European Journal of Pediatrics (2024) 183:3407–3415
https://doi.org/10.1007/s00431-024-05607-2

RESEARCH

Investigation of colistin utilization in the treatment of multidrug-resistant gram-negative nosocomial bloodstream ınfections in children and literature review

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Received: 24 December 2023 / Revised: 12 April 2024 / Accepted: 10 May 2024 / Published online: 20 May 2024

Abstract

This retrospective study aimed to assess the effectiveness and safety of colistin used in combination therapy for treating nosocomial bloodstream infections caused by multi-drug resistant gram-negative pathogens in pediatric patients. Patients aged between 1 month and 18 years consecutively hospitalized with healthcare-associated bloodstream infections necessitating the administration of intravenous colistin at Dr. Sami Ulus Training and Research Hospital between January 2015 and January 2020 were included in the study. Patient-specific detailed clinical information, prognoses, and laboratory findings on days 1, 3, and 7 of colistin treatment were obtained from medical records. The study included 45 pediatric patients receiving intravenous colistin; 26 (57.8%) were male and 19 (42.2%) were female, with a median age of 18 months. While the clinical response was observed at 82.2% and microbiological response at 91.1% with colistin treatment, two patients (4.4%) discontinued treatment due to side effects without assessing treatment response. The most common adverse effect associated with the use of colistin was nephrotoxicity, which occurred in eight patients (17.8%). Among these patients, only one had pre-existing chronic kidney failure.

Conclusion: Colistin used in combination therapy may be effective and safe for treating nosocomial infections caused by multi-drug resistant gram-negative bacteria in pediatric patients, who often have high mortality rates and limited treatment options.

What is Known:
- *Colistin is an antibacterial agent used in the treatment of infections caused by multidrug-resistant Gram-negative bacteria (MDR-GNB) and is associated with significant adverse effects such as nephrotoxicity.*
- *The increasing prevalence of hospital-acquired infections has led to the expanded use of colistin in clinical practice.*

What is New:
- *The study demonstrates a high clinical and microbiological response rate to combination therapy with colistin in the treatment of infections caused by MDR-GNB.*
- *The study highlights the importance of monitoring nephrotoxicity in pediatric patients receiving colistin, showing that these effects can be reversible after treatment cessation.*

Keywords Children · Colistin · Clinical response · Microbiological response · Side effect

Abbreviations

BUN	Blood urea nitrogen
CMS	Colistimethate sodium
CRP	C-reactive protein
KDIGO	Kidney Disease: Improving Global Outcomes
MDR-GNB	Multidrug-resistant gram-negative bacteria
WBC	Peripheral blood leukocyte count

Communicated by Tobias Tenenbaum

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Introduction

Colistin, a member of the polymyxin family, is an antibacterial agent with bactericidal activity. It is used to treat respiratory tract infections caused by multidrug-resistant Gram-negative bacteria (MDR-GNB) in cystic fibrosis patients. The increasing prevalence of nosocomial infections caused by these pathogens has resulted in the expanded use of colistin in clinical practice [1, 2].

This study investigates the efficacy and safety of systemic colistin treatment in non-cystic fibrosis children. While there is existing research on colistin's effectiveness in adults, limited

information is available regarding its use in non-cystic fibrosis children. Thus, this study aims to fill this research gap by examining the outcomes of colistin treatment in this specific population.

Patients and methods

Study design and patient selection

All patients aged between 1 month and 18 years consecutively hospitalized with healthcare-associated bloodstream infections necessitating the administration of intravenous colistin at Dr. Sami Ulus Training and Research Hospital between January 2015 and January 2020 were included in the study. We excluded newborns, cystic fibrosis patients, those who received empirical colistin treatment, and individuals with short-term colistin therapy. Patients were categorized into different age groups, and data regarding demographics, medical history, comorbidities, antibiotic usage, medical device usage, bloodstream culture results, antibiotic susceptibility of pathogens, details of colistin treatment, usage of nephrotoxic drugs, administration of sedative or analgesic agents, infection type, colistin dosage, treatment duration, side effects, outcomes of antimicrobial treatment, and patient prognosis were collected from medical records.

Microbiological methods

Bloodstream cultures were collected using aseptic techniques and processed using BACTEC 9240 and BACTEC 9120 devices. Isolated organisms were identified using the PHOENIX 100 system, and antibiotic susceptibility testing was performed. Antibiotic susceptibilities were determined using the microdilution method, and the results were interpreted according to the criteria provided by the Clinical and Laboratory Standards Institute (CLSI).

Definition of multidrug-resistant gram-negative bacterial pathogens

MDR-GNB were defined as those exhibiting resistance to at least three classes of antibiotics. Nosocomial infections, catheter-related infections, and ventilator-associated pneumonia were diagnosed based on criteria set by the Centers for Disease Control and Prevention (CDC) in the United States [3].

Colistin treatment

All patients received intravenous infusions of colistimethate sodium (CMS) at a dosage of 5 mg/kg/day (Each vial contained approximately 1 million international units (IU) of CMS (equivalent to 80 mg of CMS)), divided into three doses. Colistin was used as targeted therapy exclusively when the strain exhibited susceptibility to colistin. If there existed another antibiotic option demonstrating in-vitro susceptibility (for instance, in strains not producing carbapenemase), colistin wasn't the sole treatment alternative. However, it was incorporated into the therapy in instances where despite in-vitro susceptibility being observed, there was no clinical or microbiological response to the first-line antimicrobial agent. The treatment response was evaluated by considering clinical improvement and/or microbiological response and/or regression of acute phase reactants. Clinical improvement was determined by the resolution or improvement of initial symptoms, vital signs, fever, and physical examination findings. The microbiological response was indicated by negative bloodstream cultures. Additionally, acute phase reactants such as peripheral blood leukocyte count (WBC) and C-reactive protein (CRP) were monitored, and their regression to normal values during treatment indicated improvement.

Nephrotoxicity was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. According to KDIGO criteria, nephrotoxicity is defined by significant increases in serum creatinine levels, substantial decreases in glomerular filtration rate, or marked reductions in urine output. These criteria are internationally recognized standards used to assess kidney function and identify kidney damage associated with nephrotoxic agents or conditions [4].

Data analysis

Data analysis was performed using SPSS 22.0 statistical software. Variables' normality was assessed via methods such as histograms and the Kolmogorov-Smirnov test. Descriptive statistics, including mean, standard deviation, minimum, and maximum values, were calculated for continuous variables. Categorical variables were presented as numbers and percentages. Student's t-test compared independent groups, while the chi-square test analyzed variables determined by ratios. A p-value below 0.05 indicated statistical significance.

Findings

Patients' demographic information and clinical conditions

The study included 45 patients aged 1–18 years who were administered colistin due to positive bloodstream cultures indicating MDR-GNB. Among the patients, 57.8% were male and 42.2% were female, with a mean age of 18 months. Analysis based on age groups demonstrated an increase in colistin usage as the age groups decreased ($p = 0.003$). Underlying diseases were present in 88.9% of the patients, with the most common conditions being chronic

neurological or neuromuscular diseases (33.3%), congenital heart diseases (13.3%), and malignancies (13.3%). The average duration of colistin treatment was 12.80 ± 10.36 days, with a median duration of 10 days (2–46 days). It was found that the negative transformation duration of bloodstream cultures was significantly longer in patients using mechanical ventilation (10.3 ± 1.5 days) compared to those not using ventilation (7.8 ± 0.9 days) (p = 0.005). Table 1 shows the microorganisms isolated in the bloodstream cultures of patients and the source of infection.

In *Klebsiella pneumoniae* cases, colistin was the sole in-vitro effective agent in 53% (10/19) of the cases, in *Acinetobacter baumannii* cases it was 57% (8/14), in *Pseudomonas aeruginosa* cases it was 60% (3/5), in *Escherichia coli* cases it was 75% (3/4), and in *Sphingomonas paucimobilis* cases it was 100% (2/2), together with *Enterobacter cloacae* cases (1/1), which was 100%, as well. Overall, colistin was used in 60% of the patients (27/45) when no other effective agent was available, in 33% of the patients (15/45) with only one in-vitro effective agent, and in 7% of the patients (3/45) with two in-vitro effective agents. Colistin was administered to all patients as a part of combination therapy. The most commonly used Gram-negative effective antibiotics in combination therapy with colistin were meropenem in 75.5% of the patients (34/45), aminoglycosides in 22.2% of the patients (10/45), ciprofloxacin in 17.8% of the patients (8/45), and piperacillin-tazobactam in 13.3% of the patients (6/45). In three patients, two different bacterial agents were isolated from bloodstream cultures, and one of these agents was susceptible to in-vitro colistin. The second agents were *Serratia marcescens* and *Burkholderia cepacia*, which are intrinsically resistant to colistin. It was observed that these agents were susceptible to meropenem according to their antibiograms, and colistin was added to the treatment while meropenem was already in use. All three of these patients survived. In the bloodstream cultures of the remaining 42 patients, only one bacterial agent susceptible to in-vitro colistin was isolated.

Clinical follow-up and efficacy of colistin

Among the patients treated with colistin, 6 of them didn't achieve clinical response and died. Bloodstream culture remained positive in 2 cases, and treatment could not be continued in 2 cases due to side effects. The clinical response rate of colistin treatment was calculated as 82.2%, while the microbiological response rate was determined as 91.1%. Colistin treatment efficacy in combination therapy was assessed using WBC and average CRP levels on treatment initiation and the 3rd day (Table 2). Colistin treatment significantly reduced average CRP levels by the 3rd day ($p < 0.001$), while average WBC showed no significant change between the 1st and 3rd days ($p = 0.082$). Treatment duration increased with elevated WBC ($p = 0.005$), but no correlation was observed between CRP levels and treatment duration ($p > 0.05$). When patients were divided into two groups based on clinical and microbiological responses, the average age of responders was higher than non-responders ($p = 0.025$). Patients achieving clinical and microbiological responses showed no significant difference in WBC count and CRP levels compared to non-responders ($p > 0.05$).

Table 1 Microorganisms isolated in blood cultures of patients and the source of infection

Microorganism	**n**	**%**
Klebsiella pneumoniae		
Carbapenemase positive *K. pneumoniae*	9	20.0
Carbapenemase negative *K. pneumoniae*	9	20.0
Acinetobacter baumannii	13	28.9
Pseudomonas aeruginosa	4	8.9
Escherichia coli	4	8.9
Sphingomonaspaucimobilis	2	4.4
Enterobacter cloacae	1	2.2
Pseudomonas aeruginosa + *Serratia marcescens*	1	2.2
Acinetobacter baumannii + *Serratia marcescens*	1	2.2
Carbapenemase positive *K. pneumoniae* + *Burkholderia cepacia*	1	2.2
Source of infection	**n**	**%**
Pneumonia	20	44.4
Ventilator-associated pneumonia (VAP)	16	35.5
Non-ventilator-associated pneumonia	4	8.8
Primary bloodstream infection	19	42.2
Central venous catheter-related bloodstream infection	5	11.1
Port catheter-associated bloodstream infection	1	2.2

Table 2 Average Peripheral blood leukocyte count and CRP level at the addition of colistin treatment and at the end of day 3 of treatment, as well as Acute Kidney Function Values following colistin treatment monitoring and discontinuation

	1st day of treatment	End of 3rd day	After 7 days following the discontinuation of treatment	p
WBC (/mm3) mean (min–max)	12.157 (850–26.500)	11.618 (1200–22.000)	-	0.397
CRP (mg/L) mean (min–max)	60 (3–257)	17.7 (3–235)	-	**< 0.001**
Creatine(mg/dL) mean (min–max)	0.38 (0.23–1,80)	0.41 (0.26–2.30)	0.38 (0,21–2,10)	-
BUN (mg/dL) mean (min–max)	10 (0 – 46)	10 (2–41)	9.8 (2–43)	-

WBC white blood cell, *CRP* C-reactive protein, *BUN* Blood urea nitrogen

Adverse effects associated with colistin use

The most common adverse effect associated with the use of colistin was nephrotoxicity, which occurred in eight patients (17.8%). Among these patients, only one had pre-existing chronic kidney failure. The average age of patients who developed nephrotoxicity was 58.12 ± 43.80 months, while the average age of patients who did not develop nephrotoxicity was 45.65 ± 68.33 months. There was no significant difference in age distribution between the two groups ($p = 0.10$). Among 45 patients, 40 of them had at least one additional nephrotoxic agent added alongside colistin treatment. Meropenem was the most commonly used additional nephrotoxic agent in 34 patients (75.5%), followed by furosemide in 22 patients (48.8%), vancomycin in 16 patients (35.5%), and aminoglycosides in 10 patients (22.2%) (with some patients using two or more nephrotoxic agents simultaneously). Nephrotoxicity was diagnosed in eight patients on the third day of colistin treatment. Among these 8 patients, 5 (11.1%) were classified as stage 1 according to the KDIGO criteria, and 3 (6.7%) were classified as stage 3.

The results of renal function tests conducted on the first day, third day, and seventh day after discontinuation of colistin therapy are presented in Table 2. An increase in mean serum creatinine levels was observed on the first and third days of colistin therapy ($p < 0.001$), while no significant difference was found in serum blood urea nitrogen (BUN) levels ($p > 0.05$). After 6–7 days of colistin cessation, a decrease in serum creatinine levels was observed, returning to pre-treatment values ($p < 0.001$).

The duration of colistin use was found to be 14.19 ± 10.81 days in patients with nephrotoxicity and 6.38 ± 4.00 days in those without nephrotoxicity. There was a significant difference in the duration of colistin use between patients who developed nephrotoxicity ($p = 0.021$). One patient experienced transient hypertransaminasemia, while no cases of neurotoxicity or hypersensitivity reactions to colistin were observed.

Mortality

The characteristics of patients who died are presented in Table 3. There was no statistically significant association between underlying disease diagnosis groups and mortality ($p = 0.753$). Among patients who developed nephrotoxicity during colistin therapy, no significant association was found with mortality ($p = 0.286$). There was also no significant difference in mortality between patients with and without central venous catheter and mechanical ventilator use ($p = 0.160$). Regarding the change in WBC and CRP levels between days 1 and 3 of colistin therapy, there was no statistically significant difference in mortality ($p = 0.457$ and $p = 0.909$, respectively). However, it was observed that patients who died had a statistically longer duration of hospital stay before colistin treatment ($p = 0.029$).

Discussion

In the context of the renewed clinical utilization of colistin, Table 4 provides an overview of the largest pediatric studies conducted thus far. Our study stands out as one of the most comprehensive real-life datas conducted in the pediatric population, focusing on the effectiveness and safety of colistin. Previous studies evaluating colistin's efficacy and safety included patients who received empirical treatment without specifying the causative agent or isolation areas [2, 5–8]. In contrast, our study specifically examined patients receiving combination therapy with colistin based on antibiogram results of MDR-GNB isolated from bloodstream cultures. Therefore, our study offers a more precise evaluation of colistin's effectiveness.

In a previous study, 63.3% of the patients were under 3 years of age, and 46.8% were below 1 year of age [8]. Similarly, in our study, 42.2% of the patients were below 1 year of age, and 66.6% were under 3 years of age. The findings

Table 3 The characteristics of patients who died while under colistin treatment

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (months)	1	2	2	3	5	56
Gender	Male	Male	Female	Male	Male	Male
Underlying Disease	None	Cerebral palsy	Congenital heart disease	Chronic kidney failure	Congenital heart disease	Acute lymphoblastic leukemia
Admission Diagnosis	Primary bloodstream infection	Primary bloodstream infection	Ventilator-associated pneumonia	Ventilator-associated pneumonia	Ventilator-associated pneumonia	Central venous catheter-related bloodstream infection
Pre-colistin antimicrobial treatment	Pipercillin-tazobactam + vancomycin	Meropenem + vancomycin	Meropenem + vancomycin	Meropenem + vancomycin	Pipercillin-tazobactam	Meropenem + vancomycin + caspofungin
In-vitro effective agents against bacterial pathogens	Pipercillin-tazobactam + colistin	Meropenem + colistin	Colistin	Meropenem + colistin	Colistin	Colistin
Producing multi-drug resistant organism	*A. baumannii*	Carbapenemase-positive *Klebsiella*	Carbapenemase-positive *Klebsiella*	*E. coli*	*A. baumannii*	Carbapenemase-positive *Klebsiella*
Time to negative blood culture (days)	3	4	4	5	No clearance observed	No clearance observed
Mortality after bacteremia (days)	7	18	4	16	3	4
Nephrotoxicity	None	None	None	None	Grade 1	Grade 3
Neurotoxicity	None	None	None	None	None	None
Mechanical ventilation	None	None	Present	Present	Present	None
Central venous catheter	None	None	Present	None	Present	Present
Percutaneous enterogastric	None	Present	None	None	None	None

Table 4 The largest pediatric studies published following the resurgence of colistin use in clinical practice

STUDY	Study Year	Patient Count	Age mean (min–max)	Duration of Treatment (days)	Positive Response (%)	Nephrotoxicity (%)	Neurotoxicity (%)	Mortality (%)
Iosifidis et al. [9]	2009	13	5 years (22 days-14 years)	1–133	84.2	5	0	23
Falagas et al. [10]	2009	7	7.7 years (14 months-13 years)	10.7 (2–23)	85.7	0	0	28.5
Kapoor et al. [22]	2013	50	36 months (1 month-12 years)	-	72	10	-	28
Karlı et al. [5]	2013	35	36 months (3 months-17 years)	14 (19.8 ± 10.3)	68.3	7.3	-	14.6
Paksu et al. [2]	2013	79	30 months (3 months-18 years)	17.2 ± 8.4 (2–62)	74.7	2.3	2.3	13.8
Karbuz et al. [6]	2014	29	17 months (3 months-18 yerars)	12 (2–37)	73.7	2.6	-	26.3
Karaaslan et al. [7]	2016	61	12 months (0–216 months)	12 (3–45)	88.6	1.6	0	11.4
Bal et al. [8]	2017	94	55.9 months (41.2 -70.1 months)	12.5 ± 6.4 (2–30)	76	10.5	0	14.4
Our Study	2021	45	18 months (1 month- 18 years)	10 (2–46)	86.7	17.8	0	13.3

suggest an increasing utilization of colistin in younger patients, particularly infants. Infants are more susceptible to infections due to their immature immune systems, and the early and severe manifestation of infection symptoms in this age group contributes to the frequent use of colistin in infants. This trend highlights the need for careful monitoring and stewardship of antimicrobial usage, especially in vulnerable populations such as infants, to prevent the emergence of antimicrobial resistance and ensure effective treatment of infections.

In several retrospective studies, *Acinetobacter* spp. has been identified as the most common causative agent of nosocomial infections [2, 5–10]. Following *Acinetobacter* spp., *P.aeruginosa* and *K.pneumoniae* were found to be the second and third most common infectious agents, respectively. However, in our study, the most common pathogen was *K.pneumoniae*, followed by *A. baumannii*, *P. aeruginosa*, and *E. coli.* When we examined the surveillance data of the infection control committee of Dr. Sami Ulus Training and Research Hospital between 2009 and 2019 regarding nosocomial infections, *Klebsiella* spp. was identified as the most common bacterial agent. This variation in the most common pathogen in our study is believed to be the primary reason for the difference compared to other studies.

In a retrospective cohort study, colistin monotherapy was compared with colistin-meropenem combination therapy, the results showed no statistically significant difference in terms of clinical infection response and the development of nephrotoxicity between the two treatment approaches. However, colistin-meropenem combination therapy demonstrated a favorable survival rate [11]. In another study focusing on non-cystic fibrosis patients, a synergistic effect was found when colistin was combined with carbapenems, piperacillin-tazobactam, and ciprofloxacin [12]. Combining colistin with other antibacterial agents has been emphasized as an effective strategy for preventing colistin resistance [11, 12]. Carbapenems, especially in combination therapies with colistin, are favored due to the time-dependent increase in colistin's effectiveness in the bacterial cell membrane. A review comparing studies on colistin resistance and combination therapy indicated that the colistin-carbapenem combination exhibited low antagonism, high synergy, and low rates of resistance development, particularly against *A. baumannii* [13]. In our study, the most commonly employed treatment approach was the colistin-carbapenem combination, followed by the colistin-carbapenem-glycopeptide combination. As colistin was not used as monotherapy, a direct comparison with combination therapy could not be conducted.

In our pediatric patient group study, initiating intravenous colistin therapy based on culture results yielded a high rate of microbiological (91.1%) and clinical (82.2%) response in the treatment of nosocomial infections. A retrospective study with 35 children reported a positive outcome rate of 68.3%. Another study conducted with 61 patients showed a positive outcome rate of 88.6% [5–7]. A study involving adult patients reported a clinical and microbiological response rate of 56% [14]. These pediatric studies, including our own, demonstrate higher efficacy of colistin in children compared to adults.

In our study, a significant decrease in CRP levels was observed on the 3rd day of colistin treatment compared to the 1st day, with no significant difference in the mean WBC

count. A multicenter retrospective study reported a slight increase in CRP and procalcitonin levels at the start of treatment, followed by a rapid decrease throughout the treatment period [2]. Another study compared CRP and procalcitonin levels before and after empirical colistin treatment in 121 premature infants, showing a significant decrease after treatment [15]. The combined results of these studies indicate that the use of CRP levels as an acute-phase reactant during colistin treatment has been beneficial.

The main adverse effects of colistin treatment include nephrotoxicity and neurotoxicity [16]. One study reported a nephrotoxicity rate of 0%, while another study in pediatric intensive care units reported a rate of 10.5% [8]. Among studies involving adult patients, one reported a nephrotoxicity rate of 18.6% due to colistin [17], while in a retrospective study, nephrotoxicity was observed in 14.3% of adult patients with nosocomial infections caused by MDR-GNB, excluding colistin usage [18]. A review article examining the effects and side effects of colistin indicated a lower incidence of nephrotoxicity in pediatric studies compared to adults, along with higher reported clinical efficacy and survival rates in children [19]. In our study, the nephrotoxicity rate was found to be 17.8%, which was higher compared to other pediatric studies. A multicenter retrospective pediatric study reported a nephrotoxicity rate of 10%, primarily occurring within the first week, especially within the initial three days [2]. Another pediatric retrospective study found a nephrotoxicity rate of 10.5%, with 63% of patients experiencing nephrotoxicity on the third day of treatment [8]. Additionally, a retrospective study identified a nephrotoxicity rate of 10%, occurring between the third and sixth days of treatment [10]. Various other studies have also indicated that colistin nephrotoxicity is reversible in both adult and pediatric patients [1, 20]. In our study, nephrotoxicity occurred within the first three days of treatment and could be identified by an increase in serum creatinine levels, while no significant change was observed in serum BUN levels. Additionally, it was observed that the average serum creatinine level returned to pre-treatment levels approximately 6–7 days after discontinuation of colistin. In our study conducted without a control group, it is not possible to determine conclusively whether the increase in creatinine levels was due to colistin nephrotoxicity or potentially to the concomitant use of nephrotoxic agents or other factors (such as septic shock or pre-renal failure). We believe that further research is necessary in this regard. However, we believe that daily monitoring of serum creatinine levels during the first three days after initiating colistin treatment could be beneficial in detecting nephrotoxicity. Additionally, we suggest that the side effects of colistin nephrotoxicity may be reversible.

A prospective study examining pediatric patients treated with intravenous colistin reported that the concomitant use of nephrotoxic agents such as meropenem, aminoglycosides, vancomycin, and furosemide-facilitated renal dysfunction led to severe clinical conditions associated with nephrotoxicity [5]. Similarly, a retrospective study also indicated that the concomitant use of nephrotoxic agents with colistin treatment facilitated renal dysfunction and led to severe clinical conditions such as sepsis, septic shock, and burns [12]. In our study, all patients were diagnosed with sepsis, and almost all of them were using colistin therapy in combination with other nephrotoxic agents. Several factors might contributed to the higher rate of nephrotoxicity compared to other pediatric studies. These factors include the combination of colistin treatment with other nephrotoxic agents, a higher prevalence of underlying diseases and comorbidities, and the use of KDIGO criteria, which are more sensitive in detecting nephrotoxicity in children. Similarly to other studies in the literature, our study did not observe an association between nephrotoxicity developed during colistin treatment and mortality [19]. In the clinical context of the study, which includes critically ill patients with documented gram-negative bloodstream infections, the relatively high percentage (35.5%) of vancomycin administration can be justified despite the lack of gram-negative activity. This is because empirical use of vancomycin for broad-spectrum treatment is initiated before the identification of the gram-negative pathogen, and there may be a reluctance to discontinue broad-spectrum empiric treatment in these critically ill patients until the in vivo efficacy of colistin is observed.

Colistin's potential side effect includes neurotoxicity, yet it's rarely reported in pediatric studies [2, 10]. Our study didn't detect neurotoxicity symptoms. Notably, patients used medications like analgesics, sedatives, and neuromuscular blocking agents, which could also induce neurotoxicity. It's speculated that these medications might have concealed any signs of neurotoxicity.

Nosocomial infections caused by MDR-GNB pose a significant threat to patient health and can result in high morbidity and mortality rates [1, 21]. Several studies focusing on the pediatric population have investigated the outcomes of intravenous colistin treatment. In a retrospective analysis of 61 children treated with empirical or culture-guided colistin, the mortality rate was reported as 11.4% over an average treatment duration of 12 days [7]. Another study involving seven non-cystic fibrosis children reported the highest mortality rate of 28% after an average treatment duration of 10.7 days [10]. In our study, the 13.3% mortality rate is consistent with findings from other studies. Importantly, all deceased patients in our study showed no clinical or microbiological response after colistin was added to their

treatment regimen. This underscores the significant impact of colistin on survival and mortality outcomes.

Study limitations include retrospective design, absence of a control group, single-center nature, and heterogeneous patient population.

Conclusion

In conclusion, considering the severity and mortality of nosocomial infections caused by MDR-GNB in pediatric patients, who have high mortality rates and limited treatment options, colistin used in combination therapy might be considered a reliable option due to its acceptable level of side effects, the potential for reversibility of these side effects upon treatment cessation, and its high survival rate. Further broad studies with a control group for the treatment of MDR-GNB may highlight the efficacy and safety of colistin in pediatric patients.

Authors' contributions All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Dr. Cankat Geniş, Dr. Ayşe Kaman, Dr. Betül Öztürk, and Dr. Gönül Tanır. The first draft of the manuscript was written by Dr. Cankat Geniş and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Dr. Sami Ulus Maternity and Children's Research and Training Hospital (2020/No:E-20/12-43).

Consent to participate Informed consent was obtained from all individual participants included in the study. Written informed consent was obtained from the parents.

Consent to publish The authors affirm that human research participants provided informed consent for the publication of Tables 1, 2, 3, and 4.

Competing interest The authors declare no competing interests.

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