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

Objective: 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.

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

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.

The polymyxins were derived from a bacterium called Paenibacillus polymyxa and classified in polypeptide anti-
biotics. Colistin was developed in the 1940s, but it was withdrawn from usage due to its high toxicity.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. Therefore, in severely ill patients, colistin high nephrotoxic and neurotoxic effects should be taken into consideration. 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-clostoemty, 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. 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. 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. Neurotoxicity may manifest itself as vertigo, dizziness, seizures, diplopia, ataxia, altered mental status, delirium, paresthesia, and neuromuscular blockade.

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 ($\chi^2$) 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 non-parametric 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 leveticetam, 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 pneumonias 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
| Case | Diagnoses                      | Site of infection | Medical devices                                | Underlying facilitating factor | Microorganisms | Nephrotoxicity | Colistin dosage (mg/kg/day) | Microbiological eradication | 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 | CV, 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               | CV, tracheostomy, urinary catheter            | Motorcycle crash               | AB             | No            | N/A                      | No                         | Yes     | Yes             |
| 7    | VAP                           | BAL               | Tracheostomy                                  | Respiratory aspiration, asphyxia| AB             | No            | 4.32                     | N/A                        | Yes     | Yes             |
| 8    | Urosepsis                     | Urine             | None                                          | None                           | KP             | No            | N/A                      | Yes                        | Yes     | Yes             |
| 9    | CNS infection, pneumonia      | BAL               | ETT, EVD                                      | Epilepsy, post-resuscitation   | KP             | No            | N/A                      | Exitus                     | No      | 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                                      | Sequelaue of HIE               | PA             | No            | 5                       | No                         | Cured   | No              |
| 13   | Gastroenteritis, pneumonia    | Blood             | None                                          | Sequelaue of HIE               | AB             | No            | 3                       | Yes                        | Yes     | Yes             |
| 14   | Septic shock                  | Blood             | CV, 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               | CV, 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             | CV, ETT                                       | Prematurity                    | AB             | No            | N/A                      | Yes                        | Cured   | Yes             |
| 20   | VAP                           | Catheter          | CV, tracheostomy                              | Hypotonic infant               | AB             | Yes           | 5                       | No                         | Cured   | No              |
| 21   | Sepsis                        | CSF               | CV, 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                    | -                 | CV, urinary catheter                          | Foreign body aspiration, right lower lobectomy | -             | No            | 4.8                      | N/A                        | Cured   | Yes             |
| 24   | Septic shock                  | BAL               | CV, ETT, PEG, urinary catheter                | Epilepsy, MMR                  | AB             | No            | N/A                      | No                         | Exitus  | No              |
| 25   | Septic shock                  | Blood             | CV, 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             |
and clinical success was assessed as clinical improvement of the patients, absence of radiologic deterioration, and negative culture. In the study of Anne et al., in which 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. 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%. 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. 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%. 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%. 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. 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.
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.[23] 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 (2.4%) in our study.[23] 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%), dexamethasone (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 arise 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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