Arabian Journal for Science and Engineering
https://doi.org/10.1007/s13369-024-08830-z

RESEARCH ARTICLE-BIOLOGICAL SCIENCES

Effectiveness and Safety of Colistimethate Sodium Used in the Treatment of Neutropenic Blood Cancer Patients Infected with Multidrug-Resistant *Pseudomonas aeruginosa*

Alaa Salman[1] · Ameera Ghannam[1] · Ala'a Kittaneh[1] · Aladdin Abu-zant[2] · Yousef Sahoury[3] · Ekram Sahouri[3] · Ruba Abuamsha[4] · Mazen Salman[5]

Received: 13 December 2023 / Accepted: 31 January 2024

Abstract

The increasing incidence of multidrug-resistant (MDR) *Pseudomonas aeruginosa* is a worldwide problem, particularly among critically ill patients. Since it is not anticipated that any new treatments will be available in the near feature, our research aims to assess the efficacy and safety of colistin in the treatment of infections caused by *P. aeruginosa* in neutropenic leukemia patients. A study was conducted at two hospitals (i.e., Beit-Jala Hospital/Bethlehem; $n = 78$ and Augusta Victoria Hospital/Jerusalem; $n = 61$) over a period of 18 months. Using a confidence interval of 95%, a margin of error of 5%, and a response rate of 50%, demographic and clinical characteristics were analyzed. One of the major results of our study was that colistin-treated patients had a favorable clinical response at day six and less nephrotoxicity outcomes compared to the control group. Data analyses revealed a high incidence (50–63%; $n = 79$) of leukemia in both hospital groups. Microbiologic response, infection-related mortality, and relapse rates were not statistically significant between both groups. Our study demonstrated that colistin is highly useful and effective in the treatment of MDR *P. aeruginosa* in blood cancer patients. Colistin has proven superior to control group in terms of clinical response at day six. Our study has also shown lower nephrotoxicity rates, which is further encouraging and could support the potential of using colistin as an alternative therapy for such infections. As multidrug resistance continues to be a worldwide concern, the need for effective therapies such as colistin remains of great importance.

Keywords Colistimethate sodium · Colistin · Multidrug-resistant · Pseudomonas aeruginosa · Blood cancer · Treatment effectiveness · Nephrotoxicity

1 Introduction

Pseudomonas aeruginosa is a virulent opportunistic pathogen that is capable of causing various types of infections that can be associated with high morbidity and mortality rates. Several factors have been reported to increase the risk of having a *P. aeruginosa* infection, such as local weakening of immune defenses, collapse of the immune system, neutropenia, cancer, burns, steroid usage, and underlying lung diseases [1].

It is estimated that *P. aeruginosa* causes about 7% of all healthcare-associated infections worldwide [2, 3]. Interestingly this pathogen has been shown to cause about 20% of all ventilator-associated pneumonia (VAP) that is associated with a high (32–43%) mortality rate [4, 5]. In an appreciable proportion of the infections caused by *P. aeruginosa*, the pathogenic bacterium exhibited a multidrug resistance

✉ Mazen Salman
m.salman@ptuk.edu.ps

1 School of Medicine and Health Sciences, An-Najah National University (ANNU), Nablus, State of Palestine

2 Division of Microbiology and Immunology, Department of Biomedical Sciences, An-Najah National University (ANNU), Nablus, State of Palestine

3 Pharmacy Department, Faculty of Pharmacy, Nursing and Health Professions, Birzeit University, P.O. Box 14, Ramallah, State of Palestine

4 Department Applied and Molecular Biology, Palestine Technical University, Tulkarm, State of Palestine

5 Department Agricultural Biotechnology, Palestine Technical University, Tulkarm, State of Palestine

Published online: 06 March 2024

Table 1 Demographic information and clinical characteristics of patients in the colistin and control groups

Demographic and clinical characteristic of patients	No. (%) of patients		*P* value
	Colistin group ($n = 66$)	Control group ($n = 73$)	
Age (no [%] of patients)			
5–25	13 (19.697)	6 (8.219)	0.055
> 25–75	44 (66.667)	56 (76.71)	0.196
> 75	9 (13.636)	11 (15.068)	0.818
Sex (no [%] of patients)			
Female	25 (37.878)	24 (32.876)	0.544
Male	41 (62.121)	49 (67.123)	0.544
Underlying disease (no [%] of patients)			
Leukemia	42 (63.636)	37 (50.684)	0.129
Lymphoma/myeloma	12 (18.181)	13 (17.808)	0.954
Solid tumor	12 918.181)	23 (31.506)	0.075
ICU Stay (no [%] of patients)			
During infection	29 (43.939)	36 (49.315)	0.532
Within 30 days prior to infection	37 (56.06)	37 (50.685)	0.532
APACHE II Score (no [%] of patients)			
10–16	13 (19.696)	38 (52.054)	< 0.0001
17–22	28 (42.424)	30 (41.095)	0.876
23–28	25 (37.878)	5 (6.849)	< 0.0001
No. of patients with			
Mechanical ventilation within prior month (no [%] of patients)	30 (45.454)	49 (67.123)	0.011
Hemodialysis within prior month	21 (31.818)	16 (21.918)	0.195
Neutropenia within 30 days prior to infection	40 (60.606)	42 (57.534)	0.718
Neutropenia during infection	42 (63.636)	31 (42.466)	0.014
No. of patients with			
Pseudomonas infection or colonization (within prior year)			
Polymicrobial infection	28 (42.424)	17 (23.288)	0.018
Hospital admission within 30 days prior to infection	38 (57.576)	47 (64.384)	0.418
Nosocomial infection	27 (40.909)	18 (24.657)	0.044
Antibiotic resistance – number of classes			
Three classes	6 (9.090)	24 (32.876)	0.001
Four classes	35 (53.030)	32 (43.835)	0.286
Five classes	24 (36.363)	17 (23.287)	0.097
Six classes	1 (1.515)	0 (0)	0.475
Bacteremia	21 (31.818)	35 (47.945)	0.056
Pneumonia	33 (50)	29 (39.726)	0.230
UTI	7 (10.606)	12 (16.438)	0.332
Wound	0 (0)	2 (2.739)	0.274
Treatment duration (days)			
5–14	7 (10.606)	24 (32.876)	0.002
> 14–21	27 (40.909)	44 (60.273)	0.024
> 21–50	32 (48.484)	5 (6.849)	< 0.0001

(MDR) capability, rendering the treatment of these infections a serious clinical challenge.

The ability of *P. aeruginosa* to exhibit a multidrug resistance capability stems from its possessing natural resistance to several antibiotics as well as from its ability to develop acquired resistance to many antibiotics [2]. In addition, several factors, such as the use of carbapenem antibiotics for $\geq$ 7 days, a history of *P. aeruginosa* infection during the preceding year, and a history of chronic obstructive pulmonary disease, have been shown to promote the development of the multidrug resistance by this pathogen [6].

A worldwide multicenter retrospective study has shown that in about 30.5% of the nosocomial *P. aeruginosa* pneumonia, are MDR, explaining the high mortality rate among patients with nosocomial pneumonia caused by this pathogen [7]. A Palestinian study [8] has reported that *P. aeruginosa* accounts for about 41% of the total Gram-negative bacterial pathogens involved in infections among patients with hematologic malignancies. Another Palestinian study [9] has reported that about 21.6% and 60.8% of *P. aeruginosa* isolates obtained from clinical samples produce extended spectrum beta-lactamases (ESBLs) and metallo-beta-lactamases (MBLs), respectively, which enables these isolates to exhibit multidrug resistance.

Due to the high morbidity and mortality rates of infections caused by multidrug-resistant *P. aeruginosa*, the WHO has listed this pathogen in an urgent need to find or to develop new antibiotics that are effective for the treatment of its infections [10]. However, there is a serious concern regarding the possibility of developing new anti-pseudomonal drugs in the near future.

Colistimethate sodium, a circular polypeptide with a tripeptide side chain [11], has an excellent antibacterial activity against many Gram-negative organisms. Currently, there are many attempts to use this antibiotic for the treatment of infections caused by multidrug-resistant Gram-negative bacteria including those caused by *P. aeruginosa*. Unfortunately, the use of colistin has been limited due to its reported neurotoxicity and nephrotoxicity [12]. Despite this and in terms of the current unavailability of new anti-pseudomonal drugs, colistin represents the last resort option for the treatment of infections caused by MDR *P. aeruginosa* [13].

Many recent studies have been investigating the safety and efficacy of colistin in treating *P. aeruginosa* infections. Our study will also be evaluating similar issues, in an attempt to shed more light on the possibility of using this antibiotic for the treatment of infections caused by MDR *P. aeruginosa*, particularly in neutropenic leukemia patients. The aim of our study was to evaluate the efficacy and safety of colistin in the treatment of infections caused by multidrug-resistant *P. aeruginosa* in neutropenic blood cancer patients in comparison with other anti-pseudomonal antibiotics.

2 Materials and Methods

2.1 Study Design and Settings

A case study was conducted at two hospitals (Beit-Jala Hospital/Bethlehem and Augusta Victoria Hospital/Jerusalem, Palestine.) over a period of about 18 months to assess both the efficacy and the safety of Colistin (Colistimethate sodium) intravenous IV route of administration used for the treatment of infections of neutropenic blood cancer patients caused by multidrug-resistant *P. aeruginosa* in comparison with other anti-pseudomonal antibiotics intravenous route.

2.2 Study Population, Inclusion, and Exclusion Criteria

Neutropenic blood cancer patients from Intensive Care Unit (ICU) and non-ICU locations with normal renal function (creatinine clearance 80 mL/min) requiring at least 5 days of intravenous Colistin or other antibiotics for treatment of MDR Gram-negative infections *P. aeruginosa* infection were selected based on infection control surveillance records and microbiology laboratory database. While renal dysfunction patients or death in < 72 h were excluded criteria. Some of these patients were treated with Colistin (colistin group, $n = 66$), while others (Control group, $n = 73$) were treated by using at least one anti-pseudomonal drug (such as a beta-lactam antibiotic or a Quinolone antibiotic) to which the infecting *P. aeruginosa* was susceptible to Colistin under in vitro susceptibility testing. Patients of the Colistin group were treated with Colistin either because the infecting *P. aeruginosa* was only susceptible to colistin, or the clinical conditions of the infected patients were not improving despite the use of antibiotics to which the infecting *P. aeruginosa* was/were susceptible to the drug under in vitro conditions.

2.3 Study Tool, Validity, and Reliability

The study tool used in this research was a questionnaire covering demographic and clinical variables of the study sample. Data for this questionnaire were gathered from medical records at the two hospitals; Beit-Jala Hospital/Bethlehem and Augusta Victoria Hospital/Jerusalem, Palestine. Several measures were taken to ensure validity of our study. For instance, content validity was ensured by conducting thorough literature review before forming a questionnaire to make sure it was comprehensive and covering all aspects.

2.4 Statistical Analysis

Statistical analysis has been conducted using the XLSTAT Version 2021 (Addinosoft 2021) for Excel [14]. Initially, the

data were cleaned and data with input errors was excluded. *P* values were statistical significance if they were < 0.05.

3 Results

During the study period, 139 patients infected with multidrug-resistant *P. aeruginosa* were identified, of whom 66 were treated with Colistin and 73 were treated with other antipseudomonal agents. Data in Table 1 represent the demographic and clinical characteristics of patients in both colistin and control groups. Most patients were males (colistin group 62.12%, Control group 67.12%), and most patients aged between 25 and 75 (colistin group 66.67%, Control group 76.71%) ($p = 0.196$).

The majority of patients in both groups had leukemia as an underlying disease, with slight differences in percentage of the other diseases (leukemia 63.64%, lymphoma/myeloma 18.18%, and18.18% with solid tumor for the Colistin group, and leukemia 50.69%, lymphoma/myeloma 17.81%, and 31.51% with solid tumor for the control group) as illustrated in Fig. 1.

3.1 The Median Acute Physiology and Chronic Health Evaluation II Range

APACHE II was slightly different between both groups; the median score of the Colistin group was 17–22, compared to 10–16 in the Control group as shown in Fig. 2. Around 37.88% of Control group patients had an APACHE II score of 23–28, indicating a worse clinical state, which is expected since those patients of non-improving status were the ones with whom we resort to using Colistin. On the other hand, 52.05% of patients in the Control group had an APACHE II score of 10–16, compared to only 19.7% of Colistin patients ($p < 0.0001$).

Colistin-treated patients had significantly higher neutropenia during infection (63.64% in colistin group compared to 42.47% in control group, $p = 0.014$). They had a polymicrobial infection (42.42%) compared to the control group (23.29%), $p = 0.018$, as well as a nosocomial infection (40.1% for the colistin group, and 24.66% for the control group, $p = 0.04$) as demonstrated in Table 1.

The colistin group required significantly extended treatment durations, as about 48.48% of patients required more than 21–50 days of treatment, compared to the control group where only 6.8% required that long ($p < 0.0001$), as shown in Fig. 3.

Regarding ICU patients at the time of infection, there were 29 (43.94%) critically ill patients in the colistin group and 36 (49.32%) critically ill patients in the control group. These were neutropenic during the infection (no statistical significance). However, statistically significant difference was observed between both groups, with the colistin group showing (neutropenia 63.64%, $n = 42$) and the control group showing (42.46%, $n = 31$, $p = 0.014$) as in Table 1. Interestingly, our study has revealed statistically significant differences in nephrotoxicity outcomes between colistin group normal dosage regimen 2.5–5 mg/kg/day divided q6-12 h IV without higher doses used not to exceed 5 mg/kg/day and control group (Table 2). Specifically, Colistin resulted in nephrotoxicity in around 24.24% patients, compared to the control group where 57.53% patients exhibited nephrotoxicity ($p < 0.0001$).

Table 2 Outcomes of colistin group versus control group

Outcome	No. (%) of patients		
	Colistin group ($n = 66$)	Control group ($n = 73$)	*P* value
Nephrotoxicity	16 (24.24)	42 (57.53)	< 0.0001
Clinical response			
Day 6	23 (34.89)	0 (0)	< 0.0001
End of therapy	43 (65.15)	73 (100)	< 0.0001
Microbiologic response			
Day 6	18 (27.27)	23 (31.51)	0.592
End of therapy	48 (72.73)	50 (68.49)	0.592
Relapse	8 (12.12)	12 (16.44)	0.483
Infection-related mortality	5 (7.58)	6 (8.22)	0.897

Further analysis has shown that nephrotoxicity, as assessed by creatinine clearance, it is used to determine whether or not dose adjustment is required [Renal Impairment CrCl > 80 mL/min: No dosage adjustment required. CrCl 50–79 mL/min: 2.5–3.8 mg/kg/day IV divided q12 h. CrCl 30–49 mL/min: 2.5 mg/kg/day IV q Day or divided q12 h. CrCl 10–29 mL/min: 1.5 mg/kg IV q36 h]. Rates were similar between different underlying diseases, with slightly lower toxicity rates in patients with Solid tumors compared to others, especially in the Colistin group (Fig. 4).

As mentioned above, around half the patients in the Colistin-treated group required a longer treatment duration of > 21–50 days with dose adjustment for some patients due to an increase in the serum creatinine more than 1.35 mg/dl without any other complications appearing. On further analysis, it was noted that treatment duration had no significant statistical association on nephrotoxicity outcomes as depicted in Fig. 5; $p = 0.523$).

Finally, the results showed a statistically significant difference in clinical response of resolution of signs and symptoms of infection between the colistin group and the control group. As illustrated in Table 2, Colistin-treated patients demonstrated a much higher rate of clinical improvement on day 6

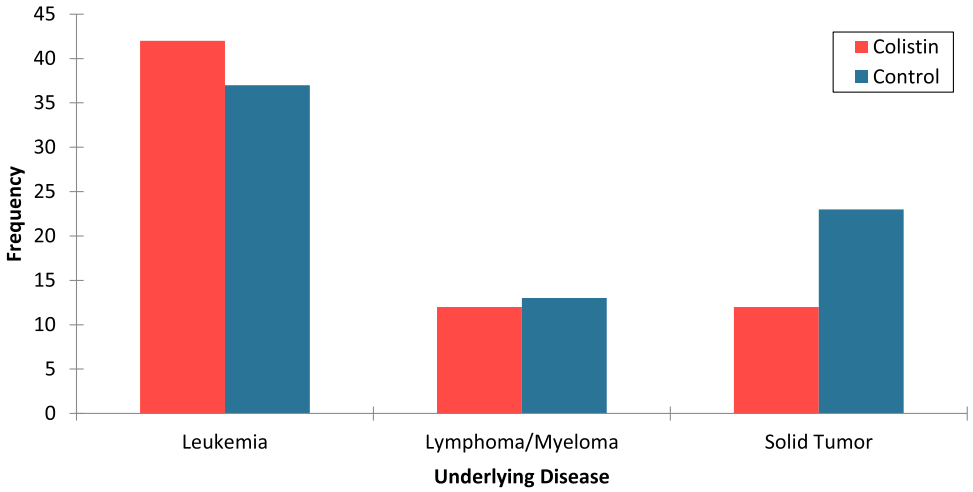

Fig. 1 Distribution of underlying diseases between the colistin versus control group

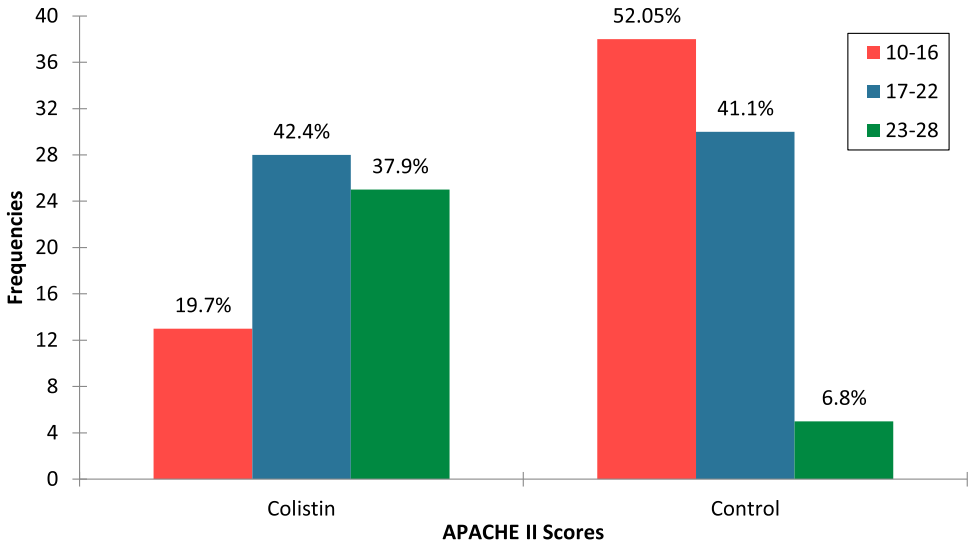

Fig. 2 Median APACHE II scores between the colistin and control groups

compared to the control group, with approximately 34.89% of patients showing a positive clinical response at that time, in contrast, all control group patients responded only at the end of therapy ($p < 0.0001$). Patients in the control group had a slightly higher relapse rate than Colistin-treated patients, reaching ~ 16.4% in the control group compared to ~ 12.1% in the colistin group, but such difference was not significant ($p = 0.483$) as shown in Fig. 6.

There were also no statistically significant differences in microbiologic response or infection-related mortality. Table 3 demonstrates the calculated odds ratios for variables and outcomes. These data suggest that patients who had bacteremia were 2.27 times more like than patients without bacteremia to have higher nephrotoxicity outcomes, with confidence interval of (1.13, 4.54) indicating strong association.

4 Discussion

An important finding in our study was that colistin indeed demonstrated better clinical response at day 6 in patients compared to the control group. Additionally, it showed lower nephrotoxicity rates. Our results about the Colistin efficacy were consistent with results reported in other studies [15–18]. Interestingly, some studies showed no difference in nephrotoxicity rates in the colistin group [15, 16, 19, 20], while others showed higher nephrotoxicity outcomes after Colistin treatment [21, 22] contrary to our study, which showed lower nephrotoxicity rates in the colistin group. All of these findings indicate that Colistin may be an alternative therapy for cancer patients infected with MDR *P. aeruginosa*; the results justify the use of Colistin in therapy.

In the late 1960s, *P. aeruginosa* emerged as a major pathogen, accounting for ~ 11% of bacteremia cases and 17% of nosocomial respiratory tract infections with high morbidity and mortality [23]. This posed a serious risk to patients

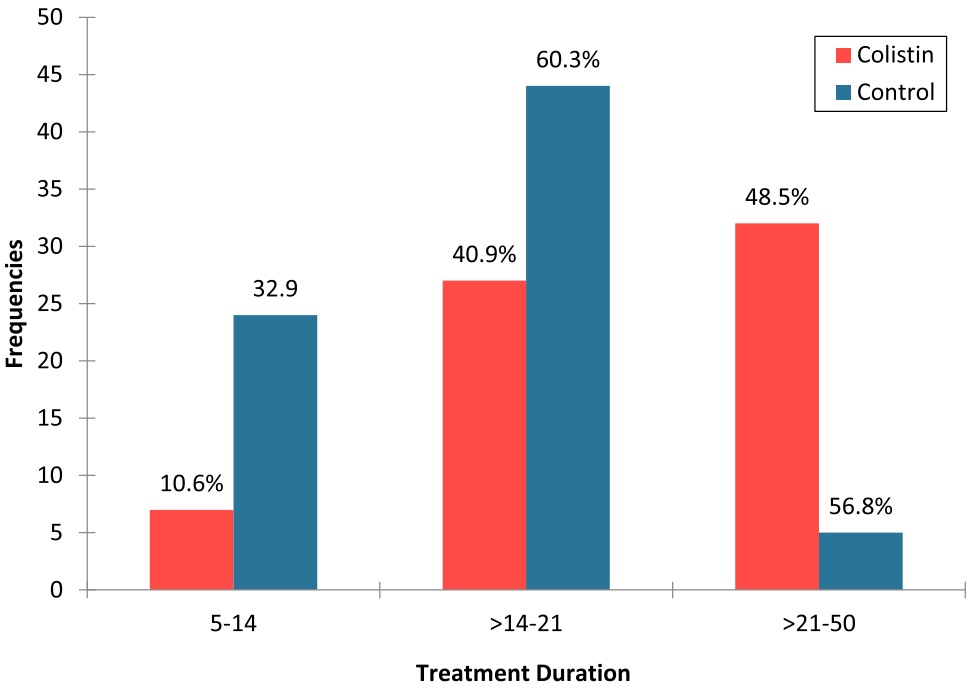

Fig. 3 Distribution of treatment duration required between the colistin group and control group

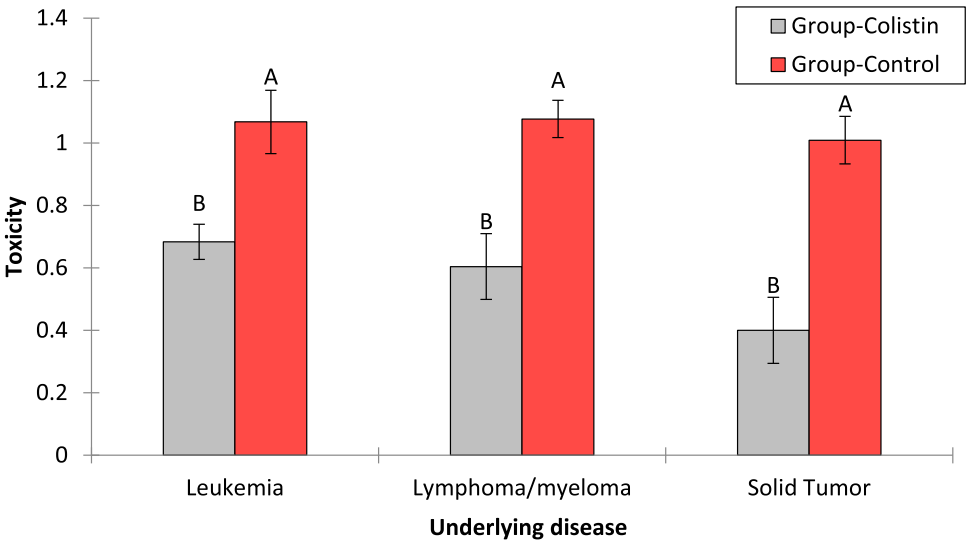

Fig. 4 Median serum creatinine change before and after treatment of colistin versus control groups in different underlying diseases. Columns of different letters are statistically significant after Tukey's HSD test using ANOVA at $p < 0.05$

with compromised immunity s including those with severe neutropenia, cystic fibrosis, and severe burn injuries. In one study, the percentage of cancer patients (many of whom had severe neutropenia) who recovered from *Pseudomonas* bacteremia was 14% [24]. Among a set of 12 studies conducted prior to 1976 on gram negative bacteremia, mortality rates ranged from 37 to 77% [16, 25].

In the recent years, the increased emergence of multidrug resistance has posed significant risk in clinical practice. More microorganisms are classified as MDR, extensive drug-resistant (XDR), and even pandrug-resistant (PDR, or totally drug-resistant TDR) [26], and are reported by many international bodies (including the WHO [27], the European Center for Disease Control and Prevention ECDC [28], the UK National Health Service NHS [29], and the US Centers for Disease Control CDC [30]), all have emphasized the importance of finding urgent treatment for those infections. MDR bacteria are associated with prolonged hospitalization, decreased quality of life (QoL), poor clinical outcome, and increased morbidity and mortality in the affected/afflicted patients [31]. *P. aeruginosa* is considered one of the members of the "ESKAPE" pathogens (***Enterococcus faecium***, ***Staphylococcus. aureus*** or recently ***Stenotrophomonas maltophilia***, ***Klebsiella pneumoniae*** or recently C: *Clostridioides difficile*, ***Acinetobacter baumannii***, P: ***P****. aeruginosa*, ***Enterobacter spp***.,); all of these bacteria in the acronym

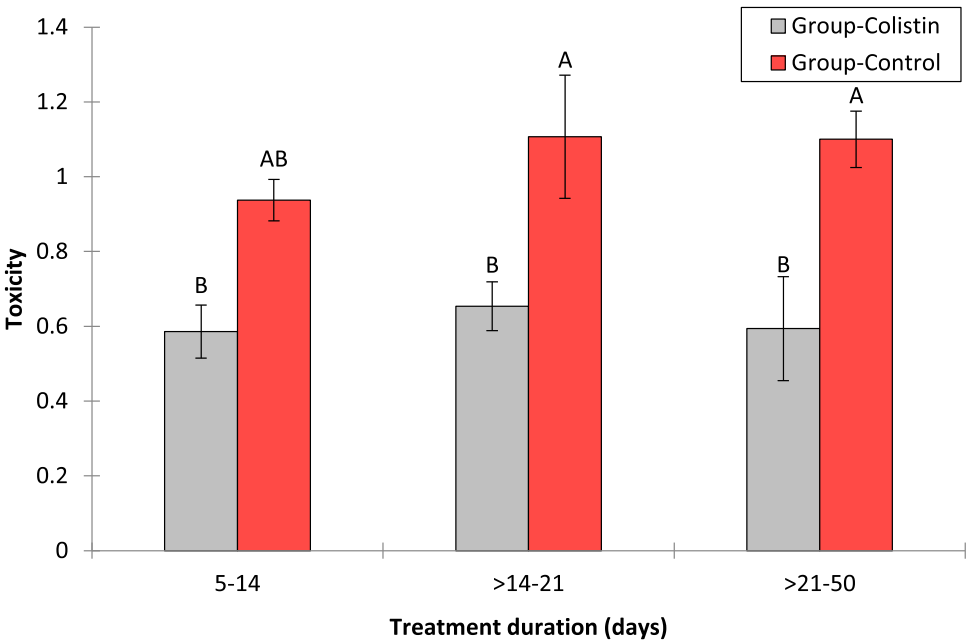

Fig. 5 Median serum creatinine change before and after treatment comparing different treatment durations in the colistin and control groups. Columns of different letters are statistically significant after Tukey's HSD test using ANOVA at $p < 0.05$

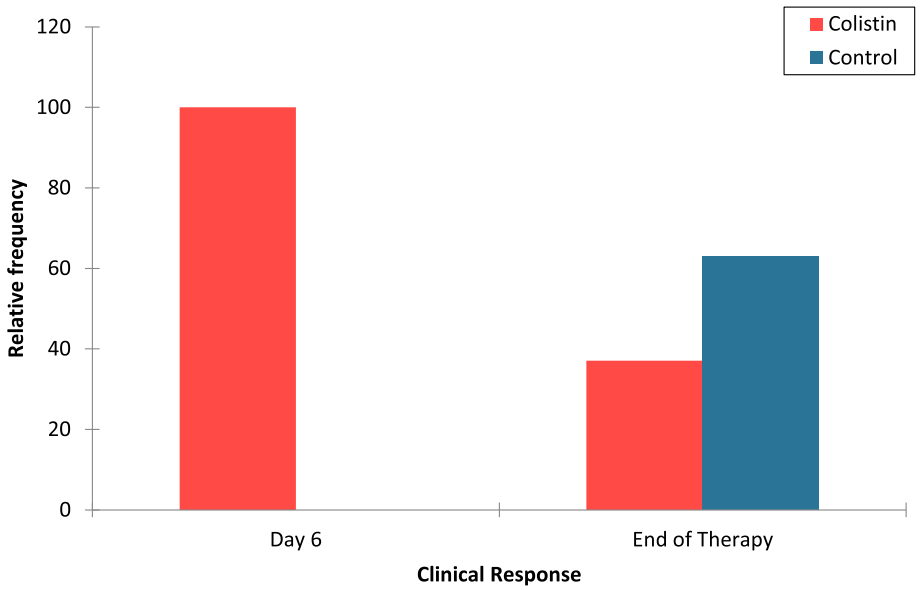

Fig. 6 Frequency of patients who showed a clinical response at day 6 compared to those who showed at the end of therapy in the colistin group compared to the control group

pose the most concern and risk from a clinical and public health perspective [32]. In a list published by the WHO, carbapenem-resistant *P. aeruginosa* was classified as a critical priority pathogen [33]. More alarmingly, a recent PDR strain of *P. aeruginosa* was described and found capable of using ampicillin as a sole carbon source [34, 35].

Considering this increased emergence of multidrug-resistant *P. aeruginosa*, ranging from 15 to 30% in some geographical areas [36–38], it has become vital to find appropriate treatment options. Colistin has been considered a last resort option for those resistant to several antibiotics, but its use has been limited due to reported nephrotoxicity in some studies [39]. Interestingly, our study has shown that nephrotoxicity outcomes were actually lower with using Colistin compared to using other antipseudomonal drugs. Similar outcomes were noted in other studies, which report less nephrotoxic incidences with polymyxin [40]; specifically, one study reporting only 6.3% patients that exhibited nephrotoxicity after treatment [41].

Our study was in agreement with several studies that reported good clinical response against resistant infections of MDR *P. aeruginosa* after using colistin, with therapeutic response of improved disease signs and symptoms after colistin use for a minimum of 5 days, followed by normalized hematological and biochemical changes, ranging

Table 3 Odds ratios and confidence intervals for variables and outcomes

	CI (95%)		
	OR	Lower limit	Upper limit
Nephrotoxicity			
Treatment	0.24	0.11	0.49
ICU stay during infection	1.25	0.64	2.46
Bacteremia	2.27	1.13	4.54
Pneumonia	0.43	0.21	0.87
Clinical response			
ICU stay during infection	1.05	0.43	2.58
Bacteremia	0.6	0.23	1.56
Pneumonia	1.17	0.48	2.86
Microbiologic response			
Treatment	0.82	0.39	1.7
ICU stay during infection	2.27	1.07	4.78
Bacteremia	0.59	0.28	1.28
Pneumonia	1.46	0.7	3.04
Relapse			
Treatment	0.7	0.27	1.84
ICU Stay during infection	0.73	0.28	1.9
Bacteremia	1.25	0.48	3.26
Pneumonia	0.8	0.31	2.11
Infection-related death			
Treatment	0.92	0.27	3.15
ICU Stay during infection	0.23	0.05	1.1
Bacteremia	1.26	0.36	4.34
Pneumonia	1.04	0.3	3.58

between 52 and 75% [15, 16]. It is important to note that most of these studies had colistin administered in combination with other antipseudomonal drugs, so its efficacy could not be accurately demonstrated [41–43], unlike in our study in which most patients received colistin alone as a monotherapy compared to a control group, and still showed lower nephrotoxicity rates and good clinical outcome. This further supports the use of colistin as an alternative therapy for *P. aeruginosa* infections.

5 Limitations and Strengths of the Study

Our study has some limitations. For instance, since our study is a retrospective case–control study, it was difficult to establish a causation between the cases and control group, as we can only establish an association. In addition, it is difficult to eliminate confounding variables related to *P. aeruginosa* strains and their drug resistance patterns as well as bacterial virulence factors affecting patients which could impact response to treatment. Analyzing those different strains and their virulence and their different response to treatment may be a compelling topic for future research. On the other hand, our study has several strengths as it has a focused research question that helped us in forming accurate association. To the best of our knowledge this study is the first of its kind in Palestine. Additionally, our sample size of 139 patients was sufficient to enhance the statistical power of our study. Finally, the resulting data are a good starting point for further exploratory research, and generation of more hypotheses about potential risk factors that may affect the clinical outcome, including the differences in *P. aeruginosa* strains, resistance patterns, and virulence factors between patients.

6 Conclusion and Recommendations

In conclusion, our study has yielded important result regarding the safety and efficacy of Colistin in the treatment of MDR *P. aeruginosa* in blood cancer patients. Our findings are encouraging and could further support the possibility of using Colistin (singly or in combination) as an alternative therapy for such clinical scenarios. For instance, colistin has proven superior to Control group in terms of clinical response at day 6, as well as showing promising results regarding lower nephrotoxicity rates. Notably, considering several studies have shown increased nephrotoxicity rates with Colistin, our study has shown lower nephrotoxicity rates, which further supports the potential of Colistin in managing such infections.

Given our study's indication that it does not significantly increase nephrotoxicity, Colistin may now be reconsidered as an alternative treatment for such patients, as the results have proven it both safe and effective.

Acknowledgements Thanks, are due to the staff of Beit-Jala Hospital/Bethlehem and Augusta Victoria Hospital/Jerusalem for facilitating this work.

Declarations

Conflict of interest All authors declare no conflict of interest.

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