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Ferraris KJB, Maramba-Lazarte CNC. Clinical Outcomes and Safety of Polymyxin-B-based Combination Therapy in the Treatment of Multidrug-resistant Gram-negative Infections in Pediatric Patients
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ORIGINAL ARTICLE

CLINICAL OUTCOMES AND SAFETY OF POLYMYXIN-B-BASED COMBINATION THERAPY IN THE TREATMENT OF MULTIDRUG-RESISTANT GRAM-NEGATIVE INFECTIONS IN PEDIATRIC PATIENTS

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ABSTRACT

Background: Multidrug-resistant gram-negative (MDR GN) infections pose a significant threat to pediatric health. One of the treatment options in resource-limited settings is polymyxin-based combination therapy. However, evidence on the safety and clinical effectiveness of polymyxin B in children is scarce.

Objectives: This study described the outcomes of mortality, bacteriologic cure and clinical response in pediatric patients with MDR GN infections treated with polymyxin-B-based combination therapy. Adverse drug events (ADE) are likewise described.

Methodology: This is a retrospective descriptive study conducted at the Philippine General Hospital (PGH) among pediatric inpatients from December 2020 to June 2023 with MDR GN infections treated with polymyxin B (PmB), combined with at least one other antibiotic with gram-negative coverage for at least 48 hours. Frequency and rates of the outcomes were measured and analyzed, in relation to the bacterial groups (Enterobacterales, Acinetobacter spp., Pseudomonas aeruginosa) and combination antibiotic regimens used, i.e., meropenem- and fluoroquinolone-containing regimen (PmB+MEM vs PmB+FQ). Frequency of ADEs were measured.

Results: A total of 172 cases in 136 patients were reviewed. The rates for 14-day mortality, failure in bacteriologic cure, and failure in clinical response were 26%, 15%, and 19%, respectively. In *Enterobacterales* infections, PmB+FQ demonstrated lower rates of mortality, failure in bacteriologic cure, and failure in clinical responses. On the other hand, in *Acinetobacter* infections, PmB+MEM numerically had lower rates for the same outcomes. The *Pseudomonas* group had conflicting data on which regimen is numerically more favorable overall. No statistically significant differences were found in the outcomes. ADEs noted were tubulopathy (5 cases), anaphylaxis (2 cases), and neurotoxicity (1 case).

Conclusion: Polymyxin-B-based combination therapy appears to be an acceptable treatment option for MDR GN infections in children, especially in settings where novel antibiotics are not accessible. Safety profiles indicate common but manageable adverse effects.

KEYWORDS: *polymyxin B, children, multidrug-resistant, gram-negative organisms*

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INTRODUCTION

Multidrug-resistant gram-negative (MDR GN) infections have increased notably, particularly during the COVID-19 pandemic,[1] and remain to be major contributors to pediatric morbidity and mortality worldwide especially in hospitalized children.[2] Between December 2020 and June 2023, over 500 cases of MDR GN infections were identified in the pediatric population at the Philippine General Hospital (PGH).[3]

The current clinical practice for treating systemic infections due to multidrug-resistant Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* in children relies on the 2023 guidance document for antimicrobial-resistant (AMR) infections from the Infectious Diseases Society of America (IDSA), which prioritizes novel or contemporary antibiotics.[4] However, only ceftazidime-avibactam is available at PGH as of this writing. In general, limited access to these newer drugs, high costs, additional regulatory restrictions, and local technical constraints in susceptibility testing hinder effective implementation. Moreover, the use of this drug is currently approved by the U.S. Food and Drug Administration only for specific conditions in children, i.e., complicated intraabdominal or urinary tract infections (UTI).[5]

Hence, the Division of Infectious and Tropical Diseases in Pediatrics (INTROP) of PGH has used the polymyxins (i.e., colistin and polymyxin B), in combination with other antibiotics, as salvage treatment to optimize therapeutic efficacy and to prevent the development of further resistance. Polymyxins are concentration-dependent antibiotics that bind to lipopolysaccharides (LPS) and phospholipids in the outer cell membrane of gram-negative bacteria (GNB), leading to disruption of the cell wall and subsequent leakage of intracellular contents and cell death. In vitro studies show that they can also neutralize the LPS itself and may reduce the endotoxin effects of GNB. They are considered highly nephrotoxic agents with narrow therapeutic indices, hence, usage of these is often deemed as a "last resort."[6]

Polymyxin B is the preferred agent for invasive infections because of its wide distribution throughout the body and lower potential to cause nephrotoxicity.[6] Unlike colistin, there is a scarcity of real-world data for the use of polymyxin B in pediatric patients.[7] The available information is often extrapolated from studies involving adults or mixed populations, those involving colistin only, or from pediatric studies with small sample sizes, underscoring the need for context-specific evidence.[8,9,10]

Thus, this study aims to describe the clinical outcomes (in terms of mortality, bacteriologic cure, and clinical response) of the pediatric patients with MDR GN infections in PGH treated with polymyxin-B-based combination therapy. The same outcomes will also be compared per two common and specific combinations of antibiotics. Adverse effects will also be described. Ultimately, this study aims to provide additional real-world evidence for use of polymyxin B in children and to contribute valuable insights for antimicrobial stewardship and prescription practices in managing MDR GN infections in children locally.

MATERIALS AND METHODS

This is a 31-month retrospective chart review done at the INTROP Division and the Department of Pediatrics of pediatric inpatients from December 2020 to June 2023. Sampling was purposive, i.e., only (1) pediatric inpatients 18 years old and below, (2) diagnosed with an infection (e.g., bloodstream infection [BSI], pneumonia, UTI, central nervous system infection [CNSI], skin and soft tissue infection [SSTI], surgical site infection [SSI] or intraabdominal infection [IAI]) (3) due to a laboratory-confirmed gram-negative bacterial isolate (that is deemed truly pathogenic by the clinician), (4) nonsusceptible to at least one agent in at least three antibiotic classes (MDR), and (5) who were treated with polymyxin B and at least one other antibiotic with gram-negative coverage for at least 48 hours, were included in the study.

The study protocol, approved by the University of the Philippine Manila Research Ethics Board, followed the guidelines set by the 2017 National Ethical Guidelines for Health and Health-Related Research and the Data Privacy Act of 2012. The principal investigator and data collector were granted access to the electronic charts through passcodes by the data privacy officer of the Health Records Management Section of the UP-PGH Health Information Management Division. The electronic data gathered and the passcodes have been stored in a password-protected folder in the Google drive of the INTROP Division and will be deleted after 5 years. All information was kept confidential and only number codes were assigned to each patient record. The data sent to the statistician were also anonymized. As this study is primarily descriptive and mainly employed chart review of a vulnerable population (i.e., pediatric age group), there was no direct benefit nor harm nor active intervention to the patients. The potential risk for breach in privacy and confidentiality is very minimal and is further decreased by data anonymization and by the precautions aforementioned. Thus, a waiver of informed consent was also requested and granted. There were no financial nor professional conflicts of interest in the conduct of this study.

Data Collection. From the census of the INTROP Division, we obtained a preliminary list of 237 pediatric inpatients who have infections caused by MDR GN bacteria and who were prescribed with polymyxin-B-based combination therapy. The passcodes of the respective electronic charts were requested from the Medical Records Section. For patients having more than one growth of MDR GN or if with recurrence, a different case report form was employed for each bout. Demographic and clinical data were collected, including age at diagnosis, sex, comorbidities, hospital ward upon diagnosis, infection type/site, isolated pathogens, the level of resistance (whether MDR, extensively drug-resistant [XDR], or pan-drug-resistant [PDR] as defined in the 2012 joint initiative document by the respective U.S. and European Centers for Disease Control and Prevention [CDC]),[11] presence of resistance genes, concurrent antibiotics with polymyxin B, vital signs at onset of illness (blood pressure, heart rate, respiratory rate, temperature, O2 saturations), and initial laboratory markers (white blood cell count, C-reactive protein, procalcitonin, and capillary blood glucose). Any adverse effects and their nature were also documented.

Key concepts in this study were defined as follows:

- *Bacteriologic cure* – an initially positive culture taken on diagnosis, followed by at least one negative repeat culture of the appropriate specimen (blood, urine, or CSF) taken on, at the earliest, day 2 to 3 of antibiotics.
- *Clinical response* – general improvement or resolution of initial symptoms and/or improvement of laboratory markers, as assessed by the physicians in charge of the patient, after at least 48 hours of antibiotics.
- *Extensively drug-resistant (XDR)* – nonsusceptibility to at least one antibiotic in all but two or fewer antimicrobial categories, i.e., bacterial isolates remain susceptible to at least one antibiotic in only one or two antimicrobial categories.
- *Mortality* – Died of any cause within 14 days of initiation of treatment.
- *Multidrug-resistant (MDR)* – Nonsusceptibility to at least one antibiotic in three or more antimicrobial categories.
- *Pandrug-resistant (PDR)* – Nonsusceptibility to all agents tested in all antimicrobial categories included.

From the list of 237, sixty-five cases were excluded upon further review: four patients were culture-negative and were only clinically diagnosed (one of which was positive in rectal swab culture only as part of carrier surveillance and not as sepsis work-up; while another was positive in a non-culture microbiologic test, i.e., respiratory multiplex

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polymerase chain reaction assay); thirty-three had non-MDR gram-negative isolates, while 28 had polymyxin B for less than 48 hours only. With these, the study included 172 infection episodes or cases from 136 distinct patients. However, for the adverse events, we incorporated an additional three cases (though they did not meet the inclusion criterion of at least 48 hours of polymyxin B) in the frequency data for the sake of discussion since these were pertinent.

Data Analysis. The frequency and rates were calculated for the demographic and clinical data, as well as for each outcome (i.e., 14-day all-cause mortality, bacteriologic cure, and clinical response) in relation to each major bacterial group of MDR GN (Enterobacterales, *Acinetobacter* species [spp.]. and *P. aeruginosa*) and the main partner antibiotic given. Only the polymyxin-B-based combinations containing either (1) meropenem (n=70) or (2) fluoroquinolone (e.g., ciprofloxacin or levofloxacin, n=88) were compared for such, without regard for the third antibiotic in the regimen. There were no combinations containing both meropenem and fluoroquinolone. The rest of the other polymyxin-B-based combinations, e.g., containing only a non-carbapenem beta-lactam or only an aminoglycoside, were not compared anymore, since those cases numbered only one to four at most, and hence, may not be feasible for analysis. Fisher's exact test was done to check for statistically significant differences (set at $p \leq 0.05$) between the groups.

RESULTS

A total of 172 cases in 136 unique patients fulfilled the inclusion criteria, ranging from two days old to 18 years old. The mean age is three years, while the median age is one month old (interquartile range of 3 years). The majority of the patients are preterm (32.3%), followed by infants of >28 days post-conceptual age (PCA) to <12 months old (27.9%). The sex is fairly distributed, with 72 males (53%) and 64 females (47%). More than half of the patients (51.5%) are from the neonatal intensive care unit (NICU).

Table 1. Demographic Profile of Pediatric Patients with MDR GN infections treated with Polymyxin-B-based Combination Therapy

	Frequency	%
Age (N=136)		
Term neonates	15	11.0
Preterm neonates	44	32.3
>28 days (PCA) to <12 months	38	27.9
1 to <5 years	9	6.6
5 to <10 years	7	5.1
10-18 years old	23	16.9
Admission Ward (N=136)		
NICU	70	51.5
General Pediatrics Ward	36	26.5
Hematology-Oncology Ward	7	5.1
Burn Unit	7	5.1
PICU	6	4.4
COVID Ward	4	2.9
Others	6	4.4
Type/Site of Infection (N=172)		
Non-CLABSI	44	25.6
CLABSI	53	30.8
Pneumonia		
Non-ventilator-associated	12	7.0
Ventilator-associated	37	21.5
CNS Infection	9	5.2
UTI		
Non-catheter-associated	3	1.7
Catheter-associated	1	0.6
Peritonitis	2	1.2
Surgical Site Infection	4	2.3
Nonsurgical Skin and Soft Tissue	7	4.1
Comorbidities		
Prematurity	44	32.2
Cardiovascular	40	29.4
Neurologic	37	27.2
Gastrointestinal/Nutritional	32	23.5
Pulmonary	28	20.6
Genetics/Syndromic	18	13.2
Hematologic/Oncologic	14	10.3
Chronic Infections	11	8.1
Renal/Genitourinary	9	6.7
Burns	7	5.1
Orthopedic	3	2.2
Endocrine	2	1.5
Rheumatologic	2	1.5
Post-Surgery	23	16.9

Excluding prematurity, the most common comorbidities are cardiovascular (40 patients; 29.4%), neurologic (37 patients; 27.2%), and

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gastrointestinal (32 patients; 23.5%) conditions. Twenty-three patients (16.9%) have a history of recent (within <12 months) major surgery upon diagnosis of MDR GN infection (Table 1).

Across the 172 cases, the most common clinical manifestations include fever (54.7%), tachypnea (48.8%), and tachycardia (73.2%). A total of 58 patients (33.7%) went into shock, with nine of them hypotensive on diagnosis. Half of the infectious episodes showed abnormal white blood cell (WBC) count at diagnosis, with 19.8% showing leukopenia and 30.2% showing leukocytosis for age. Among 168 cases with platelet count determination upon diagnosis, eighty (47.6%) showed thrombocytopenia, while 31 (18.5%) showed thrombocytosis.

Table 2. Clinical Manifestations and Laboratory Markers of Pediatric Patients with MDR GN Infections Treated with Polymyxin-B-Based Combination Therapy

Clinical Manifestations	Frequency	%
Fever	94	54.7
Hypothermia	23	13.4
Temperature instability	10	5.8
Tachycardia	126	73.2
Tachypnea	84	48.8
Shock	58	33.7
Hypotension	9	5.2
Pallor	25	14.5
Abdominal Distention	34	19.8
WBC count	*N = 172*	
Leukopenic for age	34	19.8
Normal	86	50
Leukocytosis for age	52	30.2
Platelet count (cells/L)	*N = 168*	
Thrombocytopenia (<150 x 10^9)	80	47.6
Normal	57	33.9
Thrombocytosis (>450 x 10^9)	31	18.5
Capillary blood glucose	*N = 129*	
Hypoglycemia	42	32.6
Normal	77	59.7
Hyperglycemia	8	6.2
Unstable	2	1.6
Procalcitonin (ng/mL)	*N = 165*	
≤0.25	20	12.1
>0.25 to <1.00	28	2.3
≥1.00	117	70.9
CRP (mg/L)	*N = 109*	
<12	13	11.9
≥12	96	88.1

A total of 96 (88.1%) out of 109 cases with baseline CRP showed elevated levels of at least 12 mg/L, while a total of 117 (70.9%) out of 165 cases with baseline procalcitonin showed elevated levels of at least 1 ng/mL (Table 2).

The types of infection were mainly categorized by the anatomical site where the MDR GN bacteria were isolated by culture. BSIs constituted the most frequent type, accounting for 97 cases (56.4%), fifty-three of which are associated with central lines. This is followed by 49 cases of pneumonia, which included 37 ventilator-associated instances. Other types encompassed CNSI, UTI, IAIs, SSIs, and nonsurgical SSTIs, each with fewer than ten instances (Tables 1 and 3). Only three large groups of bacteria composed the 172 cases. The most common are the Enterobacterales, comprising 97 (56.4%) episodes, distributed among *Klebsiella pneumoniae* (70 cases or 40.7%), *K. oxytoca* (10 cases or 5.8%), *Escherichia coli* (10 cases or 5.8%), *Enterobacter cloacae* (5 cases or 2.9%) and with one case each for *Citrobacter freundii* and *C. werkmannii.* The *Acinetobacter* spp. comprised the second most common bacterial group at 64 cases (37.2%), the majority of which (60 cases) are caused by *A. baumannii*. (Table 3).

Table 3. Types of Infections and Pathogens Isolated in Pediatric Patients with MDR GN Infections Treated with Polymyxin-B-Based Combination Therapy

	Non-CLABSI	CLABSI	PNA	UTI	SSI	SSTI	IAI	CNSI	Total
E	**29**	**33**	**20**	**4**	**4**	**1**	**2**	**4**	**97**
Kpn	19	25	18	2	2		1	3	70
Kox	5	5							10
Eco	4		1	2	1		1	1	10
Ecl		3	1		1				5
Cfr						1			1
Cwe	1								1
ACB	**14**	**15**	**25**			**5**		**5**	**64**
Aba	13	14	24			4		5	60
Ajo			1						1
Ano						1			1
Api		1							1
Aur	1								1
Pae	**1**	**5**	**4**			**1**			**11**
TOTAL	44 (25.6)	53 (30.8)	49 (28.5)	4 (2.3)	4 (2.3)	7 (4.1)	2 (1.2)	9 (5.2)	172

Legend: Aba = Acinetobacter baumannii. ACB = Acinetobacter group. Ajo = Acinetobacter johnsonii. Ano = Acinetobacter nosocomialis. Api = Acinetobacter pittii. Aur = Acinetobacter ursungii. Cfr = Citrobacter freundii. CLABSI = Central-line-associated bloodstream infection. CNSI = Central nervous system infection. Cwe = Citrobacter werkmanii. E = Enterobacterales. Ecl = Enterobacter cloacae. Eco = Escherichia coli. IAI = Intraabdominal infection. Kox = Klebsiella oxytoca. Kpn = Klebsiella pneumoniae. Pae = Pseudomonas aeruginosa. PNA = Pneumonia. SSI = Surgical site infection. SSTI = Skin and soft tissue infection. UTI = Urinary tract infection. (Taxonomic abbreviations based on the National Center for Biotechnology Information of the National Library of Medicine.)

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The majority of the isolates of all 3 groups are XDR (118 cases or 68.6%). Thirty-one isolates are PDR (18%), and 23 are MDR (13.4%). Of the 172 cases studied, seventy-seven (44.8%) were ESBL and carbapenemase co-producers; seventy-one (41.3%) were positive for carbapenemase alone; eleven (6.4%) were ESBL-positive; and three (1.7%) were AmpC and carbapenemase co-producers.

The 14-day all-cause mortality rate of the study group is 26%, with 45 cases (involving 43 unique patients) leading to death. The rates of mortality based on the isolates are 25.8% (25 out of 97) for Enterobacterales, while 23.4% (15 out of 64) for *Acinetobacter* spp., and 45.5% (5 out of 11) for *P. aeruginosa* (Table 4). There were 112 cases, comprised of BSIs, UTIs, and CNSIs, with repeat cultures. Within this subset, there are 95 cases (85%) that demonstrated bacteriologic cure, from which there are 58 cases with negative repeat cultures documented within 3 days of polymyxin B initiation. In contrast, seventeen cases (15%) displayed persistently positive cultures leading to antibiotic adjustments or death within 14 days of initiating polymyxin B. The failure rates of bacteriologic cure per isolate are 18.9% (13 out of 69) for Enterobacterales, while 2.8% (1 out of 36) for *Acinetobacter* spp., and 42.9% (3 out of 7) for *P. aeruginosa* (Table 4). Overall, a favorable clinical response, as assessed by the clinicians after at least 48 hours of antibiotics, was observed in 140 cases (81%). The failure rates in clinical response per isolate are 18.6% (18 out of 97) for Enterobacterales, with 17.2% (11 out of 64) for *Acinetobacter* spp., and 27.3% (three out of 11) for *P. aeruginosa* (Table 4).

Table 4. Outcomes of Pediatric Patients with Multidrug-Resistant Gram-Negative Infections treated with Polymyxin-B-based Combination Therapy

Outcomes	Frequency (%)			
	Enterobacterales	*Acinetobacter*	*P. aeruginosa*	Total
Mortality (N=172)				
Survived	72 (74.2)	49 (76.6)	6 (54.5)	127 (74)
Died	25 (25.8)	15 (23.4)	5 (45.5)	45 (26)
Bacteriologic Cure (N = 112)				
Success	56 (81.1)	35 (97.2)	4 (57.1)	95 (85)
Failure	13 (18.9)	1 (2.8)	3 (42.9)	17 (15)
Clinical Response (N = 172)				
Success	79 (81.4)	53 (82.8)	8 (72.7)	140 (81)
Failure	18 (18.6)	11 (17.2)	3 (27.3)	32 (19)

The outcomes per antibiotic regimen per major bacterial group (i.e., Enterobacterales, *Acinetobacter* spp., and *P. aeruginosa*) were also analyzed, focusing on two backbone combinations. Polymyxin B was dosed at a range of 2.5 to 4.5 mg/kg/day for patients less than two years old, and 3 mg/kg/day for two years old and above (with a loading dose of 2.5 mg/kg), divided into two doses a day. The first regimen, given to 70 cases, combined polymyxin B with meropenem (PmB+MEM) dosed at 40 mg/kg (maximum of two grams) every eight hours as a prolonged infusion over three hours. The second one, given to 88 cases, incorporated at least a fluoroquinolone (PmB+FQ), i.e., ciprofloxacin at 15 mg/kg every 12 hours or levofloxacin at 10 mg/kg every 12 hours, depending on the susceptibility report of the isolate and/or availability during diagnosis. As these are not routine and first-line drugs, the nature of the antibiotics (especially the polymyxins and fluoroquinolones) as "salvage therapy" and their respective potential benefits and adverse effects were explained first to the patients' guardians before obtaining their verbal assent and administering the medications.

Among those caused by Enterobacterales, there were 36 cases treated with PmB+MEM with noted 27.8% mortality at 14 days (10 cases), versus 55 cases treated with PmB+FQ with noted 20% mortality (11 cases), though these rates did not attain a significant difference (p = 0.45). In terms of bacteriologic cure, in the 27 cases treated with PmB+MEM and with repeat cultures, there was a 22.2% failure rate (six cases), while in the 38 cases treated with PmB+FQ and with repeat cultures, there was an 18.4% failure rate (seven cases), but with no statistically significant difference between the two (p = 0.76). In terms of clinical response, there was a 25% failure rate (9 out of 36) for PmB+MEM versus 14.5% only (8 out of 55) for PmB+FQ, but this did not reach statistical significance (p = 0.27) (Table 5).

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Table 5. Comparison of Outcomes of Pediatric Patients with Multidrug-Resistant Gram-Negative Infections per Antibiotic Regimen per Bacterial Group

	Frequency (%)		p value
	PmB+MEM	PmB+FQ	
Enterobacterales (N = 91)			
Mortality (n = 91)			
Survived	26 (72.2)	44 (80)	0.45
Died	10 (27.8)	11 (20)	
Subtotal	*36*	*55*	
Bacteriologic Cure (n = 65)			
Success	21 (77.8)	31 (81.6)	0.76
Failure	6 (22.2)	7 (18.4)	
Subtotal	*27*	*38*	
Clinical Response (n = 91)			
Success	27 (75)	47 (85.5)	0.27
Failure	9 (25)	8 (14.5)	
Subtotal	*36*	*55*	
Acinetobacter (N = 58)			
Mortality (n = 58)			
Survived	24 (80)	16 (57.1)	0.09
Died	6 (20)	12 (42.9)	
Subtotal	*30*	*28*	
Bacteriologic Cure (n = 32)			
Success	21 (95.5)	9 (90)	0.53
Failure	1 (4.5)	1 (10)	
Subtotal	*22*	*10*	
Clinical Response (n = 58)			
Success	27 (90)	20 (71.4)	0.098
Failure	3 (10)	8 (28.6)	
Subtotal	*30*	*28*	
Pseudomonas (N = 9)			
Mortality (n = 9)			
Survived	2 (50)	3 (60)	1.00
Died	2 (50)	2 (40)	
Subtotal	*4*	*5*	
Bacteriologic Cure (n = 5)			
Success	2 (100)	1 (33.3)	0.40
Failure	0 (0)	2 (66.7)	
Subtotal	*2*	*3*	
Clinical Response (n = 9)			
Success	3 (75)	3 (60)	1.00
Failure	1 (25)	2 (40)	
Subtotal	*4*	*5*	
Total (N = 158)	**70**	**88**	

From the *Acinetobacter* spp. group, there were 30 cases treated with PmB+MEM with noted 20% mortality (six cases) at 14 days, versus 28 cases treated with PmB+FQ with noted 42.9% mortality (12 cases) at 14 days. Among the 22 cases who were treated with PmB+MEM and with repeat cultures, there was one case (4.5%) of failure of bacteriologic cure. Among the 10 who were treated with PmB+FQ and with repeat cultures, there was also one case (10%) of failure. In terms of clinical response, there is a 10% failure rate (3 out of 30) for PmB+MEM versus 28.6% (8 out of 28) for Regimen PmB+FQ (See Table 5). However, all these rates did not attain statistically significant differences (p = 0.09, p = 0.53, and p = 0.098, respectively).

There were only 11 cases of infections caused by *P, aeruginosa* included in this study. However, there were only four cases treated with PmB+MEM and two of these (50%) died within 14 days, versus five cases treated with PmB+FQ, with two of these (40%) dying within 14 days. The two cases who were treated with PmB+MEM and with repeat cultures also showed evidence of bacteriologic cure (0% failure), while among the three who were treated with PmB+FQ and with repeat cultures, two (67%) of them had no evidence of such. In terms of clinical response, there is a 25% failure rate (one out of the four cases) for PmB+MEM versus 40% (two out of the five) for PmB+FQ (See Table 5). These rates did not attain statistically significant differences (p = 1.00, p = 0.40, and p = 1.00, respectively).

Adverse Drug Events. Within the 31 months of study period, eight patients had adverse drug events (ADE) to polymyxin B. These patients encompass a diverse range of ages (one month to 17 years old) and underlying health conditions, such as Chiari II malformation, disseminated tuberculosis, intracranial tumor, post-meningitic hydrocephalus, central hypoventilation syndrome, pulmonary arterial hypertension, and necrotizing fasciitis in a patient with hematologic malignancy. Five of the patients had nephrotoxicity (presenting as tubulopathy) during therapy; two had anaphylaxis after their first dose; and one had neurotoxicity manifesting as facial and nape paresthesia with secondary slurring of speech. Notably, due to the

nature of the ADEs and the fact that the polymyxin B was discontinued within less than 48 hours of initiation, those who had anaphylaxis and neurotoxicity were actually not included in the analysis of the outcomes, but were still noted for the discussion.

The anaphylactic reactions happened within an hour after the first dose of polymyxin B—one had generalized flushing, wheezing, and abdominal distension, while the other presented with angioedema and respiratory distress. They were given intramuscular epinephrine and other adjunctive therapy (corticosteroids, beta-agonist bronchodilators, and intravenous fluids), referred to pediatric allergology service, and their antibiotics were shifted to different regimens—one on ceftazidime-avibactam plus amikacin, and the other on meropenem plus tigecycline, with note of bacteriologic cure and clinical response thereafter. The paresthesia and slurring of the patient with neurotoxicity resolved in less than 24 hours upon discontinuation of polymyxin B. His regimen was shifted to meropenem plus amikacin, with note of bacteriologic cure, and he was also referred to the allergology service but eventually succumbed to his underlying condition.

All patients with tubulopathy presented with multiple electrolyte imbalances, during routine monitoring of serum electrolytes, with three of them noted on polymyxin B day 4, one of them on day 10, and another on day 16. There was no noted increase in blood urea nitrogen and serum creatinine among them, but two of them also presented with hypochloremic metabolic alkalosis and polyuria, and one also had hypercalciuria. Due to the resistance profiles of the bacterial isolates, polymyxin B had to be continued for all of the involved patients, one of whom had their dose decreased to 3 mg/kg/day. The patients were referred to pediatric nephrology service, who co-managed the monitoring of electrolytes and kidney functions every one to three days and the round-the-clock intravenous and/or oral corrections of the metabolic abnormalities. The derangements eventually corrected after completion of antibiotics and/or on follow-up.

DISCUSSION

Multidrug resistance, especially XDR and PDR, and more so in gram-negative bacteria, is already a common problem in the country and may not just be an "emerging" disease as we thought. Based on the Healthcare-Associated Infection and Antibiogram Report for 2022 by INTROP for the pediatric wards in PGH, the annual Update on PGH Antimicrobial Stewardship Program, as well as the 2022 Annual Report Summary (ARS) of the Antimicrobial Resistance Surveillance Reference Laboratory, PGH had generally higher rates of MDR than the published average national rates for the same year.[3,12,13] In our study site, about 60% of *K. pneumoniae* isolates are ESBL-positive and 40% are carbapenem-resistant compared to 47.7% and 16% rates nationally. Carbapenem resistance for *A. baumannii* was 87%, for *E. coli* 15%, and for *P. aeruginosa* 22%, as opposed to the national rates of 51.6% and 8% and 15.4%, respectively. Our ESBL positivity rate for *E. coli* was comparable with the national rate (41% vs. 43.8%).[12,13]

Additionally, our 172 MDR GN cases in 136 unique patients included in this study are still an underestimation of the burden of disease in our pediatric admissions. Based on the 31-month review of the census of INTROP, there were at least 350 more cases of MDR GN infections that did not meet our inclusion criteria. All together, these MDR GN infections comprise about 16% of the total infectious diseases referrals received by INTROP.

The clinical manifestations and laboratory results of our patients are nonspecific and are the common findings associated with infections, regardless of the presence of multidrug resistance. Unfortunately, there is still a dearth of studies on clinical manifestations and diagnostic markers specific to MDR GN infections in children that may be utilized as predictive tools for earlier diagnosis. Regarding the resistance genes detected, the

Microbiology laboratory equipment can only detect AmpC, ESBL, and carbapenemase on gram-negative isolates as of this writing. The laboratory is not yet equipped for routine testing for the specific carbapenemase type nor for enzymes conferring resistance to quinolones and aminoglycosides.

The most common comorbidities of the patients, excluding prematurity, included cardiovascular (29.4%), neurologic (27.2%), gastrointestinal (23.5%) conditions, with 16.9% of them having recent surgery within the past 12 months. More than half of the patients (51.5% or 70 patients) were admitted in the NICU at the time of diagnosis, whereas six patients (4.4%) were from PICU. In a seminal review by Aguilera-Alonso et al. of Spain in 2020, these conditions and places of admission were considered significant risk factors for carbapenem-resistant gram-negative infection and colonization.[14] A recognized important risk factor for MDR is exposure to antibiotics, especially meropenem, amikacin, antipseudomonals, and anti-anaerobes.[14,15] In our study, a total of 157 (91.3%) of the cases were given the above antibiotics during the course of the same admission.

For all-cause mortality, a cutoff of 14 days from initiation of polymyxin B was arbitrarily set to minimize the effect of mortalities caused by subsequent or intercurrent illnesses or infections, given the high nosocomial infection rate and the close proximity to each other of some episodes of such in the same patient.[3] Despite this, there are 18 cases (40% of mortalities) whose deaths were attributed to or caused by new-onset infections, and 25 cases (55.5% of mortalities) are because source control, e.g., removal of infected central lines, is precluded by logistical and patient factors (e.g., no other intravenous access). This means that a considerable number of deaths may have been avoided if infection prevention and control measures were optimized.

Bacteriologic cure does not necessarily equate to clinical cure, as evidenced by the unequal rates found in this study (85% vs. 81% overall). This seeming contradiction, i.e., the presence of a bacteriologic cure but with no considerable clinical response, could be due to a confluence of factors, such as lack or preclusion of source control, insufficient volume or low bacterial inoculum for repeat blood cultures, an intercurrent infection, or because of symptomatic pre-existing comorbidities—further underscoring the importance of infection control and prevention, appropriate diagnostics, and optimal management of underlying conditions.

Our findings—mortality rate of 26%, failure rate in bacteriologic cure of 15%, and failure rate in clinical response of 18.6%--are more favorable than the results of a 2014 retrospective cohort study by Siddiqui et al. of Pakistan, showing a crude mortality rate of 44.4% in pediatric patients with MDR GN infections in general, and a 42.9% mortality rate and 57.1% cure rate in patients given polymyxin B;[10] as well as of a 2022 retrospective analysis by Jia et al. in China, showing a 52.7% effective rate for polymyxin B in children.[9] However, these studies have small sample size. The outcomes of polymyxin B use in our study may be more favorable than those stated in the retrospective cohort analysis (though involving adult patients) by Zheng et al. in China, published in 2022 and cited in the 2023 IDSA AMR guidance document. This study compared ceftazidime-avibactam (N=82) with polymyxin-B-based regimen (also N=82) in critically ill adults, where the 30-day mortality rate for ceftazidime-avibactam was 35.4%, which is significantly lower than that of polymyxin B at 69.5% ($p < 0.001$). Furthermore, this study reported a microbiological eradication rate of 80.5% for ceftazidime-avibactam compared to 32.9% for polymyxin B.[16]

Though the rates numerically favor the fluoroquinolone-containing regimen for Enterobacterales, there is no statistically significant difference. Hence, giving high-dose prolonged-infusion meropenem remains to be an option, despite the presence of carbapenemases. Pediatric pharmacokinetic-pharmacodynamic studies suggest that the serum concentration of meropenem, if given

in higher doses and as extended infusion, can exceed the minimum inhibitory concentration (MIC) for at least 40% of the time for organisms with MICs as high as 8 mg/L, leading to better outcomes.[17] However, majority of the Enterobacterales isolates in our study have MICs of >8 mg/L, which can theoretically further decrease the time that the serum concentrations of the administered meropenem is above that MIC. This may explain why PmB+MEM, despite given as extended infusion, had numerically higher failure rates and mortality or, at least statistically, as effective as PmB+FQ for the treatment of MDR infections caused by Enterobacterales in our setting. On the other hand, this does not explain why meropenem is numerically more favored in *Acinetobacter* spp. wherein the meropenem MIC were also mostly >8 mg/L, suggesting other factors are at play.

For the *Acinetobacter* infections, PmB+MEM showed numerically better outcomes than PmB+FQ, with lower rates of mortality, failure of bacteriologic cure, and failure in clinical response. Both regimens usually included high-dose extended-infusion ampicillin-sulbactam, recommended as the backbone drug for carbapenem-resistant *A. baumannii* (CRAB) infections in the 2023 IDSA AMR guidance document. The guideline considers polymyxin B as a potential component of combination therapy but does not include meropenem and fluoroquinolones.[4] No mention or evaluation of fluroquinolones is provided, and meropenem was recently excluded as a component based on two large trials comparing colistin monotherapy and colistin-meropenem combination, showing no significant differences.[18,19] However, the outcomes favoring PmB+MEM in our study align with *in vitro* data supporting the triple combination of polymyxin B, meropenem, and ampicillin-sulbactam for CRAB eradication.[20,21]—data that were also acknowledged and referenced in the 2023 IDSA AMR guidance document. Despite the latest IDSA guidance recommendation, our study suggests that meropenem remains an acceptable option with polymyxin B combined with ampicillin-sulbactam for MDR *Acinetobacter* infections in our setting.

For the *P. aeruginosa* infections, PmB+MEM had numerically more favorable rates than PmB+FQ in terms of failure rates in bacteriologic cure (0 vs. 50%) and clinical response (25% vs. 40%). However, PmB+FQ is more favorable in terms of mortality (40% vs. 50%) compared to PmB+MEM. The absolute numbers, however, are too small (less than 10) that a robust conclusion on which regimen is overall better cannot be attained. Further studies regarding *P. aeruginosa* infections are needed, including comparing the polymyxin-B-based regimens with the novel antipseudomonal beta-lactams.

The safety of polymyxin B was evaluated in this study in the context of combination therapy and not monotherapy. In the two cases of anaphylaxis, other antibiotics aside from polymyxin B were also suspected—fluoroquinolone (i.e., ciprofloxacin) in one, and ampicillin-sulbactam (given with the PmB+MEM for a CRAB infection) in another. Among the cases with tubulopathy, there were also other drugs that could have complicated or aggravated the acute kidney injury—one was on mannitol, one on regular furosemide, and two on concomitant aminoglycosides.

There are few reports on anaphylaxis due to intravenous polymyxin B. However, there have been reports of eczema and skin eruptions with colistin[22] and anaphylactic and anaphylactoid reactions, probably histamine-mediated, with topical polymyxin B.[23] The crude rate of tubulopathies in our study (2.9%) is lower than those cited in other adult studies, such as in the systematic review by Zavascki and Nation in 2017 (20.8% to 46.1%),[24] in the prospective study by Mattos et al. of Brazil in 2019 (40.5%),[25] and in the meta-analysis done by Falagas, Kyriakidou, Voulgaris, et al. in 2020 (40.7%),[26] and even in the retrospective cohort study by Siddiqui et al. involving children in 2014 (21.4%).[10] Neurotoxicity was rare, with only one documented case in our 31-month study period, aligning with limited recent data, such as in the systematic review by Falagas and

Kasiakou in 2006,[22] who reported only four cases from 1995 to 2005. Properly dosed and administered, polymyxin B appears safe in our setting. However, vigilant electrolyte monitoring and a high index of suspicion for ADEs are crucial during its use.

CONCLUSION

MDR GN infections are already prevalent in the country. In PGH alone, such infections in children comprise about 16% of the referrals to INTROP. For pediatric patients with MDR GN infections treated with polymyxin-B-based combination therapy for at least 48 hours, the outcomes showed a mortality rate of 26%, failure rate in bacteriologic cure at 15%, and failure rate in clinical response at 18.6%--rates that are comparable with similar studies cited. Safety profiles indicate common but manageable adverse effects, i.e., tubulopathy, neuropathy, and anaphylaxis.

For MDR Enterobacterales in our institution, a fluoroquinolone may be considered as a partner drug with polymyxin B, as an alternative to meropenem, which can still be used regardless. For MDR *Acinetobacter* spp. specifically, meropenem is still a good option as partner drug as long as combined with ampicillin-sulbactam. Further prospective studies with larger sample size and controlled confounding variables must be conducted for more robust conclusions, especially in *P. aeruginosa* infections. Given the lack of statistically significant differences, the choice of antibiotic/s partnered with polymyxin B remains to be based on clinical judgment, with consideration of the patient's profile, the antibiotic history, the isolate, the MICs, the site of infection, effectiveness, and cost, among others.

With these, polymyxin-B-based combination therapy appears to be a treatment option for MDR GN infections in children, especially important in settings where novel antibiotics are not accessible. Because of the intrinsic nephrotoxic potential and the narrow therapeutic index of polymyxin B, close monitoring and having a high index for suspicion for adverse events are important.

Management of MDR GN infections in children will not be optimized without antimicrobial stewardship, close monitoring of any adverse effects in the light of combination therapy, as well as adequate management of pre-existing comorbidities, and proper infection control and prevention, e.g., implementing bundles of care against device-related infections and timely source control.

LIMITATIONS AND RECOMMENDATIONS

As a descriptive and exploratory study, a significant limitation is the lack of a control or comparator group, especially since the use of polymyxin-B-based combination therapy is currently the best available therapy in our institution for children with MDR GN infections, particularly those who have XDR or PDR isolates.. Another significant limitation is the lack of multivariate analysis, including unexplored factors, such as timing of source control and development of new-onset or recurring infections. Matching the polymyxin B group with patients who received alternative antibiotic regimens (e.g., ceftazidime-avibactam) for their MDR infections, or with patients whose infections are caused by non-MDR GN bacterial isolates may provide valuable insights. Although our study has the largest sample size to date compared to cited studies involving polymyxin B use in children, it remains relatively small, hindering the detection of statistically significant differences across analyzed groups. More robust conclusions will require a larger sample size. A subgroup analysis on a specific pediatric patient cohort, e.g., NICU patients, may also be done.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. U.S. Centers for Disease Control and Prevention (CDC). COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022 [Internet]. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022 February [cited 2023 Aug]. Available from: https://www.cdc.gov/drugresistance/covid19.html

2. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al.. The Mortality Burden of Multidrug-resistant Pathogens in India: A Retrospective, Observational Study. Clin Infect Dis. 2019 Aug 1;69(4):563-570. doi: 10.1093/cid/ciy955. PMID: 30407501; PMCID: PMC6669283.

3. Division of Infectious and Tropical Diseases in Pediatrics (INTROP). Annual and Midyear Nosocomial Infection Rate Report 2022. Manila, Philippines. Division of Infectious and Tropical Diseases in Pediatrics, Department of Pediatrics, University of the Philippines – Philippine General Hospital. 2022 February.

4. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Clin Infect Dis. 2023 Jul 18:ciad428. doi: 10.1093/cid/ciad428. Epub ahead of print. PMID: 37463564.

5. Olney KB, Thomas JK, Johnson WM. Review of novel β-lactams and β-lactam/β-lactamase inhibitor combinations with implications for pediatric use. Pharmacotherapy [Internet]. 2023 Jul [cited 2023 Aug];43(7):713-731. doi: 10.1002/phar.2782. Epub 2023 Mar 12. PMID: 36825478.

6. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy [Internet]. 2019 Jan [cited 2023 Aug];39(1):10-39. doi: 10.1002/phar.2209. PMID: 30710469; PMCID: PMC7437259.

7. Thomas R, Velaphi S, Ellis S, Walker AS, Standing JF, Heath P, et al. The use of polymyxins to treat carbapenem resistant infections in neonates and children. Expert Opin Pharmacother [Internet]. 2019 Mar [cited 2023 Aug];20(4):415-422. doi: 10.1080/14656566.2018.1559817. Epub 2018 Dec 21. PMID: 30576264.

8. Lexicomp. Polymyxin B: Pediatric drug information. In: Post T, editor. UpToDate. [Internet]. Waltham, Mass.: UpToDate; 2023 [cited 2023 Aug]. Available from: www.uptodate.com

9. Jia X, Yin Z, Zhang W, Guo C, Du S, Zhang X. Effectiveness and Nephrotoxicity of Intravenous Polymyxin B in Carbapenem-Resistant Gram-Negative Bacterial Infections Among Chinese Children. Front Pharmacol [Internet]. 2022 May 27 [cited 2023 Aug];13:902054. doi: 10.3389/fphar.2022.902054. PMID: 35712713; PMCID: PMC9197179.

10. Siddiqui NU, Qamar FN, Jurair H, Haque A. Multi-drug resistant gram negative infections and use of intravenous polymyxin B in critically ill children of developing country: retrospective cohort study. BMC Infect Dis [Internet]. 2014 Nov 28 [cited 2023 Aug];14:626. doi: 10.1186/s12879-014-0626-9. PMID: 25430979; PMCID: PMC4262978.

11. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect [Internet]. 2012 Mar [cited 2023 Aug];18(3):268-81. doi: 10.1111/j.1469-0691.2011.03570.x. Epub 2011 Jul 27. PMID: 21793988.

12. Hospital Infection Control Unit (HICU). Update on PGH Antimicrobial Stewardship Program 2024. Hospital Infection Control Unit. University of the Philippines – Philippine General Hospital. 2024 February.

13. Antimicrobial Resistance Surveillance Program (ARSP). Antimicrobial resistance surveillance program annual report 2022. Manila, Philippines: Department of Health – Research Institute of Tropical Medicine, Antimicrobial Resistance Surveillance Reference Laboratory; 2023.

14. Aguilera-Alonso D, Escosa-García L, Saavedra-Lozano J, Cercenado E, Baquero-Artigao F. Carbapenem-Resistant Gram-Negative Bacterial Infections in Children. Antimicrob Agents Chemother [Internet]. 2020 Feb 21 [cited 2023 Aug];64(3):e02183-19. doi: 10.1128/AAC.02183-19. PMID: 31844014; PMCID: PMC7038253.

15. Mills JP, Rojas LJ, Marshall SH, Rudin SD, Hujer AM, Nayak L, et al. Risk Factors for and Mechanisms of *CO*listin *R*esistance Among *E*nterobacterales: Getting at the CORE of the Issue. Open Forum Infect Dis {Internet]. 2021 Apr 21 [cited 2023 Aug];8(7):ofab145. doi: 10.1093/ofid/ofab145. PMID: 34285928; PMCID: PMC8286092.

16. Zheng G, Cai J, Zhang L, Chen D, Wang L, Qiu Y, et al. Ceftazidime/Avibactam-Based Versus Polymyxin B-Based Therapeutic Regimens for the Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infection in Critically Ill Patients: A Retrospective Cohort Study. Infect Dis Ther [Internet]. 2022 Oct [cited 2023 Aug];11(5):1917-1934. doi: 10.1007/s40121-022-00682-0. Epub 2022 Aug 17. PMID: 35976531; PMCID: PMC9618002.

17. Hsu AJ, Tamma PD. Treatment of multidrug-resistant Gram-negative infections in children. Clin Infect Dis [Internet]. 2014 May [cited 2023 Aug];58(10):1439-48. doi: 10.1093/cid/ciu069. Epub 2014 Feb 5. PMID: 24501388.

18. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis [Internet]. 2018 Apr [cited 2023 Aug];18(4):391-400. doi: 10.1016/S1473-3099(18)30099-9. Epub 2018 Feb 16. PMID: 29456043.

19. Kaye KS, Marchaim D, Thamlikitkul V, Carmeli Y, Chiu CH, Daikos G, et al. Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms. NEJM Evid [Internet]. 2023 Jan [cited 2023 Aug];2(1):10.1056/evidoa2200131. doi: 10.1056/evidoa2200131. Epub 2022 Dec 6. PMID: 37538951; PMCID: PMC10398788.

20. Lenhard JR, Smith NM, Bulman ZP, Tao X, Thamlikitkul V, Shin BS, et al. High-Dose Ampicillin-Sulbactam Combinations Combat Polymyxin-Resistant Acinetobacter baumannii in a Hollow-Fiber Infection Model. Antimicrob Agents Chemother [Internet]. 2017 Feb 23 [cited 2023 Aug];61(3):e01268-16. doi: 10.1128/AAC.01268-16. PMID: 28052852; PMCID: PMC5328540.

21. Beganovic M, Daffinee KE, Luther MK, LaPlante KL. Minocycline Alone and in Combination with Polymyxin B, Meropenem, and Sulbactam against Carbapenem-Susceptible and -Resistant Acinetobacter baumannii in an *In Vitro* Pharmacodynamic Model. Antimicrob Agents Chemother [Internet]. 2021 Feb 17 [cited 2023 Aug];65(3):e01680-20. doi: 10.1128/AAC.01680-20. PMID: 33318006; PMCID: PMC8092495.

22. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care [Internet]. 2006 Feb [cited 2023 Aug];10(1):R27. doi: 10.1186/cc3995. PMID: 16507149; PMCID: PMC1550802.

23. Zhan Y, Ma N, Liu R, Wang N, Zhang T, He L. Polymyxin B and polymyxin E induce anaphylactoid response through mediation of Mas-related G protein-coupled receptor X2. Chem Biol Interact. 2019 Aug 1;308:304-311. doi: 10.1016/j.cbi.2019.05.014. Epub 2019 May 25. PMID: 31132327.

24. Zavascki AP, Nation RL. Nephrotoxicity of Polymyxins: Is There Any Difference between Colistimethate and Polymyxin B? Antimicrob Agents Chemother [Internet]. 2017 Feb 23 [cited 2023 Aug];61(3):e02319-16. doi: 10.1128/AAC.02319-16. PMID: 27993859; PMCID: PMC5328560.

25. Mattos KPH, Gouvêa IR, Quintanilha JCF, Cursino MA, Vasconcelos PENS, Moriel P. Polymyxin B clinical outcomes: A prospective study of patients undergoing intravenous treatment. J Clin Pharm Ther [Internet]. 2019 Jun [cited 2023 Aug];44(3):415-419. doi: 10.1111/jcpt.12801. Epub 2019 Jan 21. PMID: 30666679.

26. Falagas ME, Kyriakidou M, Voulgaris GL, Vokos F, Politi S, Kechagias KS. Clinical use of intravenous polymyxin B for the treatment of patients with multidrug-resistant Gram-negative bacterial infections: An evaluation of the current evidence. J Glob Antimicrob Resist [Internet]. 2021 Mar [cited 2023 Aug];24:342-359. doi: 10.1016/j.jgar.2020.12.026. Epub 2021 Jan 21. PMID: 33486122.