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Original Article

Outcome and Safety of Colistin Usage in Pediatric Cancer Patients with Carbapenem-Resistant Enterobacteriaceae Bacteremia at Children Cancer Hospital Egypt

Nagla Adel, Reham Khedr[1,2], Mervat Elanany[3,4], Hala F. Zaki[5], Hanafy Hafez[1,2], Hanan El-Abhar[5]

Departments of Pharmaceutical Services, [2]Pediatric Oncology and [4]Microbiology, Children's Cancer Hospital Egypt, Cairo, [1]Department of Pediatric Oncology, National Cancer Institute, Cairo University, [3]Department of Clinical Pathology, Cairo University, [5]Department of Pharmacology, Toxicology and Biochemistry Faculty of Pharmacy, Future University in Egypt, Giza, Egypt

Abstract

Background: Carbapenem resistant Enterobacteriacae (CRE) bloodstream infection (BSI) causes complicated infections, especially in immunocompromised patients. This study aimed to assess the renal toxicity and the efficacy of therapy with colistin in a cohort of pediatric cancer patients with BSIs due to CRE and sensitivity to colistin. **Patients and Methods:** This was an observational, prospective cohort study from May 2017 to October 2017 in Children's Cancer Hospital Egypt 57,357. All patients who had blood stream infections due to CRE receiving intravenous colistin were prospectively enrolled. We used a standardized case form to record patient characteristics, including age, sex, weight, underlying comorbidities, type of infection, causative organism, and antibiotic susceptibility testing. Daily doses, duration of colistin therapy, and co-administered antibiotics (aminoglycosides, vancomycin) were collected. Furthermore, clinical and microbiological responses to treatment were reported. The dosing schedule was based on a loading dose of 5 MU and a 5-MU twice-daily divided maintenance dose, titrated on renal function. Clinical cure, bacteriological clearance, and daily serum creatinine were recorded. **Results:** One hundred and forty-one Blood Stream infectious episodes mainly due to Klebsiella Species (pneumoniae and Oxytoca) (27%) and *Escherichia coli* (68%) were analyzed. All strains were susceptible to colistin with Minimum inhibitory concentration (MICs) of 0.19–1.5 mg/L. Patients were predominantly females (69%), with a mean age of 7 years. It was used as a combination therapy with carbapenems (69.2%) or aminoglycosides (80%). The median duration of treatment was 9 days (Range 1–50 days). Clinical and microbiological cure was observed in 110 cases (80%). Acute kidney injury developed during five treatment courses (4%) in which colistin was used in combination with amikacin. No renal replacement therapy was required and subsided within 7 days from colistin discontinuation. **Conclusions:** Our study showed that colistin had a high efficacy without significant renal toxicity in severe infections due to CRE Gram-negative bacteria.

Keywords: Carbapenem-resistant enterobacteriaceae, cancer, children, colistin

Résumé

Carbapenem-resistant Gram-negative (CRE) bloodstream infection (BSI) causes complicated infections, especially in immunocompromised patients .This study aimed to assess the renal toxicity and the efficacy of therapy with colistin in a cohort of pediatric cancer patients with BSIs due to CRE and sensitivity to colistin. colistin proved to be effective and safe in managing CRE in children with cancer.

Mots-clés: Colistin, cancer, children, and Carbapenem-Resistant Enterobacteriaceae

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Address for correspondence: Dr. Reham Khedr, Department of Pediatric Oncology, National Cancer Institute, Cairo University, Cairo, Egypt.
Department of Pediatric Oncology, Children's Cancer Hospital Egypt, Cairo, Egypt.
E-mail: reham.khedr@cu.edu.eg

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Introduction

Overall, childhood cancer survival has improved markedly over the past 30 years due to new and improved treatment.[1] Although significant improvements have been achieved in supportive care, approximately 16% of the deaths are due to treatment-related complications.[2] Infection-related mortality continues to be one such life-threatening complication in immunocompromised children.[3]

In recent years, a shift from Gram-positive to Gram-negative organisms has been documented in the etiology of the bloodstream infection (BSI).[4] However, the infection rate with Gram-negative bacteria is higher in the U.S. and Latin America, while Gram-positive bacteria are more prevalent in Europe.[5]

Treatment of emerging (CRE) organisms is a challenge. Emerging antibiotic resistance has led to the re-use of the old antibiotic colistin;[6] colistin was withdrawn because of its nephrotoxicity and neurotoxicity (after the 1970s).[7] It belongs to the antimicrobial class designated polymyxins, which originate from the organism *Paenibacillus polymyxa*.[8] A little is known about Colistin use and its toxicities in children. Furthermore, optimal administration strategies (e.g., dosing, interval) remain unclear in this population.[9]

The 68th assembly of the World Health Organization, held in May 2015, adopted the Global Plan of Action on Antimicrobial Resistance.[10] This plan focused on antimicrobial stewardship activities and reports in the form of drug-pathogen ("drug-bug") combinations (Antibiogram). We performed an observational study to review the outcome and safety of colistin in our pediatric cancer patients.

Patients and Methods

Patient population

A prospective, observational study was performed from May 2017 to October 2017 in Children's Cancer Hospital Egypt 57,357. All patients with CRE who received intravenous colistin were enrolled. Data collection included patients' demographics, microbiological data, colistin therapy, other drugs, comorbidities during the infectious episode, intensive care unit (ICU) admission and sepsis, and D30 mortality.

Colistin dosing

The dosing schedule was based on a loading dose of 5 MU and a 2.5-MU twice-daily maintenance dose, titrated on renal function. For each colistin course, the following data were recorded: clinical cure, bacteriological clearance, daily serum creatinine, and mortality at day 30.

Microbiology data

All the clinical samples were inoculated on routine culture media, and identification of the isolated organism was performed by biochemical tests and the Vitek-2 compact system. Antimicrobial susceptibility to colistin was tested using the disk diffusion method following the Clinical Laboratory Standards Institute guidelines.[9]

Definitions

Fever and neutropenia were defined per our institutional guidelines adopted from the Infectious Diseases Society of America.[11] The diagnosis of BSI was based on clinical features and isolation of bacteria from a normally sterile site. Standard definitions for nosocomial infections were used, according to the Centre for Disease Control and Prevention.[12] Multidrug resistant (MDR) Gram-negative bacterial pathogens were defined by resistance to at least three classes of antimicrobial agents, regarded as potentially effective against the particular pathogens.[13] Immunocompromised patients' episode was defined by fever and neutropenia besides BSI-related clinical symptoms. Where fever is defined as temperature is >38.3 once or 2 records of 38 1 h apart and neutropenia if the neutrophilic count is <500 × 106/L.[14,15] The proposed treatment algorithm for carbapenem-resistant Gram-negative organisms is adopted from the European Society of Clinical Microbiology and Infectious Diseases 2013 guidelines.[16] A course of IV colistin administration was defined as at least 48 h or a minimum of six doses of continuous colistin administration. Clinical response was defined as resolving to present signs and symptoms. Treatment failure was defined as the persistence or worsening of a new infection's signs and symptoms or development. Nephrotoxicity development during colistin therapy was defined as an increase in serum creatinine of at least two-fold of the baseline and a creatinine clearance value of <60 ml/min.[17] The creatinine clearance was estimated from serum creatinine, the patient's height, and a proportionality constant using the Schwartz method.[18]

The clinical response to colistin was classified as a good, delayed, and poor response. Good response was assessed by resolution of fever, leukocyte count, and other symptoms of CRE-related infection within 15 days at the end of colistin treatment. Likely, partial/delayed response, but the resolution of symptoms extended to more than 15 days. Poor response/clinical failure was defined as failing to meet all criteria for good or delayed clinical response.

Similarly, microbiological response was defined as obtaining two consecutive negative CRE cultures from the site of infection after the initial positive culture within 15 days can be considered a good microbiological response, and more than 15 days delayed response. Microbiologic failure was defined as the persistence of the original causative organism in the subsequent specimen cultures. Nephrotoxicity was described as a doubling of creatinine serum value from the baseline and creatinine clearance value of <60 ml/min. Drugs are accused of toxicity if administered during or within 3 days before creatinine doubles.

Therapeutic options indications

An antibiogram was used to describe and illustrate the therapeutic options for treating the target population regarding CRE infection. It displays the overall susceptibility of bacteria to a variety of antibiotics. All the antibiograms were prepared using isolates from the patients enrolled in this study (local laboratory data).

Antibiograms coding

The new color-coded formatting of the antibiograms makes it easy to choose an antibiotic for empiric treatment based on the suspected microorganism.

Primary outcome

Primary outcome included microbiological clearance as well as clinical outcome.

Secondary outcome

Safety and toxicity

Number of adverse drug events (Time Frame: 21 days of follow-up). The safety of colistin was determined by renal function deviation from the baseline after administering colistin. Furthermore, the study of drug-related adverse reactions, including interaction with other nephrotoxic drugs, was documented–co-administered antibiotics, including other nephrotoxic agents (aminoglycosides, acyclovir, and vancomycin) were reported.

Statistical analysis

Categorical variables were compared with Chi-square or Fisher's exact test as appropriate and continuous variables using parametric (*t*-test or analysis of variance) or nonparametric (Mann–Whitney U or Kruskal–Wallis test) according to a number of groups and distribution. Univariate logistic regression was applied to measure the effect of risk factors on survival. Significant risk factors were entered in the multivariate model. R Foundation for Statistical Computing, Vienna, Austria version 3.6.0, was used for the statistical analysis. R packages used in the analysis were tidyverse version 1.2.1 for data wrangling and web version 0.1.4.1 for plotting pie charts.

Results

One hundred and ninety-two Colistin prescriptions were registered during the study, representing 147 patients. However, 31 patients out of 147 were observed to have repeated admissions for supportive care during their chemotherapy course. The Flow chart for the study is shown in Figure 1.

The patient's demographics and clinical presentation were reported. Isolated pathogens, duration of hospital and ICU stay, the reason for colistin treatment, colistin regimen administered, other antimicrobial agents used for the management of the index infection, and treatment outcomes are presented in Tables 1-3.

Types of CRE Pathogens detected by blood cultures

One hundred and thirty-three blood stream infectious episodes mainly due to *Escherichia coli* 80 (60.2%), *Klebsiella* Species (pneumoniae and Oxytoca) 35 (26.3%), *Acinetobacter baumannii* 11 (8.3%), and Pseudomonas species (Aeruginosa and putida) 5 (3.8%) were analyzed two isolates were excluded (1 stenotrophomonas maltophilia and 1 mixed growth). All strains were susceptible to Colistin with MICs of 0.19–1.5 mg/L.

Regarding therapeutic options for the study population against 21 antimicrobial agents from different antibiotic classes include only three types with considerable susceptibility options aminoglycosides (amikacin and gentamicin), colistin, and tigecycline [Table 2].

The median duration of colistin treatment was 9 days (Range 1–50 days). Clinical and microbiological cure was observed in 94/135 cases (70%).

Nephrotoxicity was defined as a doubling of creatinine and a creatinine clearance value of <60 ml/min. In all episodes,

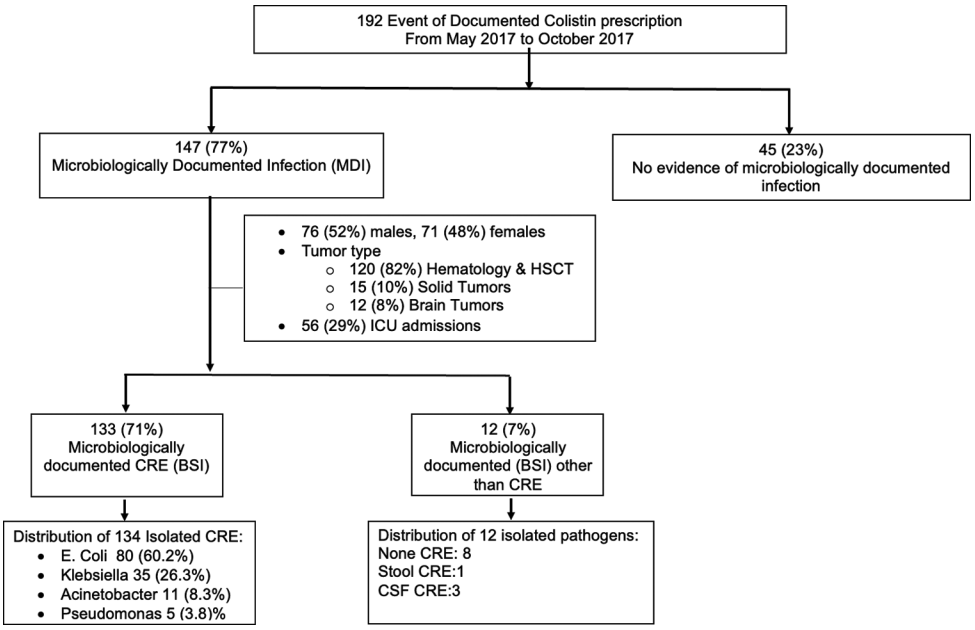

Figure 1: Study Flow Diagram. BSI = Bloodstream infection, ICU = Intensive care unit, MDI = Microbiologically Documented Infection, HSCT = Hematopoietic stem cell transplantation

nephrotoxicity was observed in 30/147 patients (20%) of the reported children during colistin treatment. One hundred and ninety two Only five patients' episode (2.6%) developed nephrotoxicity accused by Colistin alone , while nephrotoxicity was observed in combinations of colistin with amikacin, vancomycin, and acyclovir.

Drugs were accused of toxicity if administered during or within 3 days before creatinine doubled. Along with colistin, three main drugs were investigated; vancomycin, acyclovir, and amikacin. Thirty patients had nephrotoxicity accounting for 20.4% of the total cohort. Vancomycin was accused in 14 patients (46.6%), acyclovir was accused in 9 patients (30%), and amikacin was accused in 19 patients (63.3%) [Figure 2].

Out of the 30 patients with renal toxicity, only 25 patients have at least a single drug accused. No renal replacement therapy was required and resolved spontaneously within 7 days from the discontinuation of colistin. No correlation was found between variation in serum creatinine and daily doses of colistin.

D30 mortality was reported in 38 patients (25%). Risk factors achieving significance at the level of $P < 0.05$ on univariate analysis were identified and entered into a stepwise multivariate logistic regression analysis [Table 3].

Table 1: Patient's characterizations and demographics

Levels	Dead	Alive	Total	*P*
Sex				
Female	33 (60.0)	38 (41.3)	71 (48.3)	0.043
Male	22 (40.0)	54 (58.7)	76 (51.7)	
Age group				
≤1	13 (23.6)	7 (7.6)	20 (13.6)	0.006
1-13	31 (56.4)	73 (79.3)	104 (70.7)	
>13	11 (20.0)	12 (13.0)	23 (15.6)	
Weight group				
≤10	10 (18.2)	5 (5.4)	15 (10.2)	0.043
10-50	38 (69.1)	76 (82.6)	114 (77.6)	
≥0	7 (12.7)	11 (12.0)	18 (12.2)	
Diagnosis				
BMT	1 (1.8)	2 (2.2)	3 (2.0)	0.009
Brain T	3 (5.5)	8 (8.7)	11 (7.5)	
Hematology	39 (70.9)	78 (84.8)	117 (79.6)	
Solid	12 (21.8)	3 (3.3)	15 (10.2)	
Others: Brain asp		1 (1.1)	1 (0.7)	

BMT= Bone Marrow Transplantation

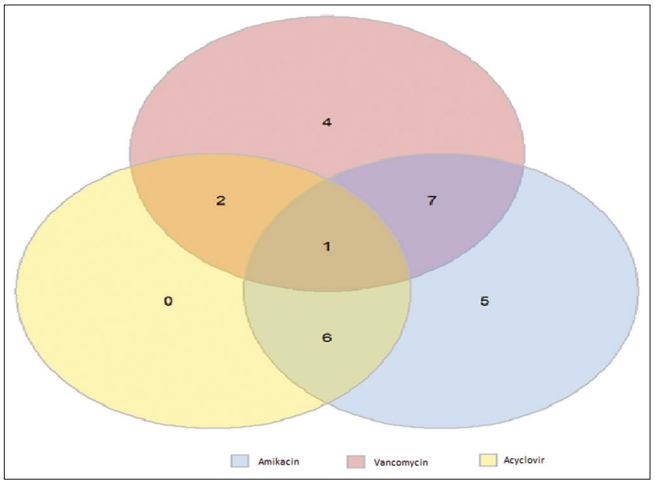

Figure 2: Venn diagram for the accused drug for toxicity

Table 2: Antibiotic susceptibility pattern of carbapenem-resistant Enterobacteriaceae isolates (antibiogram)

Organism	*Pseudomonas*	*Klebsiella*	*Escherichia coli*	*Acineto*
Amikacin	90	34	66	8
Amoxicillin/Clavulanate	0	0	2	2
Ampicillin/Sulbactam	NA	0	2	38
Cefazolin	NA	0	3	0
Cefepime	50	10	6	8
Cefotaxime	0	2	4	0
Cefoperazone/Sulbactam	0	0	9	6
Ceftazidime	2	4	2	38
Ceftriaxone	2	4	2	0
Ciprofloxacin	8	6	12	62
Colistin	94	100	89	100
Gentamicin	11	48	43	63
Imipenem	8	25	17	52
Levofloxacin	28	9	12	NA
Meropenem	8	18	18	43
Nitrofurantoin	0	0	0	NA
Piperacillin/Tazobactam	6	7	1	55
Rifampin	89	NA	NA	NA
Tigecycline	63	98	90	6
Tobramycin	18	18	20	56
Trimethoprim/Sulfa	16	4	15	0

Table 3: 30 days mortality risk factors

Patient episodes *n*=133				
Predictors	**Variables**	**Dead**	**Alive**	***P***
Pathogen	*Acinetobacter baumannii*	10 (18.9)	1 (1.2)	<0.001
	Others	1 (1.9)	1 (1.2)	
	Escherichia coli	18 (34.0)	62 (77.5)	
	Klebsiella	22 (41.5)	13 (16.2)	
ICU admission	Yes	42 (79.2)	5 (6.2)	<0.001
	No	11 (20.8)	75 (93.8)	
Colistin days	Mean (SD)	7.9 (7.9)	11 (7.5)	0.023

SD=Standard deviation, ICU=Intensive care unit

Discussion

Healthcare-associated infections caused by multidrug-resistant Gram-negative organisms are a significant cause of morbidity and mortality, especially among patients with cancer.[19,20]

In this study, we report the efficacy and the toxicity profiling of Ccolistin in our pediatric cancer patients for the definite or empiric treatment of infections due to MDR Gram-negative bacteria. All of these infections were improved on colistin therapy. Our study shows that colistin has a high efficacy without significant renal toxicity in infections due to CRE gram-negative.

A few studies have investigated the efficacy and safety of colistin therapy in children.[19] The majority have been performed in specific patient groups such as newborns and patients with cystic fibrosis or burn injuries.[21,22]

In a pediatric ICU setting a study by Ramasubban and another by Kapoor *et al*. reported 50 critically ill children who received IV colistin, with a median age of 36 months (range: 1 month–12 years) and a male: female ratio of 3:2.[23] A favorable clinical outcome occurred in (72%), and (28%) died due to severe sepsis.[23,24] This broadly agrees with our study, which reported male predominance (52%) and a median duration of colistin therapy of 9 days (range 1–50). A favorable clinical and microbiological cure occurred in (68%) of the cases, and D30 mortality was (32%).

D-30 mortality was associated with patient's age ($P = 0.006$), weight ($P = 0.043$), length of colistin therapy ($P = 0.023$) along with the type of pathogen ($P < 0.001$). Interestingly, Acinetobacter and Klebsiella have a worse outcome with a $P = 0.015$ and 0.009. The ICU admission was an independent prognostic outcome measure with a $P < 0.001$.

Wang *et al*. described the profile of patients and the characteristics of all MDRGN infections to assess mortality in 138 patients over 4 years; clinical characteristics, antibiotic therapy, and in-hospital mortality were analyzed. The in-hospital mortality rate was 25.4%.[25]

In Cox regression analysis, mortality was independently associated with the age ($P = 0.034$) and hospitalization in an ICU ($P = 0.04$), as reported in our study. Postantibiogram therapy was associated with hospitalization in an ICU ($P = 0.006$), Charlson comorbidity index score ($P = 0.003$), and inadequate initial antimicrobial treatment ($P < 0.001$).[26]

In this study, the predominant isolated pathogen was the *E. Coli* (60.2%), followed by Klebsiella species (26.3%), *A. baumannii* (8.3%), and Pseudomonas species (3.8%). According to CLSI 2015, recommendations for reporting CRE that suggested clustered drug-pathogen ("drug-bug") combinations reports in the form of antibiogram.[27]

We applied an antibiogram to the study population, which revealed that the combination of colistin with amikacin tigecycline was the only option for the clinician in the management of a CRE infection.

In a study by Visanu, which was done to monitor the effectiveness and safety of colistin or therapy in resistant Gram-negative bacterial infections at Siriraj Hospital, *A. baumannii* was the most common cause of infections (79.7%), followed by *Pseudomonas aeruginosa* (22.4%), and Enterobacteriaceae (22.4%). Nearly all isolates of *A. baumannii* and *P. aeruginosa* were resistant to carbapenems. Most Enterobacteriaceae were extended-spectrum beta-lactamases producing strains.[28] They reported that 19.6% of patients received colistin alone while most received concomitant antibiotics, especially carbapenems and piperacillin-tazobactam. Favorable clinical outcome was observed in 71.7% of patients at the end of colistin therapy.[28]

In a study by Hsu and Tamma.[10] focusing on the effectiveness and toxicity of colistin treatment in a case series of children with burns, the most commonly identified organisms were multidrug-resistant pseudomonas (67.4%), multidrug-resistant *Acinetobacter baumannii* (11.9%), and carbapenemase-producing Enterobacteriaceae (13.0%). They suggested that colistin is an active drug with an acceptable safety profile for treating MDR Gram-negative infections in critically ill children.

The incidence of nephrotoxicity was detected only in 2% of our study cohort, indicating the safety of colistin use among our children with adequate efficacy (70%). Additional nephrotoxic drugs were administered to 84% of patients and 22% of children experienced nephrotoxicity. Renal function dropped to baseline in all patients. Five children exhibited reversible neurotoxicity.[11] In the study by Pogue *et al*., renal toxicity occurred in five children and was associated with multiple-organ failure in three and coadministration of vancomycin in two patients. No neurotoxic adverse effects were reported. Acute tubular necrosis leading to disturbed renal functions is the main concern with IV colistin.[9]

Other studies reported that patient mortality at the end of colistin therapy and 30 days after completion of colistin was 23.2% and 39.9%, respectively. Microbiological eradication of target bacteria at the end of colistin therapy was found in 50% of patients. The overall incidence of acute kidney injury was 39.9%, with most cases classified as either risk (20.3%) or

injury (13%). Colistin-related renal dysfunction was reversible in most cases.[28]

In another study, including a small number of pediatric children without cystic fibrosis by Falagas *et al*.[19] looked into the safety profile of colistin; he suggested that colistin has a role in the treatment of infections caused by MDR Gram-negative bacteria in the critically ill pediatric patients without toxicity.[17] Hartzell *et al*. demonstrated a nephrotoxicity rate of 45% in their cohort, which is much higher than our report. However, their study group consisted of relatively young patients with low comorbidities.[29] Temocin *et al*.[30] reported a higher rate of nephrotoxicity rate (48%) and (71%) without scoring or reporting any comorbid conditions.

Conclusion

Our study showed that colistin has a high efficacy without significant renal toxicity in severe infections due to CRE Gram-negative bacteria in children. Regarding the failure of microbiological cure despite the sensitivity to colistin, a complementary study of the isolates at the genetic level for resistance is recommended.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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