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Original Research

Colistin Treatment for Multidrug-Resistant Gram-Negative Infections in Children: Caution Required for Nephrotoxicity

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Abstract

Objectives: Colistin has come to the fore as a treatment option, especially with the occurrence of multidrug-resistant Gram-negative infections across the world. However, the high nephrotoxic effects of colistin should be taken into consideration in children. The study's primary outcome was to determine the clinical success of the colistin treatment, and the secondary outcome was to detect the side effects related to colistin.

Methods: The patients who received intravenous colistin in our hospital's last 5 years were included in the study. In addition to the patients' demographic and clinical characteristics, the clinical success of the colistin treatment, 28-day infection-related mortality of the patients, and side effects of colistin were recorded.

Results: A total of 37 patients received colistin therapy during 2015–2019. Four of these patients had colistin treatment twice a year, so we accepted them as separate cases in each infection attack. Therefore, 41 cases were included in the study. The median age of the cases was 26 months (IQR: 4.50–144.50) and 27 (65.9%) were male. Twenty-seven cases (65.9%) had sepsis. The median dose of colistin was 4.2 (IQR: 3–5) mg/kg/day. Among 44 cultures obtained from the patients, the most common microorganism was Acinetobacter baumannii, with 58.5%. The clinical success was detected in 18 patients (43.9%). While overall nephrotoxicity developed in 14 (34.1%) patients, only two of them needed dialysis.

Conclusion: Colistin should not be considered the first choice in treating Gram-negative infections but should be kept as salvage therapy in multidrug-resistant Gram-negative infections across the world. During the treatment process, close monitoring of renal function tests and urinary output were recommended due to the risk of developing nephrotoxicity.

Keywords: Children, colistin, multidrug-resistant gram-negative microorganism, nephrotoxicity

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A worldwide increase in the incidence of multidrug-resistant Gram-negative bacterial infections (MDR-GNIs) has driven clinicians to seek agents other than conventional antibiotics for treatment success. Polymyxin E (colistin), which is useful on many Gram-negative bacilli, including *Acinetobacter* spp., *Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Salmonella spp*., *Shigella* spp., *Yersinia* spp., and *Citrobacter* spp., comes to mind at this stage. [1] The polymyxins were derived from a bacterium called *Paenibacillus polymyxa* and classified in polypeptide anti-

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biotics.[2,3] Colistin was developed in the 1940s, but it was withdrawn from usage due to its high toxicity. However, it was reintroduced as a rescue therapy in infections caused by MDR Gram-negative bacilli. The revival was not because of colistin improved side effect profile but because of the obligation to use it as a last resort.[4] Therefore, in severely ill patients, colistin high nephrotoxic and neurotoxic effects should be taken into consideration.[5]

This study aimed to determine colistin effect in pediatric patients infected with MDR Gram-negative bacteria. The study's primary outcome was to determine the clinical success of the colistin treatment. The secondary outcome was to detect side effects related to colistin and analyze the clinical and laboratory findings of the patients who received intravenous colistin.

Methods

Study Population

In this study, 37 pediatric patients who received intravenous colistin between 2015 and 2019 in our hospital were included in the study. Four of these patients had colistin treatment twice a year, so we accepted them as separate cases in each infection attack. Therefore, 41 cases were included in the study. The statistical analyses were performed with the data of 41 cases. Having at least 14 days interim with negative culture results from the last dose of first colistin therapy to the initial dose of second colistin therapy in the same patient was accepted as the criteria of declaring as separate cases. Including criteria were being children aged from newborn to 18 years, and receiving colistin by intravenous route, whereas excluding criteria were receiving colistin <48 h and <2 doses. Demographic characteristics such as age and gender; diagnosis (sepsis, pneumonia, etc.) and underlying conditions such as trauma, cardiovascular disease, neurologic disease, medical devices (presence of a central venous catheter, ventriculoperitoneal shunt, external ventricular drain, tracheostomy, ileostomy-colostomy, and endotracheal tube), length of hospitalization, length and dose of colistin therapy, concurrent other antibiotic usage, concomitant nephrotoxic agent usage, microorganisms isolated from different body side's culture and their antibiograms, the type of infection side, laboratory analyses of the patients, nephrotoxicity, and neurotoxicity due to colistin, clinical success, microbiological eradication status, and 28-day infection-related mortality of the patients were recorded retrospectively from the hospital records.

Definitions and Clinical Practices

MDR Gram-negative organism is defined as being resistant against at least three different types of antibiotics that have an intrinsic activity to Gram-negative bacteria.[6] The isolates were identified to species level using the MALDI TOF MS (Bruker Daltonics). Colistin susceptibility test was performed by broth microdilution test as recommended by the EUCAST. The patients' diagnoses were determined according to the body sides (blood, bronchoalveolar lavage fluid, cerebrospinal fluid [CSF], and wound culture swab), where a Gram-negative organism was obtained. We observed MDR-GNIs in the body sides, so we decided to initiate colistin treatment for documented MDR-GNIs. There was clinical worsening in some patients despite using conventional antibiotics with intrinsic activity to Gram-negative organisms, including carbapenems. We could not demonstrate a documented infection of those patients' cultures; therefore, colistin was started empirically. The decision to initiate colistin was made after the pediatric infectious diseases' consultation. Clinical success was assessed as patients' survival in 28 days and microbiological eradication of the culprit agent within 7 days of the colistin initiation.[7] In patients who had the colistin treatment as empirically and absent control culture for determining the eradication, only survival situation was assessed to detect the clinical success. Patients were monitored in terms of renal functions, neurologic findings, and other laboratory parameters. Nephrotoxicity was defined according to RIFLE (acronym indicating Risk of renal dysfunction; Injury to the kidney; Failure of kidney function, Loss of kidney function and End-stage kidney disease) criteria. If a patient was consistent with the findings even at the first step of RIFLE criteria (risk of renal dysfunction; urinary output <0.5 mg/kg/h × 6 h, increased serum creatinine × 1.5, and GFR decrease >25%), it was accepted as nephrotoxicity, and colistin therapy was immediately discontinued.[8] Neurotoxicity may manifest itself as vertigo, dizziness, seizures, diplopia, ataxia, altered mental status, delirium, paresthesia, and neuromuscular blockade.[9]

Statistical Analysis

Descriptive statistics were used to represent the subjects' baseline characteristics, depending on the normality of distribution. Values for continuous variables were provided either as mean-standard deviations (SD) or as medians (interquartile range). Frequencies of nominal variables were presented as percentages. Comparisons between groups for categorical variables were made using the Chi-square (χ^2) test. For two-group comparisons of independent variables, the Student's t-test was used as a parametric test, whereas the Mann–Whitney U-test was the preferred nonparametric test. Statistical analyses were performed using SPSS v25.0 (IBM Corp., Armonk, New York, USA) statistical package. Statistical significance was defined as $p<0.05$.

Ethical Considerations

Ethics committee approval was obtained for non-interventional clinical research on January 23, 2020, and with the 2020/1–14 protocol number at our hospital's ethics committee. All investigational procedures conform to the Declaration of Helsinki guiding principles.

Results

The median age of the 41 cases included in the study was 26 months (interquartile range [IQR]: 4.50–144.50). Twenty-seven (65.9%) of the cases were male and 14 were female (34.1%). Almost all of the patients (97.5%) had an underlying disease or a facilitating factor. Diagnoses of the cases were evaluated; 27 of them (65.9%) had sepsis, 8 (19.5%) had pneumonia, 4 (9.8%) had central nervous system infection, and 2 (4.9%) had soft-tissue infection.

Twenty cases (48.8%) were hospitalized in a pediatric intensive care unit (PICU), 5 (12.2%) in neonatal intensive care unit (NICU), 2 (4.8%) in neonatal surgical intensive care unit, and 1 (2.5%) in anesthesia intensive care unit. The other patients (n=13, 31.7%) were in pediatrics clinics and neurosurgical clinics. The mean hospitalization day was 78.17 (±52.38) days and the median treatment time was 14 days (IQR: 10–18). The median dose of colistin was 4.2 (IQR: 3–5) mg/kg/day.

The preferred combination antimicrobial therapies with colistin for synergistic impact were meropenem (51.2%), aminoglycosides (36.6%), and ceftazidime or sulbactam-ampicillin (12.2%). Other concomitant antimicrobials were antifungal agents (51.2%) and glycopeptides (43.9%). No resistance occurred during colistin treatment.

As for the usage of other nephrotoxic agents, 12 cases (29.2%) received ranitidine, 11 cases (26.8%) received levetiracetam, 10 cases (24.4%) received epinephrine, 4 cases (9.7%) had topiramate, 3 cases (7.3%) had caffeine, 3 cases (7.3%) had dexmedetomidine, and 2 cases had tacrolimus (4.8%). *Acinetobacter baumannii* was isolated in 58.5% of the patients, *Klebsiella pneumoniae* in 20%, and *Pseudomonas aeruginosa* in 12.2%. The agents were detected in 44 cultures; blood in 18 cultures (40.9%), and BAL fluid in 11 cultures (25%) preponderantly. Other cultures were obtained from urine, CSF, wound swap, catheter, and peritoneal fluid. Of 41 cases, 33 (80.5%) had at least one medical device. The 28-day infection-related mortality was found 29.3% in our study. Microbiological eradication was detected in 14 patients (34.1%), and clinical success was detected in 18 patients (43.9%). Clinical and bacteriologic characteristics of the patients are shown in Table 1.

When the relationship of clinical and laboratory features on clinical success was evaluated, the mean platelet count was significantly lower (p=0.007), the median of the C-reactive protein was significantly higher (p=0.022), and the ICU admission was more frequent in those with clinical failure (p<0.001). Comparison laboratory analyses and intensive care unit hospitalization ratio in both groups are summarized in Table 2.

Nephrotoxicity developed in 14 of the patients (34.1%) and two of them needed dialysis. Nephrotoxicity and its relation with age, gender, and the ward where the patients were hospitalized, underlying conditions, dose of colistin, length of colistin treatment, and usage of concomitant nephrotoxic agents were analyzed. No statistical relation was found with age, gender, the ward, underlying condition, dose of colistin, length of colistin treatment, and concomitant nephrotoxic agent usage (p=0.173, p=0.123, p=0.308, p=0.466, p=0.542, p=0.609, and p=0.129, respectively). One patient (2.4%) had facial paralysis, which is counted in neurotoxicity.

Discussion

Colistin, which is used in treating many Gram-negative microorganisms, is preferred as a last resort, especially in infections caused by *A. baumannii* and *P. aeruginosa*.[10-12] In particular, *A. baumannii* is of great concerning pathogen with mortality rates up to 72.7%, especially in central nervous system infections, and needs to be treated not only by intravenous antibiotics but also intraventricularly or intrathecally routes in certain patients.[13] Canturan et al. remarked that in the intensive care unit, among overall ventilator-associated pneumoniae in adults, 63% was caused by *A. baumannii* and that it was a growing concern in terms of rapidly gaining resistance against antimicrobial agents.[14] It was noted that over half of the patients (58.5%) had *A. baumannii* in our study, similar to the literature.

When the characteristics of the patients were evaluated, as in other studies, male gender was predominantly seen in our study (65.9%).[15-17] Most of them had an underlying disease, facilitating factor, or medical devices that might make our population vulnerable to infectious agents. We frequently encounter MDR-GNI due to carbapenems' constant usage, especially in PICU and NICU in our hospital. In the study we conducted, a high ratio of ICU admission was noted, and the most common concurrent antibiotic was meropenem as well. The most common diagnosis was sepsis (65.9%) among the cases. In the study conducted by Karbuz et al. in 2014, ventilator-associated pneumonia was the most frequent diagnosis.[18]

The clinical success with colistin therapy was detected 43.9% in our study. In Sahbudak et al.'s study. the clinical response was found to be 76% colistin treatment courses

Table 1. Clinical and bacteriologic characteristics of the patients

Case	Diagnoses	Site of infection	Medical devices	Underlying facilitating factor	Microorganisms	Nephrotoxicity	Colistin dosage (mg/kg/day)	Microbiological eradicationc	Outcome	Clinical success
1	Stump infection	Wound swab	None	Arm amputation	KP	No	3.4	N/A	Cured	Yes
2	Septic shock	Blood, urine, BAL	CVC, ETT, thorax tube	VSD, pulmonary hypertension	KP, AB	Yes	N/A	No	Exitus	No
3	VAP	BAL	CVC, ETT	Down syndrome, AVDS	AB	Yes	N/A	No	Exitus	No
4	CNS infection	-	CVC, VP shunt, EVD	Hydrocephalus	-	Yes	5	N/A	Cured	Yes
5	VAP	BAL	Tracheostomy	Hypotonic infant	AB	No	N/A	No	Cured	No
6	VAP	BAL	CVC, tracheostomy, urinary catheter	Motorcycle crash	AB	No	N/A	Yes	Cured	Yes
7	VAP	BAL	Tracheostomy	Respiratory aspiration, asphyxia	AB	No	4.32	N/A	Cured	Yes
8	Urosepsis	Urine	None	None	KP, *Acinetobacter spp.*	No	N/A	Yes	Cured	Yes
9	CNS infection, pneumonia	BAL	ETT, EVD	Epilepsy, post-resuscitation	KP	No	N/A	N/A	Exitus	No
10	Sepsis	Blood	CVC, ETT	ALL-HRG	AB	No	N/A	No	Cured	No
11	Sepsis	Blood, catheter	CVC, ETT	ALL-HRG	AB	No	N/A	Yes	Exitus	No
12	Gastroenteritis, pneumonia	Blood	CVC, ETT	Sequelae of HIE	PA	No	5	No	Cured	No
13	Gastroenteritis, pneumonia	Blood	None	Sequelae of HIE	AB	No	3	Yes	Cured	Yes
14	Septic shock	Blood	CVC, ETT	CP, epilepsy	AB	No	N/A	Yes	Cured	Yes
15	Urosepsis	Urine	CVC	Short bowel syndrome, malnutrition	PA	No	5	No	Cured	No
16	Urosepsis	Urine	Clean intermittent catheterization	MMC, hydrocephalus, neurogenic bladder	AB	No	2.5	No	Cured	No
17	VAP	BAL	CVC, ETT	HLH, MOD	AB	Yes	N/A	No	Exitus	No
18	Sepsis	Blood	VP shunt	Hydrocephalus	AB	No	4	Yes	Cured	Yes
19	Sepsis	Blood	CVC, ETT	Prematurity	AB	No	N/A	Yes	Cured	Yes
20	VAP	Catheter	CVC, tracheostomy	Hypotonic infant	AB	Yes	5	No	Cured	No
21	Sepsis	CSF	CVC, ETT, urinary catheter	Motorcycle crash	AB	No	2x150 mg/day	No	Exitus	No
22	Sepsis	Blood	None	Hydronephrosis	AB	No	N/A	Yes	Cured	Yes
23	Convulsion	-	CVC, urinary catheter	Foreign body aspiration, right lower lobectomy	-	No	4.8	N/A	Cured	Yes
24	Septic shock	BAL	CVC, ETT, PEG, urinary catheter	Epilepsy, MMR	AB	No	N/A	No	Exitus	No
25	Septic shock	Blood	CVC, PEG	Epilepsy, MMR	AB	No	3.1	No	Exitus	No
26	Septic shock	BAL	None	Pulmonary tuberculosis	AB	Yes	4.6	N/A	Cured	Yes
27	Sepsis	Blood	Umbilical catheter, ETT	Prematurity, SGA	AB	Yes	3	Yes	Exitus	No
28	Sepsis	-	CVC	Short bowel syndrome	-	Yes	4	N/A	Cured	Yes

Table 1. CONT.

Case	Diagnoses	Site of infection	Medical devices	Underlying facilitating factor	Microorganisms	Nephrotoxicity	Colistin dosage (mg/kg/day)	Microbiological eradicationc	Outcome	Clinical success
29	Sepsis	Peritoneal fluid	CVC, ETT, gastrostomy, urinary catheter	Short bowel syndrome	KP	Yesa	5	No	Cured	No
30	Ventriculitis	BOS	CVC, ETT, thorax tube, EVD	Hydrocephalus	KP	No	3	Yes	Exitus	No
31	Sepsis	Blood	None	CP, epilepsy, truncus arteriosus	PA	Yes	0.6	No	Cured	No
32	Sepsis	BAL, blood	CVC, ETT	PDA, TAPVR	AB	Yesb	N/A	No	Exitus	No
33	Urosepsis	Blood, urine	None	Exstrophy vesicae	AB	No	5	Yes	Cured	Yes
34	Sepsis	Blood	ETT	Intestinal perforation	KP	No	5	No	Cured	No
35	Sepsis	BAL, blood	CVC, ETT	Sequelae of encephalitis, hydatid cysts	AB	No	N/A	No	Cured	No
36	Sepsis	Blood	CVC, ETT	CP, epilepsy, hypertension	PA	Yes	N/A	No	Cured	No
37	Septic arthritis	Tissue biopsy	None	Knee injury with a cutting tool	PA	No	3	N/A	Cured	Yes
38	CNS infection	BOS	VP shunt, EVD	Hydrocephalus	AB	Yes	4	Yes	Cured	Yes
39	Sepsis	Catheter	Port catheter, ileostomy	Intestinal pseudo-obstruction	KP	Yes	5	N/A	Cured	Yes
40	Sepsis	Urine	CVC, ETT	Prematurity	KP	No	5	Yes	Exitus	No
41	Sepsis	Blood	CVC, tracheostomy	SMA type I	AB	No	2.5	Yes	Cured	Yes

[a]Case 29 needed hemodiafiltration (HDF) due to renal insufficiency. [b]Case 32 needed peritoneal dialysis due to renal insufficiency. [c]The patients who had the colistin treatment as empirically or absent control culture were classified in N/A. VAP: Ventilator-associated pneumonia; CNS: Central nervous system; BAL: Bronchoalveolar lavage; CSF: Cerebrospinal fluid; CVC: Central venous catheter; ETT: Endotracheal tube; VP: Ventriculoperitoneal; EVD: External ventricular drain; PEG: Percutaneous endoscopic gastrostomy; VSD: Ventricular septal defect; AVSD: Atrioventricular septal defect; ALL: Acute lymphoblastic leukemia; HRG: High-risk group; HIE: Hypoxic ischemic encephalopathy; CP: Cerebral palsy; MMC: Meningomyelocele; HLH: Hemophagocytic lymphohistiocytosis; MOD: Multiorgan dysfunction; MMR: Motor-mental retardation; SGA: Small for gestational age; PDA: Patent ductus arteriosus; TAPVR: Total anomalous pulmonary venous return; SMA: Spinal muscular atrophy; KP: Klebsiella pneumoniae; AB: Acinetobacter baumannii; PA: Pseudomonas aeruginosa; N/A: Not applicable.

and clinical success was assessed as clinical improvement of the patients, absence of radiologic deterioration, and negative culture.[10] In the study of Anne et al., in where the clinical response was evaluated in children with extensively drug-resistant Gram-negative urinary tract infection, patients who received combination therapy with colistin had a higher clinical success rate than the patients who were treated without colistin.[19]

Moreover, there are also adult studies regarding colistin treatment success. In Li and Abad CLR's. study demonstrated that patients who had MDR-GNI and were treated with colistin, the clinical success rate was found to be 61.2%.[20] With a wide range of clinical success rates, this difference could be attributed to variations in clinical success' criteria. The conclusion shared by different studies is that only clinical improvement or solely microbiological eradication should not be considered a reliable indicator of clinical success. In Paul et al.'s study that determined the effect of the meropenem and colistin combination therapy and colistin treatment alone on clinical success, no significant difference has found between both regimens.[21] None of the children in our study received colistin therapy alone. Therefore, the effect of combination or colistin treatment alone could not have been determined in our patients.

The 28-day infection-related mortality was found to be 29.3% in our study. Mortality was detected to be more frequent in those hospitalized in ICUs and those with thrombocytopenia. In the study of Karli et al., it was observed that the infection-related mortality rate was 14.6%.[22] In the study of Karageorgos et al., while the crude mortality rate was 29.5%, the infection-related mortality rate was reported as 16.6%.[23] The infection-related mortality ratio was the lowest (11%) in Ozsurekci et al.'s study and the second (11.5%) in Paksu et al.'s study among the articles published within 10 years.[11,15] The relatively high mortality rate of our study could be attributed to an underlying disease in most of our patients and the presence of medical devices that our patients had to use.

Table 2. Comparison laboratory analyses and intensive care unit hospitalization ratio between the patients with clinical success and failure

	Clinical success (n=18)	Clinical failure (n=23)	p
Laboratory analyses			
Hemoglobin (gr/dL)[a]	10.74 (2.63)	9.34 (1.30)	0.50
WBC (×10³/uL)[b]	12.8 (10.0–16.8)	10.3 (7.7–15.4)	0.248
ANC (×10³/uL)[b]	8.1 (4.7–11.6)	7.8 (5.1–9.7)	0.700
ALC (×10³/uL)[b]	2.2 (1.9–4.9)	1.6 (1–2.7)	0.059
PLT (×10³/uL)[a]	356 (220)	191 (147)	0.007*
CRP (mg/L)[b]	18.1 (2.5–64.3)	55.1 (22.9–124.1)	0.022*
PCT (µg/L)[b]	1.25 (0.37–19.8)	13.2 (1.5–36.0)	0.136
Overall intensive care units[c]	7 (38.9)	21 (91.3)	<0.001*
Overall pediatric services[c]	11 (61.1)	2 (8.7)	

[a]Values were given as mean (SD); [b]values were given as median (IQR); [c]values were given as n (%); SD: Standard deviation; IQR: Interquartile range; WBC: White blood cell; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; PLT: Platelets; CRP: C-reactive protein; PCT: Procalcitonin.

Since colistin is eliminated from the kidneys, the most common side effect, which may lead to the discontinuation of colistin treatment, is nephrotoxicity. However, since the drug's first market introduction, a safer area of use has emerged thanks to purified colistin, colistin sulfate instead of colistimethate, determination of a more appropriate dosage schedule considering renal functions, and development of pediatric intensive care follow-up.[24] After intravenous administration of the prodrug colistimethate sodium, colistimethate sodium is hydrolyzed to the active drug colistin.[25] The colistin nephrotoxicity mechanism is considered damaging to renal tubular cells, probably due to the detergent effects on the cell membrane and increasing permeability.[26] In our study, we found the frequency of nephrotoxicity at 34.1%. While Sahbudak Bal et al. detected nephrotoxicity in 10.5%, Celebi et al. and Karbuz et al. reported in only 1 patient (5.8%).[10,18,27] Our high nephrotoxicity rate may be attributed to concomitant antibiotic usage, including aminoglycosides, glycopeptides, and antifungal agents. Concomitant nephrotoxic drugs that our patients used were ranitidine (29.2%), levetiracetam (26.8%), epinephrine (24.4%), topiramate (9.7%), caffeine (7.3%), dexmedetomidine (7.3%), and tacrolimus (4.8%) which might aggravate the renal injury. Although we did not find a statistically significant relation between nephrotoxicity and the usage of nephrotoxic agents, these agents may still contribute to renal injury that we did not prove through statistics because of our small sample size.

Similar studies mentioned above were conducted with critically ill patients admitted to ICUs as well, and the same risk factors for mortality and nephrotoxicity were in question. At this point, there needs to a rise in a comprehensive evaluation regarding the definitions of nephrotoxicity. In Karbuz et al.'s and Sahbudak Bal et al.'s study, nephrotoxicity was defined as an increase >50% of the baseline creatinine level compared with the value at treatment initiation or as a decline in renal function.[10,18] However, Celebi et al. defined it as an increase in serum creatinine at least 2-fold of the baseline or a 30% decrease of creatinine clearance.[27] On the other hand, we accepted oliguria alone (<0.5 mg/kg/h × 6 h) as nephrotoxicity according to RIFLE criteria. The diversity of definitions within research might affect the results.

The other reported adverse effect of colistin is neurotoxicity. The high lipid content of colistin is associated with the interaction of the neurologic structures.[28] Hypoxia, concurrent medication usage, and impaired renal function precipitate the occurrence of neurotoxicity.[24] Karageorgos et al. reported neurotoxicity due to colistin in two patients with tonic-clonic seizures on the 1st day of colistin. Neurotoxicity was detected in only 1 patient (2.4%) in our study.[23] The patient in question was diagnosed with hemophagocytic lymphohistiocytosis but died soon after the newly developed facial paralysis on the 17th day of colistin without enlightened whether it is peripheral or central. Although the facial paralysis appeared late in the days after colistin had been administered, it was accepted as neurotoxicity since no other cause existed.

There are several limitations regarding our study. First, the sample size was relatively small and might be insufficient to determine the general population. Second, most of the patients were critically ill, having multiorgan failure, and multiple concomitant antibiotic usages, affecting the infection-related mortality and nephrotoxicity ratio. Third, the data obtained retrospectively from the hospital records were insufficient to detect the microbiological elimination. As a result, we could not determine the clinical improvement of the patients. Nevertheless, we think that the study would provide beneficial insights into using colistin in pediatric patients.

Conclusion

MDR-GNIs are related to high mortality, especially in intensive care units. Initializing colistin therapy can be considered as a means of treatment against these challenging microorganisms. Adverse effects, especially nephrotoxicity, may develop during colistin treatment, and it is vital to follow up on renal functions and daily urinary output. For those reasons, treating patients with MDR by colistin are like any port in a storm for clinicians.

Disclosures

Ethics Committee Approval: Ethics committee approval was obtained for non-interventional clinical research on January 23, 2020, and with the 2020/1–14 protocol number at our hospital's ethics committee. All investigational procedures conform to the Declaration of Helsinki guiding principles.

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References

1. Cai Y, Lee W, Kwa AL. Polymyxin B versus colistin: an update. Expert Rev Anti Infect Ther 2015;13:1481–97. [CrossRef]
2. Storm DR, Rosenthal KS, Swanson PE. Polymyxin and related peptide antibiotics. Annu Rev Biochem 1977;46:723–63. [CrossRef]
3. Stansly PG, Shepherd RG, White HJ. Polymyxin: a new chemotherapeutic agent. Bull Johns Hopkins Hosp 1947;81:43–54. [CrossRef]
4. Ortwine JK, Kaye KS, Li J, Pogue JM. Colistin: understanding and applying recent pharmacokinetic advances. Pharmacotherapy 2015;35:11–6. [CrossRef]
5. Pastor M, Basas J, Vairo C, Gainza G, Moreno-Sastre M, Gomis X, et al. Safety and effectiveness of sodium colistimethate-loaded nanostructured lipid carriers (SCM-NLC) against P. aeruginosa: in vitro and in vivo studies following pulmonary and intramuscular administration. Nanomedicine 2019;18:101–11. [CrossRef]
6. Falagas ME, Karageorgopoulos DE. Pandrug resistance (PDR), extensive drug resistance (XDR), and multidrug resistance (MDR) among Gram-negative bacilli: need for international harmonization in terminology. Clin Infect Dis 2008;46:1121–2. [CrossRef]
7. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant klebsiella pneumoniae bacteremia. Antimicrob Agents Chemother 2017;61:e00883–17.
8. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204–12.
9. Cheng CY, Sheng WH, Wang JT, Chen YC, Chang SC. Safety and efficacy of intravenous colistin (colistin methanesulphonate) for severe multidrug-resistant Gram-negative bacterial infections. Int J Antimicrob Agents 2010;35:297–300. [CrossRef]
10. Sahbudak Bal Z, Kamit Can F, Yazici P, Berna Anil A, Duyu M, Yilmaz Ciftdogan D, et al. The evaluation of safety and efficacy of colistin use in pediatric intensive care unit: Results from two reference hospitals and review of literature. J Infect Chemother 2018;24:370–5. [CrossRef]
11. Ozsurekci Y, Aykac K, Cengiz AB, Bayhan C, Sancak B, Karadag Oncel E, et al. Is colistin effective in the treatment of infections caused by multidrug-resistant (MDR) or extremely drug-resistant (XDR) gram-negative microorganisms in children? Diagn Microbiol Infect Dis 2016;85:233–8. [CrossRef]
12. Tamma PD, Newland JG, Pannaraj PS, Metjian TA, Banerjee R, Gerber JS, et al. The use of intravenous colistin among children in the United States: results from a multicenter, case series. Pediatr Infect Dis J 2013;32:17–22. [CrossRef]
13. Mohammed N, Savardekar AR, Patra DP, Narayan V, Nanda A. The 21st-century challenge to neurocritical care: the rise of the superbug Acinetobacter baumannii. A meta-analysis of the role of intrathecal or intraventricular antimicrobial therapy in reduction of mortality. Neurosurg Focus 2017;43:E8. [CrossRef]
14. Canturan SY, Yilmazer N, Sarikaya R, Avsar Z, Ertek M, Uyaner I. Retrospective assessment of ventilator-associated pneumonias due to Acinetobacter baumannii in an oncology hospital. Sisli Etfal Hastan Tip Bul 2021;55:193–6. [CrossRef]
15. Paksu MS, Paksu S, Karadag A, Sensoy G, Asilioglu N, Yildizdas D, et al. Old agent, new experience: colistin use in the paediatric Intensive Care Unit--a multicentre study. Int J Antimicrob Agents 2012;40:140–4. [CrossRef]
16. Levin AS, Barone AA, Penço J, Santos MV, Marinho IS, Arruda EA, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. Clin Infect Dis 1999;28:1008–11.
17. Lakshmi KS, Jayashree M, Singhi S, Ray P. Study of nosocomial primary bloodstream infections in a pediatric intensive care unit. J Trop Pediatr 2007;53:87–92. [CrossRef]
18. Karbuz A, Özdemir H, Yaman A, Kocabaş BA, Odek Ç, Güriz H, et al. The use of colistin in critically ill children in a pediatric intensive care unit. Pediatr Infect Dis J 2014;33:e19–24. [CrossRef]
19. Batalla-Bocaling CAP, Tanseco PVP, Chua ME. Treatment outcome and predictors of poor clinical response in extensively drug-resistant gram-negative urinary tract infection among children: A single-institution experience. Can Urol Assoc J 2021;15:E148–52. [CrossRef]
20. Li KL, Abad CLR. The clinical profile and outcomes of adult patients given intravenous colistin for multidrug-resistant gram negative infections in a Philippine tertiary hospital. Int J Infect Dis 2020;93:9–14. [CrossRef]
21. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis 2018;18:391–400. [CrossRef]
22. Karli A, Paksu MS, Karadag A, Belet N, Paksu S, Guney AKet al. Colistin use in pediatric intensive care unit for severe nosocomial infections: experience of an university hospital. Ann Clin Microbiol Antimicrob 2013;12:32. [CrossRef]

23. Karageorgos SA, Bassiri H, Siakallis G, Miligkos M, Tsioutis C. Intravenous colistin use for infections due to MDR Gram-negative bacilli in critically ill paediatric patients: a systematic review and meta-analysis. J Antimicrob Chemother 2019;74:2497–506.
24. Spapen H, Jacobs R, Van Gorp V, Troubleyn J, Honoré PM. Renal and neurological side effects of colistin in critically ill patients. Ann Intensive Care 2011;1:14. [CrossRef]
25. Bergen PJ, Li J, Rayner CR, Nation RL. Colistin methanesulfonate is an inactive prodrug of colistin against Pseudomonas aeruginosa. Antimicrob Agents Chemother 2006;50:1953–8. [CrossRef]
26. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care 2006;10:R27. [CrossRef]
27. Celebi S, Hacimustafaoglu M, Koksal N, Ozkan H, Cetinkaya M. Colistimethate sodium therapy for multidrug-resistant isolates in pediatric patients. Pediatr Int 2010;52:410–4. [CrossRef]
28. Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med 1970;72:857–68. [CrossRef]