravenous (IV) colistin use in newborns [6,7]. In this study we aimed to investigate the efficacy and safety of colistin use in MDR-GNB infections that occur in the neonatal period.

Material and Methods

The files of newborn patients infected with MDR-GNB and treated with colistin were evaluated retrospectively. Patients whose diagnostic culture tests confirmed the MDR infection and who were treated with colistin for at least 72 h between January 2013 and June 2015 were included in the study. We recorded demographic data, underlying diseases, hospitalization time in the NICU, ventilator care, surgical procedures, isolated microorganism, location of isolation, antibiotic sensitivity, colistin dose and duration, baseline serum creatinine, level of creatinine during and after colistin treatment, use of other nephrotoxic antibiotics and/or medications, and clinical and microbiological course. The diagnosis of infection was made based on the clinical findings and isolation of bacteria from sterile body sites outlined in the Centers for Disease Control and Prevention (CDC) guideline [8].

The MDR was considered as a Gram-negative microorganisms resistant to at least 3 different antibiotic groups. Clinical response was accepted as resolution of initial symptoms and signs, tolerance to oral feeding, and weight gain. Clinical unresponsiveness was considered as continuation or worsening of the initial signs and symptoms, development of new infection, or radiological deterioration. Clinical outcome was assessed based on patient survival or loss after treatment. Patients that were lost were further evaluated to investigate whether their cause of death was infection.

Renal impairment was considered as an at least 0.5 mg/dl increase in serum creatinine compared to basal levels at any time after 24 h had passed since colistin treatment was initiated or 2-fold increase of serum creatinine levels compared to baseline levels.

Cultures were taken from patients with suspected infection at the beginning and throughout the treatment: venous blood, central venous catheter (CVC), endotracheal aspirate (ETA), cerebrospinal fluid (CSF), and urine. Blood culture samples were seeded into BACTEC Peds Plus/F (BD, Sparks, MD) culture flasks. All microbiological samples were inoculated into routine culture media (MacConkey agar, blood agar, and chocolate agar). The identification of microorganisms was done by biochemical tests and the Vitek-2 compact system. The antimicrobial susceptibility to colistin was tested by E-test based on the Clinical Laboratory Standards Institute (CLSI) guideline. Among the isolated bacteria, the ones that had the minimum inhibitory concentration (MIC) of ≤2 mg/dl were considered to be sensitive to colistin.

The colistin treatment was initiated in patients that did not have any other options based on their culture results. The empirical colistin treatment was initiated based on the clinical surveillance data and/or in patients not responsive to other broad-spectrum antibiotics. However, the study only included patients who were identified to have MDRGNB based on their culture results. Patients were administered a commercial formulation that contained 150 mg of colistin in each vial. All patients received standard colistin treatment of 5 mg/kg/day given in 3 doses as infusion in 5 ml saline for at least 30 min. Patients were evaluated for clinical and microbiological response, as well as for adverse effects of colistin. All patients were followed-up for 10 days after the end of treatment in order to monitor for nephrotoxicity. Control cultures were obtained from all patients 48–96 h after the initiation of colistin treatment.

Parents of all patients were informed about the treatment and verbal consent was obtained from all of them prior to the treatment. The Ethics Committee of Bursa Şevket Yılmaz Education and Research Hospital approved the study.

Statistical analyses

The SPSS 18.0 for Windows (SPSS, Chicago, IL) program was used for statistical analysis. The Shapiro-Wilk test was used to determine whether the variables followed normal distribution. The variables that followed normal distribution are expressed as mean (±SD) and the ones that did not follow normal distribution are expressed as median (min–max) and frequency (n,%).

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Table 1. The demographic data and the list of diagnosis.

Demographic data		Admission diagnosis*			Health care-associated infections		
Gestational age	33.6±4.3 weeks	RDS	38	(58.5%)	BSI	39	(60%)
Age	11.8±9.4 days	ACHD	12	(12.2%)	VAP	9	(13.8%)
Weight	2,452±1,119 g	Sepsis	7	(10.8%)	NEC	5	(7.6%)
Birth weight	2,363±1,113 g	Meningomyelocele	4	(6.2%)	Meningitis	4	(6.1%)
Hospital stay	36.3±17.6 days	HIE	3	(4.6%)	USI	3	(4.6%)
Gender (Female)	52.3%	TTN, bronchiolitis, BPD	2	(3.1%)	CABS	2	(3%)
		SCHD, MSUD, IDM, USI, ARF, anencephaly, citrullinemia, esophageal atresia	1	(1.5%)	Pneumonia, NEC + VAP and NEC + pneumonia	1	(1.5%)

ARF – acute renal failure; ACHD – acyanotic congenital heart disease; BPD – bronchopulmonary dysplasia; BSI – bloodstream infection; CABS – catheter related bloodstream infection; SCHD – cyanotic congenital heart disease; HIE – hypoxia ischemia encephalopathy; IDM – infant of diabetic mother; MSUD – maple syrup urine disease; NEC – necrotizing enterocolitis; RDS – respiratory sistress syndrome; TTN – transient tachypnea of the newborn; USI – urinary system infection; VAP – ventilator-associated pneumonia.
* Some patients were diagnosed with more than one disease.

Table 2. Site of isolated microorganisms and isolated microorganisms.

Site of isolated microorganisms			The isolated bacteria (MDR)			Other microorganisms		
Blood	48	(73.8%)	*K. pneumonia*	26	(40%)	MRCNS	9	(13.8%)
ETA	5	(7.7%)	*A. baumannii*	20	(30.7%)	*Candida albicans*	3	(4.6%)
Blood and CSF	4	(6.2%)	*E. coli*	10	(15.3%)	Enterococcus spp and *Candida parapsilosis*	2	(3.1%)
Blood and ETA	4	(6.2%)	*P. aeuroginosa*	5	(7.6%)	*Stenotrophomonas maltophilia* and MRSA	1	(1.5%)
Urine	3	(4.6%)	*Enterobacter cloacae*	4	(6.1%)			
CSF	1	(1.5%)						

CSF – cerebrospinal fluid; ETA – endotracheal aspirat; MRCNS – methicillin-resistant coagulase negative Staphylococci; MRSA – methicillin-resistant Staphylococcus.

Results

Sixty-five patients that met the criteria were included in the study. Eighteen patients were full-term, while 47 were preterm. None of the patients received 2 or more courses of colistin treatment. The demographic data and Admission Diagnosis and Health Care-Associated Infections (HAIs) are given in Table 1.

The presence of bacteria was shown with cultures from at least 1 site in all patients. The isolated microorganisms and their locations are given in Table 2. All of these isolates were susceptible to colistin. Several antimicrobials had been used prior to or with colistin (Table 3).

In our study, 20% of the microorganisms were sensitive to amikacin, 4.6% to ciprofloxacin, and 4.6% were sensitive to both ciprofloxacin and amikacin. While the mortality with microorganisms that are only sensitive to colistin was 21.7%, the mortality related to infections by microorganisms that were sensitive to amikacin and/or ciprofloxacin was 21%. Moreover,

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Table 3. Antimicrobial treatment prior to and concurrent with colistin.

Antimicrobial treatment prior to colistin			Antimicrobial treatment concurrent with colistin		
Vancomycin	19	(29.2%)	Meropenem	49	(75.4%)
Meropenem	18	(27.7%)	Vancomycin	16	(24.6%)
Piperacillin-tazobactam and ampicillin	17	(15.4%)	Amikacin	12	(18.5%)
Cefotaxime	8	(12.3%)	Ciprofloxacin	7	(10.8%)
Amikacin	6	(9.2%)	Amphotericin B	4	(6.2%)
Amphotericin B and cefepime	2	(3.1%)	Fluconazole and caspofungin	2	(3.1%)
Caspofungin and ciprofloxacin	1	(1.5%)	TMP-SMX	1	(1.5%)

TMP-SMX – Trimethoprim sulfamethoxazole.

Table 4. The clinical and laboratory data of patients that died during the treatment.

Case No	Gestational age (week)	Postnatal age (day)*	Gestational weight (g)	Primary disease	HCAI	Blood culture	Accompanying antibiotic therapy	Duration of treatment of colistin	Accompanying nephrotoxic agents	Toxicity
1	24	6	675	RDS, PDA	NEC,VİP	*E. coli, Enterococcus spp.*	Meropenem, Vancomycin	18	Ibuprofen	Not
2	25	5	710	RDS, PDA	BSI	*K. pneumoniae*	Meropenem	12	Ibuprofen	Not
3	26	9	1005	RDS	NEC	*A. baumannii, C. albicans*	Amphotericin b, Meropenem	18	Not	Not
4	27	48	1195	RDS, BPD	VAP	*A. baumannii*	Amikacin,, Meropenem, Vancomycin	12	Not	Not
5	29	10	975	RDS	NEC	*K. pneumoniae, C. albicans*	Amikasin, Amphotericin b	23	Not	Not
6	30	35	1760	RDS	BSI	*A. baumannii*	Amikacin, Vancomycin	10	Not	Not
7	30	5	1400	RDS, PDA	VİP	*K. pneumoniae*	Amphotericin b, Meropenem, Vancomycin	9	Ibuprofen	Not
8	35	6	2120	Meningo-myelocele	Meningitis	*K. pneumoniae, C. parapsilosis*	Caspofungin, Meropenem, Vancomycin	16	Not	Not
9	34	31	1630	ARF	BSI	MRCNS, *K. pneumoniae*	Meropenem, Vancomycin	14	Not	Convul-sion
10	37	12	3800	Sepsis	BSI	*E. coli*	Ciprofloxacin	15	Not	Not
11	38	9	4000	Meningo-myelocele	Meningitis	*C. parapsilosis, A. baumannii*	Caspofungin, Meropenem	15	Contrast agents	Not
12	40	7	4040	Anencephaly	BSI	*E. cloacae*	Meropenem, Vancomycin	6	Not	Not
13	41	8	4630	Meningo-myelocele	BSI	*K. pneumoniae*	Meropenem	10	Not	Apnea
14	41	5	4010	Meningo-myelocele	Meningitis	*Klebsiella oxytoca*, MRCNS	Meropenem, Vancomycin	22	Not	Not

ARF – acute renal failure; HCAI – healthcare associated infections; RDS – respiratory distress syndrome; BPD – bronchopulmonary dysplasia; PDA – patent ductus arteriosus; NEC – necrotizing enterocolitis; BSI – blood stream infection; VAP – ventilator associated pneumonia; MRCNS – meticillin-resistant coagulase negative Staphylococcus. * The age of the patient at the beginning of the treatment.

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Table 5. Characteristics of patients with induced drug toxicity.

Case No	Gestational age (week)	Postnatal age (day)	Gestational weight (g)	Primary disease	HCAI	Blood culture	Accompanying antibiotic therapy	Duration of treatment of colistin	Toxicity	Result
1	38	5	2340	TTN	BSI	*K. pneumoniae*	Meropenem	15	Nefrotoxicity (*1.5)	Survived
2	29	8	1310	RDS	NEC	*E. coli*, MRSA	Meropenem, Vancomycin	14	Nefrotoxicity (*1.7)	Survived
3	40	14	4870	Bronchiolitis	BSI	*K. pneumoniae*	Meropenem	10	Nefrotoxicity (*1.6)	Survived
4	34	31	1630	ARF	BSI	*K. pneumoniae*, MRCNS	Meropenem, Vancomycin	14	Convulsion	Died
5	35	7	2480	HIEP	VAP	*K. pneumoniae*	Amikacin	15	Convulsion	Survived
6	36	16	3120	IDM	BSI	*A. baumannii*	Meropenem	14	Convulsion	Survived
7	41	8	4630	Meningomyelocele	BSI	*K. pneumoniae*	Meropenem	10	Apne	Died

ARF – acute renal failure; HIEP – hypoxic ischemic encephalopathy; HCAI – healthcare associated infections; IDM – infant of diabetic mother; RDS – respiratory distress syndrome; TTN – transient tachypnea newborn; NEC – necrotizing enterocolitis; BSI – blood stream infection; VAP – ventilator associated pneumonia; MRCNS – meticillin-resistant Coagulase negative Staphylococcus; MRSA – meticillin-resistant Staphylococcus aureus. * Creatinine values.

nephrotoxic drugs such as ibuprofen were used in 6 patients (9.2%) and contrast agents in 3 patients (4.6%). The complete elimination of microorganisms from infection sites was achieved in all patients. While complete clinical remission was achieved in 51 patients (78.5), 14 patients (21.5%) died during the treatment. Four patients (6.2%) died due to another infection and none of these patients developed colistin toxicity (Table 4).

Nephrotoxicity was observed in 3 patients, but clinical improvement was achieved in all 3. Their renal function returned to normal after discontinuation of colistin (Table 5).

Convulsions appeared in 3 patients and apnea developed in 1 patient. While 1 of the patients that developed convulsions had HIE, the other 2 had no organic pathology to explain the cause of seizures (Table 5). The patient with apnea had meningomyelocele and was receiving treatment due to BSI. This patient died on the 10th day of treatment. Gastric residual increase was observed in 3 patients. Two patients developed rash, but their rashes recovered spontaneously without any need to interrupt the treatment.

Discussion

Colistin is a cationic polypeptide antibiotic belonging to the polymyxin family, that kills bacteria by disrupting cellular functions [9]. It also has a potent antiendotoxin property. Parenteral colistin use in newborns was first reported in 1970. However, at that time colistin was administered via intramuscular routes and in high doses, leading to high rates of toxicity [6,7]. Lately, the use of colistin in MDR infections has increased due to increasing resistance to GNB. However, there is not enough data about use and dosage of colistin in newborns. Our series will be the largest series to address this subject.

The success rate of colistin in MDR-GNB infections in pediatric treatment studies has been reported to vary between 70% and 87.5% [6,10].

Colistin has been used at 2.5–6 mg/kg/day in 3–4 doses [10,11]. All of our patients were administered the standard 5 mg/kg/day in 3 doses. None of the patients required intrathecal or intraventricular treatment.

Long-term use and reaching high tissue concentrations, especially while treating infections such as ventriculitis and pneumonia, may lead to development of resistance to colistin [7]. In our study, none of the patients developed colistin resistance during treatment.

Studies with adult patients showed that colistin was less toxic than previously reported [12]. Similar results have been reported in recent studies performed with pediatric patients [6,13–15]. The data on the efficacy and safety of colistin are insufficient and there are almost no data regarding the use of colistin in the neonatal period.

It was reported that pediatric patients were treated with colistin for 40, 42, 46, 51, 70, and 93 days, 1 patient received an IV colistin treatment for 133 days, and this long-term use of colistin did not lead to development of toxicity [7]. In an experimental study, animals were given high-dose (12–24 mg/kg/day) colistin for 15 days and none of the animals developed nephrotoxicity [16]. In our study, the longest colistin treatment was for 24 days with a dose of 5 mg/kg/day and no toxicity was observed in this patient.

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Before 1980, colistin toxicity was reported to occur in 20–50% of treated patients [9]. However, recent studies have shown that the nephrotoxicity is rarer [7,9,13,15]. This reduction in nephrotoxicity can be explained by the use of less toxic colistimethate sodium, better patient monitoring in the ICU, and avoiding the simultaneous use of nephrotoxic drugs [17]. Nephrotoxicity arises due to concurrent use of nephrotoxic drugs such as aminoglycosides [7,18,19]. Studies have shown that use of antibiotics other than colistin may lead to higher rates of nephrotoxicity compared to that of colistin [20]. Moreover, colistin has been reported to be less nephrotoxic than tobramycin or amikacin [19]. In our study, it is noteworthy that 29% of the patients were treated with aminoglycosides prior to or with colistin and none of them developed nephrotoxicity.

In some cases, nephrotoxic effects of colistin may develop very rapidly. Colistin-associated nephrotoxicity mostly occurs within the first 5 days to a week and patients that develop nephrotoxicity have higher mortality rates [21–23]. However, its progression is often mild and is improved when the use of colistin is discontinued [1,3,24–26]. Although the population in our study was very sensitive, the nephrotoxicity developed after the 10th day, and consistent with the literature, improved rapidly when colistin was discontinued.

Neurotoxicity was often observed when colistin was first introduced [5,27], but studies conducted in recent years showed very little or no colistin-associated neurotoxicity [7,9,10].

Neurotoxicity is dose-dependent and reversible. It may lead to weakness, facial and peripheral paresthesia, ophthalmoplegia, dysphagia, ataxia, ptosis, partial deafness, vision disorders, vertigo, confusion, hallucinations, seizures, and neuromuscular blockade [12,28].

In our study, convulsions were seen in 3 patients. However, 1 of these patients had hypoxia sequels, as well as other neurological problems. Moreover, the patient who developed apnea had meningomyelocele concomitant with hydrocephaly. Therefore, we believe that apnea was associated with the primary disease (Table 5). Despite these 4 patients, the neurotoxicity rate was not very high. Although the low rate of neurotoxicity could be due to low levels of colistin-associated neurotoxicity, it might also be because the study was conducted retrospectively, most of the patients were premature infants, and because patients had received sedoanalgesia.

The sensitivity of active microorganisms to the second antibiotic may affect the clinical and microbiological response. However, in our study there was no difference between the group that was sensitive to colistin alone and the group that was sensitive to a second antibiotic in terms of mortality and microbiological response.

The retrospective design and lack of a control group are limits of our study. Prematurity, other treatments, and sedoanalgesics received by the patients made it difficult to assess adverse effects, especially neurological ones. Moreover, some patients were receiving medications in addition to colistin, which made it impossible to evaluate the effects of colistin alone. Furthermore, patients received other nephrotoxic drugs, thus it was not fully understood how much of the toxicity was due to colistin.

Conclusions

Our study has demonstrated that colistin is well tolerated by newborns. We believe that given the severity and mortality of the disease, the adverse effects of colistin are acceptable. We found that colistin is highly effective and safe in treating infections caused by MDR-GNB. Lastly, since colistin is one of the "last resort" medications against infections caused by MDR-GNB, its rational use is crucial.

Statement

No financial support was received for this study, and the authors have no conflicts of interest to report.

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