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Research Article

Colistin Pharmacokinetics in Pediatric Cancer Patients in Egypt

Yosr-Samia M. Abou Sedira[a], Lamia M. El Wakeel[b*], Omran M. Mervat[c], Iman Sidhom[d,e], Samia A. Shouman[c]

[a]*Department of Clinical Pharmacy, National Cancer Institute, Cairo University, Cairo, Egypt*
[b]*Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Abbassia, Cairo 11566, Egypt*
[c]*Pharmacology Unit, Cancer Biology Department, National Cancer Institute, Cairo University, Cairo, Egypt*
[d]*Department of Pediatric Oncology, National Cancer Institute, Cairo University, Cairo, Egypt*
[e]*Department of Pediatric Oncology, Children's Cancer Hospital, Cairo, Egypt*

Abstract

Colistin has been reintroduced to clinical practice after the emergence of multidrug-resistant gram-negative (MDR-GN) and the failure of other antibiotics. Pharmacokinetics and pharmacodynamic data in the pediatric population are scarce. This study aimed to highlight the pharmacokinetics of 2 colistin doses, 2.5, and 5 mg/kg/day, in febrile neutropenia pediatric cancer patients regarding patient outcomes. In a prospective, comparative study, patients suffering from MDR-GN infection were randomly recruited to receive either 2.5 or 5 mg/kg/day colistin doses. The demographic, microbiological, and treatment outcomes were collected before and after treatment. Colistin levels were determined using HPLC/MS/MS. Peak, trough, area under the concentration-time curve (AUC_{24}), and the ratio of AUC_{24} to the minimum inhibitory concentration (AUC_{24}/MIC) were assessed. Clinical cure was achieved in 14 (77.8%) cases in the Low-Dose (LD) group vs. 13 (81.3%) in the High-Dose (HD) group. Four (25%) patients vs. 4 (33.3%) in the LD and HD group (P= 0.69) attained an optimal plasma AUC_{24}/MIC, respectively, while the therapeutic level of colistin was reached in all patients in the LD group compared to 14/16 (87.5%) in the HD group. Microbiological eradication was achieved in 93.8% and 91.6% of patients in the LD and HD groups, respectively. However, the median time to clearance was significantly lower in the LD group, 4 days vs. 7 days in the HD group (P= 0.022). In conclusion, the current study suggests that LD may be as efficacious and safe as HD in treating MDR-GN infection. However, LD colistin was associated with a shorter clearance time than HD colistin.

Keywords: *Colistin; pediatric cancer patients; MDR gram-negative infection; plasma concentration; pharmacokinetics.*

***Correspondence** | Lamia M. El Wakeel; Department of clinical pharmacy, Faculty of Pharmacy, Ain Shams University, Abbassia, Cairo 11566, Egypt. Email: lamia.elwakeel@pharma.asu.edu.eg

Iman Sidhom and Samia Shouman Contributed equally as the last author.

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1. Introduction

Febrile neutropenia (FN) is common in hematological and solid malignancies as a consequence of cytotoxic chemotherapy and is a contributor to death in children. About one-third of children treated with these cytotoxic drugs experienced FN during the neutropenic period.

During FN, there are bloodstream infections with MDR-GNB, and the defective inflammatory and immunologic responses lead to sepsis and death **[1]**. Consequently, this medical emergency mandates prompt administration of antibiotic therapy to treat these patients **[2]**.

Colistin was initially discovered in the 1940s and was used in several countries. However, its association with nephrotoxicity and neurotoxicity limited its use. Colistin, a member of the polymyxin family of antibiotics, has been reintroduced to clinical practice after the increased incidence of infections caused by MDR-GNB **[3]**. Colistin methanesulphonate (CMS) is a prodrug of colistin that hydrolyses in vivo, yielding the active colistin base **[4]**. Colistin is now used as 2nd line agent in the treatment of carbapenem-resistant Enterobacteriaceae (CRE) and MDR-GN infections **[1]**. Its effectiveness against most gram-negative bacteria, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, is well documented **[2]**. An excellent index to measure the efficacy of colistin is the pharmacokinetic/pharmacodynamic index (PK/PD), defined as the ratio of the area under the concentration-time curve from 0 to 24 h (AUC_{24}) to the minimum inhibitory concentration (MIC). In 2019 International Consensus Guidelines for the Optimal Use of Polymyxins recommended a target $AUC_{24} \geq$ 50 mg.h/L to equate to a target steady-state concentration of 2 mg/L. However, lower respiratory tract infections may require a higher target AUC_{24}. It is recommended to consider the dose that provides the maximum exposure to colistin with the least side effect **[5]**.

Currently, the FDA-recommended doses for pediatric patients are 2.5-5 mg/kg /day of CBA in 2-4 divided doses **[5]**. However, pharmacodynamic and pharmacokinetic data in the pediatric population are still lacking.

In this study, we aimed to study the pharmacokinetic/pharmacodynamics parameters of the two currently used doses of colistin to evaluate their effectiveness and treatment outcomes in pediatric oncology patients suffering from febrile neutropenia caused by MDR-GN infection.

2. Patients and Methods

2.1. Study design and ethical consideration

The study was a prospective, randomized clinical study comparing two different colistin doses in pediatric cancer patients with MDR gram-negative infection. This is a sub-group analysis of a larger cohort of patients focusing only on the pharmacokinetic data of colistin.

Patients were recruited at the Pediatric Oncology Unit and the Pediatric Intermediate Care Unit at the National Cancer Institute, Cairo University. The Research Ethics Committee of the Faculty of Pharmacy, Ain Shams University, approved study protocol number (103). The study was conducted following the declaration of Helsinki and was registered at clinicaltrials.gov (ID number NCT03397914). The patient's caregiver or legal guardian was counseled about the study, and informed consent was obtained before participation.

2.2. Patients

Thirty-four pediatric cancer patients diagnosed with MDR-GN organism infection with either active or based on a previous history of GNB received intravenous colistin during hospitalization were enrolled for this study. Patients were excluded if colistin was used for less than 6 doses, i.e., 3 days, serum creatinine was more than 2 mg/dL before treatment with colistin commencement, or the patient was suffering from septic shock. In addition to colistin, all patients received carbapenem, amikacin, or tigecycline as part of the MDR-GNB treatment protocol).

2.3. Randomization

Patients were randomized using "simple computer-generated" randomization techniques to receive either a low dose (LD) (Loading dose of 2.5 mg/kg followed by a maintenance dose of 1.25 mg/Kg as a short infusion every 12 h) or a high dose (HD) (Loading dose of 5 mg/kg followed by maintenance dose 2.5 mg/Kg as a short infusion for 30min every 12 h).

2.4. Colistin administration

Colistin was supplied under the trade name Colomycin® and manufactured by Forest Laboratories, Pharma BV company, Netherlands. It is obtained as powder vials containing either 1 million (30 mg) or 2 million units (60 mg). The powder is diluted with 2.1 mL or 4.2 mL, respectively, of sterile water for injection, yielding a concentration of 15 mg/mL (0.5 million units/mL). The volume corresponding to the calculated dose is withdrawn and further diluted with a compatible solution [dextrose 5% D5w or normal saline (NS)]. The calculated dose was dissolved in 100 mL of normal saline and was administered as a 30 min intravenous infusion.

2.5. Methods

2.5.1. Data collection

All patients' data were collected from the patient's files, including demographic and clinical characteristics. Other clinical data included clinical cure (resolution of clinical signs and symptoms of infections), time to defervescence (fever resolution), microbiological clearance (disappearance of MDR-GN bacterial isolates on follow-up cultures), time to microbiological clearance **[6]**, mortality, the development of nephrotoxicity (assessed and graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC AE) v5.0) and length of hospital stay and adjusted length of stay (time from the start of colistin till the discharge of the hospital or death).

2.5.2. Microbiological data & antimicrobial susceptibility

Specimens from blood were obtained as clinically indicated. Identification and susceptibility testing of all gram-negative microorganisms grown on blood agar/ MacConkey agar were performed based on routine microbiological methods using Vitek automated system (Gram-negative panel).

Antimicrobial susceptibility testing for colistin used was the E-test (BioMerieux, SA, France) for MIC determination. The isolates were considered susceptible if the MIC was ≤2 mg/L according to the Clinical and Laboratory Standards Institute (CLSI) **[6, 7]**.

2.5.3. Determination of colistin levels in patient plasma using liquid chromatography-tandem mass spectrometry (LC/MS/MS) analysis

2.5.3.1. Blood samples

Blood samples were withdrawn from the patients after reaching a steady state (after 4 days) of CMS therapy. Two blood samples (3 mL) of venous blood were drawn into a heparinized tube, the trough concentrations (C_{min}) were collected just before the next dose, and peak concentrations (C_{max}) were collected 30 min after the end of the CMS infusion. The plasma was separated by centrifugation at 2500g for 10 min within 2 h of collection. The resultant plasma was stored at -70 ºC until assayed.

2.5.3.2. Methods

One hundred microliters of plasma were mixed thoroughly with 400 μL acetonitrile (Alliance Bio, USA), vortexes for 30 sec, and centrifuged at 10,000 g for 10 min at 4 °C. Twenty μL of the resultant clear supernatant was then injected into LC; Agilent 1260 series

chromatograph; Agilent Technologies, coupled with a tandem mass spectrometry (MS/MS; AB SCIEX API 3200 LC-MS/MS system; Applied Biosystems, Q TRAP, Germany). The analytical column used was Waters X Bridge C18-5 µm (2.1x150 mm Column, Germany) at 39 °C. The mobile phase consists of a mixture of 0.1% formic acid/water and 0.1% formic acid/acetonitrile (60/40 v/v) isocratic flow, delivered at a flow rate of 0.2 mL/min. The mass spectrometer was operated in the positive ESI mode with the spray voltage set at 5.5 kV, at a temperature of 600 °C, and a curtain gas flow of 30 L/h **[8]**. The calculation is done by the Multiquant software program. Serial dilutions of standards were prepared at different concentrations for colistin in drug-free plasma and extracted as mentioned in sample preparation to make a calibration curve. They were detected at a retention time of 2.32 min. Quantification was performed with multiple reactions monitoring (MRM) by using curtain gas collision-induced dissociation and the following ion transitions: m/z 585.5/101.2, for Colistin A & m/z 578.5/101.2, for Colistin B with the de-clustering potential set at 51 V and the collision energy at 53 eV.

2.5.3.3. Pharmacokinetic calculation

The pharmacokinetics parameters colistin peak and trough labeled C_{max} and C_{min}, and AUC_{24} were calculated using the following equation:

$$AUC_{24} = \frac{t\prime(C_{max}+C_{min})}{2} + \frac{C_{max}-C_{min}}{k_{el}} \quad \textbf{[9]}$$

Where t′ is the time of infusion (h), C_{max} is the peak concentration at the end of infusion, C_{min} is the trough concentration at the end of the dosing interval, and K_{el} is the elimination rate constant.

The elimination rate constant (K_{el}) was calculated based on the Sawchuk-Zaske method

$$k_{el} = \frac{ln\left(\frac{C_{max}}{C_{min}}\right)}{t} \quad \textbf{[9]}$$

Where t is the time difference in time between the 2 concentrations.

The number of patients reaching therapeutic concentration (≥2mg/L), The number of patients reaching the target $AUC_{24} \geq 50$ mg.h/L, and the number of patients achieving a target AUC_{24} / MIC= 60 mg.h/L **[10]** were assessed **[5]**.

2.5.4. Statistical analysis

Statistical analysis was done using IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as median and range. Qualitative data were expressed as frequency and percentage. Pearson's Chi-square test or Fisher's exact test examined the relationship between qualitative variables. For quantitative data, two groups were compared using the Mann-Whitney test (non-parametric t-test) for not normally distributed data. All tests were two-tailed. A $P<0.05$ was considered significant.

3. Results

Thirty-four pediatric oncology patients were enrolled in this study. Eighteen patients were assigned to the LD group compared to 16 patients in the HD group.

There were no significant differences in terms of age, sex, weight, diagnosis, and disease stages at presentation between groups. Their median age was 4.5 (1.8-13) years in the LD group compared to 7 (2.5-16) years in the HD group. Data are presented in **Table 1**.

3.1. Microbiological data

The most commonly isolated organism was *Klebsiella pneumonia* [8 (44.4%) vs. 4 (26.7%)], followed by *E coli* [4 (22.2%) vs. 4 (26.7%)] in the LD and HD groups, respectively. Details of causative organisms are presented in **Table 2**. Susceptibility of bacterial isolates collected from patients in the study had a median MIC of 0.75 (0.5-2) µg/mL vs. 0.88 (0.75-3) µg/mL in the LD and HD groups, respectively.

Table 1. Baseline Demographics Characteristics of Pediatric Cancer Patients with Febrile Neutropenia

Parameter	LD Group N=18	HD Group N= 16	P-value
Age(yrs.)			
Median (R)	4.5 (1.8-13)	7 (2.5-16)	0.102§
Sex, N (%)			
Male	12 (66.7%)	11 (68.8%)	0.897 #
Female	6 (33.3 %)	5 (31.3%)	
Weight (kg):			
median (R)	14.5 (8-35)	23 (10-47)	0.075 §
Diagnosis; N (%)			
Solid malignancies	2(11.1%)	0(0%)	
Hematologic malignancies	16(88.9%)	16(100%)	
Diseases Stages, N (%)			
Induction (newly diagnosed)	8(44.4%)	8(50%)	
Complete Remission	9(50%)	7(43.8%)	
Relapse/progression	1(5.6%)	1(6.3%)	

Statistical tests: # Pearson - Chi-square test $ student t-test § Mann Whitney test
* p values < 0.05 are considered significant

Table 2. Baseline Microbiological Data of Pediatric Cancer Patients with Febrile Neutropenia

Parameter	LD Group (n=18)	HD Group (n=16)$^{\sigma}$	P-value
Results of initial blood culture (causative MDR organism); N (%)			--
No growth	2(11.1%)	3(20%)	
Klebsiella pneumonia	8(44.4%)	4(26.7%)	
E. coli	4(22.2%)	4(26.7%)	
Acinetobacter species	1(5.6%)	1(6.7%)	
Pseudomonas species	0(0%)	2(13.3%)	
Enterobacter coloacea	0(0%)	1(6.7%)	
Mixed growth	3(11.5%)	0(3.7%)	
Microbiological parameter of colistin ^{f}			
E test (MIC) (mg/L);			
median (R)	0.75(0.5-2)	0.88(0.75-3)	0.371§
Colistin zone diameter (mm);			
median (R)	12(11-15)	12(11-15)	0.698§

N, number; S.D, standard deviation; mm, millimeters. Statistical tests: # Pearson Chi-square test $ Student t-test
* p values < 0.05 are considered significant**.** σ one blood culture was not available**.** *f*, for the LD group N= 16, for the HD group N= 12

3.2. Colistin plasma level

Colistin A and B measures revealed a significant difference in the trough level (C_{min}) of both colistin A and B; the LD group had median trough levels of [0.42 (0.00-1.43) & 0.08 (0.00-0.3) µg/mL] for colistin A and B respectively, compared to [0.91 (0.2-2.68) & 0.26 (0.05-0.83) µg/mL] in the HD group (P= 0.014 and 0.001). However, the peak levels (C_{max}) were comparable, with no significant difference between the 2 groups. The LD group showed a C_{max} of [8.29 (1.85-14.61), 2.09 (0.37-3.91) µg/mL] for colistin A and B, respectively, compared to [5.85 (0.79-14.99) and 2.01(0.2-3.85) µg/mL] in the HD group, P= 0.330 and 0.986.

The total colistin trough level was significantly higher in the HD group [1.16 (0.2-3.51) µg/mL] compared to the LD group [0.54 (0-1.71) µg/mL] with P= 0.009, **Table 3, Fig. 1.** On the other hand, the median levels of the peak concentration of total colistin (C_{max}) were insignificantly different between the LD and HD groups, [10.6 (2.22-18.52) µg/mL] vs. [7.52 (0.99-18.84) µg/mL] respectively, P= 0.528. The median duration of colistin treatment was 7.5 days in both the LD and HD groups, without significant differences between the two groups, P= 0.825.

The AUC_{24} and AUC_{24}/ MIC were calculated using the equation described above. Non-significant differences were observed between the two groups. Data are described in **Table 3**.

Table 3. Colistin pharmacokinetic parameters of Febrile Neutropenic Pediatric Cancer Patients treated with Colistin

Parameter	LD Group (n=18) *f* 2.5 mg/kg/day	HD Group B (n=16) *f* 5 mg/kg/day	P-value
Colistin A			
Trough (µg/mL)			
Median (R)	0.42(0.00-1.43)	0.91(0.2-2.68)	0.014*§
Peak (µg/ml)			
Median (R)	8.29(1.85-14.61)	5.85(0.79-14.99)	0.330§
Colistin B			
Trough(µg/mL)			
Median (R)	0.08(0-0.3)	0.26(0.05-0.83)	0.001*§
Peak (µg/mL) **Median (R)**	2.09(0.37-3.91)	2.01(0.2-3.85)	0.986§
Total colistin			
Trough (µg/mL)			
Median (R)	0.54(0-1.71)	1.16(0.2-3.51)	0.009§*
Peak (µg/mL)			
Median (R)	10.6 (2.22-18.52)	7.52 (0.99-18.84)	0.528§
AUC $_{24}$			
Median (R)	37.9(11.4-75.97)	44.19(11.14-98.74)	0.422§
AUC/MIC			
Median (R)	47.2(14.7-131.7)	45.1(6.2-131.7)	0.631§

R, range; N, number; S. D, standard deviation; µg/mL, microgram per milliliter.

Statistical tests: # Pearson Chi-square test $ student t-test § Mann Whitney test. ¢ Fisher exact

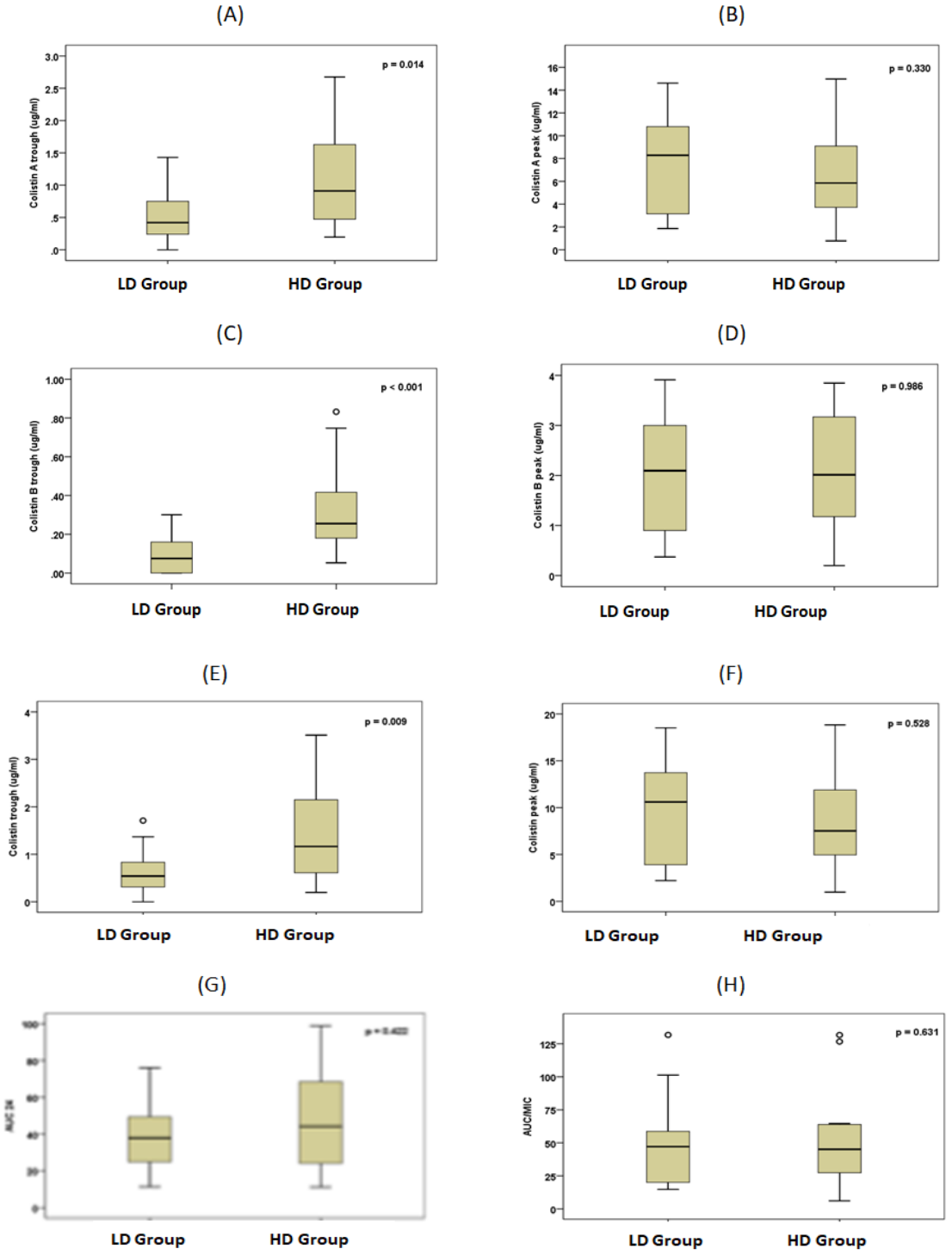

Fig. 1. Box plot presenting serum levels of trough and peak concentrations of colistin A, colistin B, and total colistin. A. Colistin trough A, B. Colistin A peak, C. Colistin B, D. Colistin B peak, E. total Colistin, F. total Colistin peak, G. AUC 24, H. AUC/MIC.

3.3. Clinical outcomes

Table 4 and Fig. 2 describe the clinical outcome observed in both groups. The median time to clearance was significantly lower in the LD group, showing a median of 4 days vs. 7 days in the HD group; however, microbiological clearance was attained in a comparable number of patients in both groups. The LD group had clinical cures observed in 14/18 (77.8%) patients compared to 13/16 (81.3%) patients in the HD group, P= 1.

Only grade 1-2 nephrotoxicity was experienced in 3/18 (16.7%) and 3/16 (18.8%) patients in the LD and HD groups, respectively. (P= 1) Both groups showed a similar length of stay, adjusted length of stay, and mortality. Details are described in **Table 4**.

Non-significant differences existed between the numbers of patients reaching a therapeutic level in both groups. All patients in the LD group and 14/16 (87.5%) in the HD group reached therapeutic plasma concentration (≥2mg/L) **[5]**. The two current doses achieved a target AUC_{24}/MIC>60 mg.h/L in only 4/16 (25%) and 4/12 (33.3%) in the LD and HD groups, respectively.

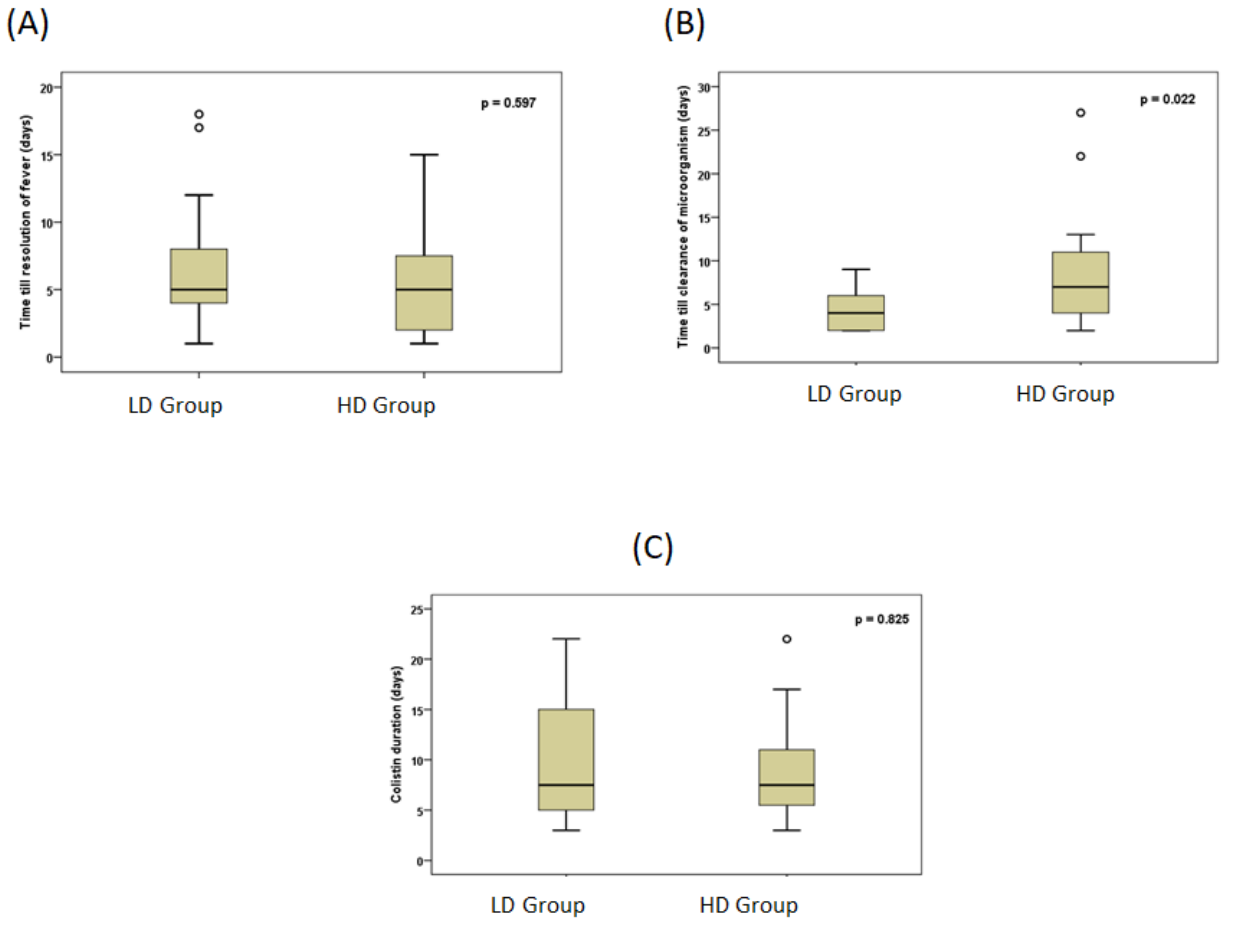

Fig. 2. Box plot presenting different outcomes in both 2.5 mg/kg/day (LD group) and 5 mg/kg/day (HD group), A. days till fever resolution, B. days till microbiological clearance, C. colistin duration.

Table 4. Treatment Outcome of Febrile Neutropenic Pediatric Cancer Patients treated with colistin

Parameter	LD Group, N=18	HD Group, N =16	P-value
Patients with Microbiological clearance:			
N (%) Œ	15 /16 (93.8%)	11 / 12 (91.6%)	--
Days of clearance microorganism			
median (R)	4 (2-9)	7(2-27)	0.022§*
Mortality			
N (%)	4(22.2%)	3(18.8%)	1¢
The total length of stay (days);			
median (R)	29.5(5-89)	29.5(3-82)	0.621§
Adjusted length of stay (days);			
median (R)	13(4-27)	11.5(5-62)	0.932§
Number of patients achieving therapeutic level;			
N (%)	18 (100 %)	14/16 (87.5%)	-
The number of patients achieving AUC >50mg.hr\L			
N (%)	4/18(22.2%)	5/16(31.25%)	0.551#
The number of patients achieving AUC /mic >60mg.hr\L Œ			
N (%)	4/16 (25%)	4/12(33.3%)	0.691¢

R, range; n, number; S.D, standard deviation; %, percentages, AUC, area under the curve

Statistical tests: # Pearson Chi-square test ¢ Fisher exact test § Mann Whitney test

* p values < 0.05 are considered significant

Œ % calculated on n= 16 in the LD group and n= 12 in the HD group (who had positive blood culture)

4. Discussion

Colistin may be a valuable option in treating severe pediatric nosocomial infections caused by MDR-GN organisms **[1]**. Yet, pediatric literature addressing colistin dosing, pharmacokinetics, and dynamics is scarce. The study aims to assess colistin pharmacokinetic parameters (C_{max}, C_{min}, AUC_{24}, and AUC_{24}/MIC) in the pediatric cancer population treated with 2.5 or 5 mg/kg/day, aiming to fill the gap of knowledge in this age group and to better elucidate the optimal dose to fight MDR-GN infections.

The current study showed that median trough levels were 0.54 (0-1.71) µg/mL for the LD group; compared to Sorlí et al. study, the observed trough concentrations (C_{min}) were 1.14 (0.11-5) µg/mL, for a colistin dose of 2 million units [equivalent to 2.9 mg/kg/day colistin base activity (CBA)] in 3 divided doses. Whereas for the HD group of the current study, the median trough levels were 1.16 (0.2-3.51) µg/mL, compared to the levels observed for the 3 million units [equivalent to 4.4 mg/kg/day CBA] three times daily group in the Sorlí study [1.84 (0.45-5.99) µg/mL] **[11]**. This difference may be related to the dosing interval difference in both studies.

In the HD group, the observed C_{max} was lower than in the LD group. This may be explained by the phenomenon of augmented

renal clearance (ARC) in patients suffering from sepsis. A proposed hypothesis is that augmented renal clearance (ARC) is usually observed in patients suffering from systemic inflammatory response syndromes (SIRS), like patients suffering from burns, trauma, or sepsis. The SIRS causes an increased cardiac output resulting in enhanced renal blood flow. Thus, the kidneys clear CMS too rapidly, leading to reduced colistin bioavailability **[12, 13]**.

Adults' pharmacokinetic studies reported that at steady-state, typical C_{max} was estimated to be 2.3-2.65 µg/mL following the administration of CMS by IV infusion at a dose of 3-5 million units every 8 h **[14, 15]**. Karaiskos, in 2015, used a loading dose of 9 million units CMS, followed by repeated administration of 4.5 million units CMS every 12 h. The average C_{max} of colistin A plus B was found to be 2.65 mg/L (equivalent to 2.65 µg/mL) with a time-to-maximum concentration (T_{max}) of 8 h **[16]**.

The studies mentioned above reported a lower steady-state concentration than the concentration observed in the current study in both low-dose [10.6 (2.22-18.52) µg/mL] and high-dose [7.52 (0.99-18.84) µg/mL] groups. These discrepancies may be attributed to the studied population's differences in pharmacokinetics and pharmacodynamics. There is a scarcity of literature addressing colistin pharmacokinetic studies in the younger population.

However, in a study by Mesini et al., addressing the pediatric population, they reported the C_{max} and C_{min} concentration of colistin following the administration of a loading dose of 150 000 IU/kg (equivalent to 5 mg/kg) followed by a maintenance dose of 75000 IU/kg (equivalent to 2.5mg/kg) every 12h during 9 treatment courses to 7 children. They observed a range of C_{max} (4.3-18.9 mg/L) and a C_{min} (0.4-3) mg/L **[17]**. They calculated the AUC_{24}, ranging from (33-92 mg.h/L). These findings are comparable to the results of our study.

According to previous studies, a wide range of serum colistin peak levels was observed in both groups; however, no standard levels were reported in earlier literature.

According to 2019 international consensus guidelines for the optimal use of colistin and polymyxin, the target AUC_{24} for colistin is 50 mg.h/L **[5]**.

In a study by Fan et al., they conducted a pharmacokinetic analysis of colistin on 12 healthy volunteers; they administered a dose of 2.5 mg/kg every 12 h for 7 days, and they reported a $C_{ave,\ ss}$ of 1.27±0.27 µg/mL, and an AUC_{12} of 15.28±3.29 h.µg/mL **[4]**. Compared to the current study, the observed median AUC_{24} was 37.9 (11.4-75.97) vs. 44.19 (11.14-98.74) in the LD and HD groups, respectively. This difference in AUC_{24} may be due to the difference in the pharmacokinetics of the population examined; the current study is based on a pediatric population, while the study by Fan et al. is based on healthy adult volunteers.

According to Garonzik et al. and Sorlí et al. studies, the AUC/MIC is the most predictive PK/PD index for efficacy. Based on recent pharmacokinetic literature, the target AUC/MIC is ≥60 mg h/L. In Sorlì's study, this target was achieved in only 33.3% of patients receiving different doses of colistin, similar to our study, where this target was achieved in 25% of patients in the LD group and 33.3% in the HD group **[10, 18]**.

Despite failing to attain the target AUC_{24}/MIC level, the clinical cure was observed in 77.8% and 81.3% of patients in the LD and HD groups, respectively. Compared to pediatric literature, which reported a clinical cure of 68-89% of studied pediatric patients **[19-21]**.

The current study demonstrated that colistin has relatively safe and tolerable toxicities. The observed nephrotoxicity was only graded 1-2 and was reported in 16.7% and 18.8% of the LD and HD groups, respectively. These data were corroborated by Tamma et al., in their study, they administered 2.5 mg/kg BID, and nephrotoxicity was reported in 22% of studied children **[22]**. However, Bal et al. reported an incidence of 10% following the administration of 5 mg/kg in 3 divided doses, compared to the HD group of our study. The difference may be due to the administration of a loading dose, thus higher colistin exposure, and the dosing intervals (every 12 h) in the current study **[23]**.

The limitations of this study were the small number of patients examined as well as the use of only two blood samples (trough and peak) from each patient; we need more sampling at different time intervals that will give a more accurate estimate of the AUC_{24} and the AUC_{24}/MIC. In addition, plasma protein binding was not measured for colistin; therefore, this study's AUC/MIC values were for total colistin.

The strength of this work is being a prospective and randomized study. We are also addressing limited data regarding colistin PK and PD studies in the pediatric population, aiming to improve their clinical outcomes.

Conclusion

In conclusion, our study demonstrates that the low dose of colistin may be as efficacious and safe as the high dose in treating MDR-GN infection. However, low-dose colistin was associated with a shorter time to clearance than high-dose colistin. The current study suggests the benefit of monitoring colistin concentrations in plasma. No significant differences were observed between groups in terms of C_{max} and AUC_{24}; however, the study is limited to the small number in both groups. Future research should target a larger sample of pediatric patients to validate these findings.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Availability of data and materials

Data is available upon reasonable request to the authors.

Competing interests

No competing interests were declared by the authors

Funding statement

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Author’s contributions

All authors contributed to data analysis, drafting, or revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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