AFRICAN JOURNAL OF PHARMACY AND ALTERNATIVE MEDICINE

https://doi.org/10.58460/ajpam.v3i01.114

Open Access

RESEARCH ARTICLE

MJM BIOLABS

Effectiveness and Nephrotoxicity of Polymyxin B among Intensive Care Unit Patients: A Clinical Evaluation

Claire Moki[1*], Gabriel Kigen[2], Naftali Busakhala[3]

[1]Department of Pharmacology and Toxicology, Moi University; Department of Pharmaceutical Services, Baringo County

[2, 3] Department of Pharmacology and Toxicology, Moi University

*Corresponding Author: mokiche18@gmail.com

Article History

Submitted: 9th October 2024

Accepted: 14th October 2024

Published Online: 19th October 2024

To read this paper online, please scan the QR code below:

ABSTRACT

Polymyxin B is a reserve antibiotic, but there has been an upsurge in its use due to a rise in multidrug-resistant gram-negative bacteria. However, nephrotoxicity and resistance concerns persist, with global resistance rates reaching 29%. Effectiveness of Polymyxin B (clinical and microbiological response) and the frequency of nephrotoxicity is not well documented in resource limited settings. Research is essential to guide optimization of Polymyxin B therapy and inform the adoption of measures for early detection of kidney injury to prevent damage. This study aimed to assess the effectiveness of Polymyxin B by evaluating clinical and microbiological responses and determining nephrotoxicity incidence using KDIGO criteria in ICU patients at Moi Teaching and Referral Hospital (MTRH). A prospective observational cohort study was conducted at MTRH ICUs between December 2021 and November 2022, on patients treated with Polymyxin B. Data on demographics, comorbidities, Polymyxin B dosage regimens, clinical responses, and microbiological results were collected. Descriptive statistics summarized patient characteristics, while associations between dosage regimens and outcomes were evaluated using Fisher's exact test and multivariate regression, with a $p<0.05$ considered statistically significant. Forty-four patients with a mean age of 48 years were included; 66% were male, and cerebrovascular disease was the most common comorbidity. All patients had multidrug-resistant gram-negative infections qualifying for Polymyxin B therapy. Most (89%) received monotherapy, with 86% achieving a good clinical response, 7% experiencing treatment failure, and 7% dying. Doses of 20,000–25,000 IU/Kg/day were associated with microbiological eradication and good clinical response ($p<0.001$), while 15,000 IU/Kg/day was associated with treatment failure. Acute kidney injury occurred in 48% of patients, with 68% developing hypomagnesemia. Polymyxin B at doses of between 20,000-25,000IU/Kg/day should be considered as a starting dose due to the association with good clinical response, with alternate-day monitoring of serum creatinine levels for early detection of nephrotoxicity.

Keywords: *Polymyxin B, Nephrotoxicity, Effectiveness, Intensive Care Unit, Hypomagnesemia*

How to Cite this Article: Moki, C., Kigen, G., & Busakhala, N. (2024). Effectiveness and Nephrotoxicity of Polymyxin B among Intensive Care Unit Patients: A Clinical Evaluation. *African Journal of Pharmacy and Alternative Medicine*, 3(01). https://doi.org/10.58460/ajpam.v3i01.114

INTRODUCTION

Polymyxin B use has been on an upsurge due to a rise in multidrug resistant gram-negative bacteria, however the associated nephrotoxicity is still a concern (Justo & Bosso, 2015). Studies have also reported increased polymyxin use in low and middle-income countries (Klein et al., 2018). The World Health Organization (WHO) has identified multidrug-resistant bacteria as the third most pressing threat to global human health (WHO, 2021). A retrospective prevalence study done at Moi Teaching and Referral Hospital- Eldoret (MTRH) between 2002 and 2013 on multidrug resistant *Klebsiella pneumoniae*, reported 8% of the samples being multidrug resistant (Apondi et al, 2016). Similarly, studies on antimicrobial susceptibility in surgical site infections at MTRH showed multidrug resistance of *Acinetobacter spp* with 100% multi-drug resistance in the isolates (Langat, 2018). Further, more than 50% multidrug resistance of *Acinetobacter spp* in pus isolates was reported in a study on antimicrobial susceptibility patterns at MTRH (Onyango, 2018).

Gram-negative pathogens like *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter*—collectively known as ESKAPE pathogens—are responsible for many hospital-acquired infections, including pneumonia, bloodstream infections, and intra-abdominal sepsis (Rice, 2008). In intensive care units (ICUs), these drug-resistant infections contribute to higher morbidity, mortality, and healthcare costs, placing a heavy burden on patients and families (WHO, 2017). Treating critically ill patients with these infections remains a challenge, underscoring the need for appropriate antibiotic use.

Polymyxin B is classified as a reserve antibiotic, used for treating infections caused by multidrug-resistant gram-negative bacteria. In Kenya, the Ministry of Health has adopted the WHO's Access, Watch, and Reserve (AWaRe) classification, reserving Polymyxin B for use in level 5 and 6 hospitals under specialist supervision (MOH, 2019). Despite being a last-resort treatment at MTRH, emerging reports of resistance and nephrotoxicity are raising concerns about its continued efficacy. Studies in Brazil and Europe have documented Polymyxin B resistance, with 15% of *K. pneumoniae* isolates in Brazil found to be resistant (Rodrigues et al., 2019) and 38% of carbapenem-resistant isolates in Europe showing resistance (EARS-Net, 2022). However, research on dosage-related resistance is limited, and no studies on Polymyxin B resistance have been published in Kenya. Furthermore, nephrotoxicity during Polymyxin B use has been reported at rates ranging from 11.8% to 50.6% in critically ill patients (Aggarwal & Dewan, 2018; Cai et al., 2020).

Despite the rising use of Polymyxin B, there remains a significant gap in local data regarding its effectiveness and nephrotoxicity, particularly in critically ill patients. This study seeks to fill that gap, offering insights into the safety and efficacy of Polymyxin B in resource-limited settings like Kenya's ICUs. The findings may inform future strategies to mitigate nephrotoxicity and guide prescribing practices.

METHODOLOGY

Study Location

The study took place in the Intensive Care Units (ICUs) of Moi Teaching and Referral Hospital (MTRH), a major referral facility serving patients primarily from the western part of Kenya, as well as nationwide. As the country's second national referral hospital, MTRH receives ICU admissions both from within its wards and from other healthcare facilities.

Study Design

This was a prospective observational study conducted from December 2021 to November 2022, aimed to assess the effectiveness, and nephrotoxicity associated with Polymyxin B.

Target Population

The study population consisted of all ICU patients treated with intravenous Polymyxin B.

Sampling Framework

A census sampling method was applied, enrolling 44 patients due to the limited number of ICU patients who receive Polymyxin B annually

Data Collection Tools

Data collection was performed using a structured data collection form, which was piloted on five ICU patients to validate and adjust the tool as necessary.

Data Collection

Eligible patients were recruited if they had documented pre-treatment serum creatinine levels and provided informed consent. The demographics and clinical data were obtained from the file or from any referral letters from previous hospitals attended. The type of infection, causative pathogen, and patient response to treatment was then assessed.

Clinical response was evaluated at baseline (0 hours), 72 hours, and at the end of therapy (day 7 or 14). Outcomes were categorized as good clinical response, treatment failure, relapse, or death. A good clinical response indicated improvement in infection symptoms, WBC count normalization, absence of fever, and improved PaO_2/FiO_2 ratios. Treatment failure involved clinical deterioration, while relapse indicated a worsening of symptoms after initial improvement. Microbiological response was assessed at the end of therapy, with outcomes classified as eradication, persistence, or super-infection. Serum creatinine levels were measured on day 1 and alternate days to assess nephrotoxicity. The Kidney Disease Improving Global Outcomes (KDIGO) criteria were used to define acute kidney injury (AKI), characterized by a rise in serum creatinine of ≥26.5 µmol/L within 48 hours or an increase to ≥1.5 times the baseline within 7 days.

Data Analysis

Data analysis was conducted using SPSS version 29. Descriptive statistics were used to summarize patient demographics, clinical responses, and nephrotoxicity rates. Fisher's Exact Test and multivariate logistic regression analyses were performed to identify associations and independent predictors of outcomes, with $p < 0.05$ considered statistically significant.

Ethical Considerations

Approval for the study was obtained from the Moi University/MTRH Institutional Research Approval number FAN:0004024 and Ethics Committee and the National Commission for Science, Technology, and Innovation (NACOSTI) license number NACOSTI/P/22/15302.

RESULTS

a. *Demographic and clinical characteristics*

Of the 44 patients enrolled, 66% (29) were male, with an age range of 14 to 84 years and a median age of 48 years (IQR: 37–61.5). In addition, 39% of patients fell within the 41–60-year age range. All patients had underlying conditions, with cerebrovascular diseases being the most prevalent (32 patients), followed by pneumonia (15 patients) and hypertension (14 patients). Most patients (73%) had no prior exposure to nephrotoxic agents, while 7 had previously received fluoroquinolones. Additionally, 84% (37) had received antibiotics prior to Polymyxin B therapy, with carbapenems prescribed in 22 cases. Initial serum electrolyte levels were within normal ranges, though serum creatinine levels varied widely, with a mean of 55.5 µmol/L (SD: 23.3), and albumin levels were borderline low at 30.5 g/L (SD: 4.6).

Ventilator-associated pneumonia (VAP) was the most common infection, affecting 95% (42) of the patients. The predominant pathogen was *Acinetobacter baumannii*, responsible for 82% (36) of the cases, reflecting its known resistance profile and prevalence in ICU settings. Polymyxin B monotherapy was the primary treatment in 89% (39) of cases, while 4% (2) received it in combination with meropenem, and 7% (3) alongside either vancomycin, a fluoroquinolone, or an aminoglycoside. The median cumulative Polymyxin B dose was 14 x 10^6 IU (IQR: 4, 21), administered over a median duration of 10 days (IQR: 7, 14). A loading dose was given to 7% (3) of patients.

b. *Clinical and microbiological response*

A good clinical response was observed in 86% (38) of cases, with these patients showing resolution of symptoms by the end of therapy. Microbiological response mirrored this, with 86% (38) achieving bacterial eradication. Higher Polymyxin B doses (20,000–25,000 IU/Kg/day) were associated with higher eradication rates compared to lower doses (15,000 IU/Kg/day), highlighting the dose-dependent nature of the therapy. Treatment failure occurred in 7% (3) of cases, while 7% (3) died during therapy, though these deaths were attributed to causes unrelated to Polymyxin B therapy. The mean duration for repeat cultures was 12.7 days (SD: 3.4). Patients receiving combination therapy with Polymyxin B and carbapenem all showed good clinical response, compared to 77.3% of patients who received Polymyxin B monotherapy.

c. *Factors Associated with Good Clinical Response*

Bivariate analysis using Fisher's Exact test and the Kruskal-Wallis test identified several significant predictors of good clinical response, including bacterial eradication, a daily Polymyxin B dose of 25,000 IU/Kg/day, a cumulative dose of 14 x 10^6 IU (IQR: 12.0, 16.6), and a treatment duration of 11 days (IQR: 8, 14) as in table 1.

Table 1:

Bivariate analysis of characteristics of patients who achieved good clinical response to IV Polymyxin B compared to those with treatment failure or death

Variable	Good clinical response n=38	Treatment failure n=3	Death n=3	P value
Demographics, mean (± SD), median (IQR) or n (%)				
Age (years)				0.745[1]
>60 years	11 (91.7)		1 (8.3)	
<60years	27 (84.4)		5 (15.6)	
Male	25 (86.2)		4 (13.8)	1[1]
BMI (kg m^{-2})	22.7 (18.4, 30.1)		21.1 (19.8, 23.4)	0.783[2]
Comorbidities, n (%)				1[1]
Cerebrovascular disease	26 (89.7)		3 (10.3)	
Malignant disease	3 (75)		1 (25)	
Hypertension	10 (76.9)		3 (23.1)	
Diabetes	4 (50)		4 (50)	
Pneumonia	12 (85.7)		2(14.3)	
HIV	1 (50)		1(50)	
Congestive heart failure	0 (0)		1(100)	
Infection type, n (%)				0.257[1]
Ventilator associated pneumonia	37 (88.1)	3 (7)	2 (5)	
Bloodstream infection	1 (50)	0(0)	1 (50)	
Baseline condition n (%), mean (± SD) or median (IQR)				
Albumin (g L^{-1})	30.5 (27.2,34.4)		23.37 (26.2,30.9)	0.27[2]
Serum creatinine (µmol L^{-1})	55.5 (23.31)		56.69 (23.35)	0.634[1]
White blood cell ($\times 10^9$ L^{-1})	19.16 (4.03)		20.3 (4.37)	0.243[1]
Microorganism targeted by Polymyxin B, n (%)				0.404[1]
Acinetobacter baumannii	32 (84.2)	3 (8)	1 (2)	
Others (KP/AB+KP/AB+PA/ AB+KP+PA)	6 (75)	0 (0)	2 (25)	
Eradication of target bacteria	38 (86)	3(7)	3(7)	**<0.001[1]**
Polymyxin B dose regimen, n (%), mean (± SD) or median (IQR)				
Load at first dose	2 (67)		1 (33)	0.363[1]
Daily dose				
25,000 (IU/Kg)	11 (100)	0(0)	0(0)	**0.028[1]**
20,000 (IU/Kg)	15 (100)	0(0)	0(0)	**0.015[1]**
15,000 (IU/Kg)	12 (66)	3(17)	3(17)	**0.046[1]**
Cumulative dose (*10^6IU)	14 (12.0,16.6)	7.5(4,12)	9(7,14)	**0.021[2]**
Treatment time (days)	11 (8,14)	10(7,3)	7(5,14)	**0.003[2]**
Polymyxin B regimen, n (%)				0.538[1]
Polymyxin B monotherapy	34 (87.2)	3(7.7)	2 (5.1)	
Polymyxin B + Meropenem/ Levofloxacin/Amikacin/ Vancomycin	4 (80)	0(0)	1 (20)	

[1] Fisher's Exact Test; [2] Kruskal-Wallis Test (Abbreviations: BMI- body mass index, IQR-interquartile range, IU- international units, Kg- Kilogram, SD- standard deviation, AB- *Acinetobacter baumannii*, KP- *Klebsiella pneumoniae*, PA- *Pseudomonas aeruginosa*)

In the multivariate analysis, bacterial eradication remained the only independent predictor of favorable outcomes (OR = 0.76, 95% CI 1.06–1.21) as in table 2, underscoring its role in treatment success.

Table 2:
Multivariate analysis of factors associated with good clinical response

Variable	AOR (95% CI)	p value
Polymyxin B daily dose (IU/Kg/day)	0.13 (0.04, 0.15)	0.26
Cumulative Polymyxin B dose (IU)	0.11 (0.02, 1.00)	0.4
Polymyxin B treatment duration (days)	0.82 (0.48, 1.43)	0.49
Favourable microbiological response	0.76 (0.6, 1.21)	**<0.001**

immunosenescence, factors which can impair infection recovery (Fulop et al., 2018). Additionally, the treatment duration appears to play a crucial role in therapeutic outcomes. For instance, Ismail et al. (2018) highlighted that shorter antibiotic courses could increase treatment failure risks in septic patients. Therefore, the adherence to a suggested treatment duration of 10 to 14 days for Polymyxin B in ICU settings is essential for maximizing clinical outcomes and minimizing the risk of relapse or resistance development.

Regarding microbiological response, our findings align with those reported by Ye et al. (2022) and Zhang et al. (2021), where bacterial eradication rates of 75% and 77.65% were observed, respectively. Conversely, Ngamprasertchai et al. (2018) reported that only 56.2% of patients achieved microbiological clearance, despite a clinical resolution rate of 78.1%. This suggests that while Polymyxin B can significantly alleviate symptoms, it may not always achieve complete bacterial eradication. The observed variations in microbiological response could be due to differences in bacterial resistance levels among the studied populations, as well as local antibiotic usage patterns, infection control practices, and prevalence of specific bacterial strains (Gales, 2001). These factors underscore the need for tailored treatment approaches based on regional resistance patterns, rather than a universal application of Polymyxin B therapy.

In this study, bacterial eradication was significantly associated with a good clinical response, with an odds ratio of 0.76 (95% CI: 1.06–1.21). This finding emphasizes the importance of complete pathogen clearance for optimal clinical outcomes. A median treatment duration of 11 days and Polymyxin B doses of 20,000 IU/kg/day to 25,000 IU/kg/day were associated with improved clinical response, suggesting that both adequate dosing and duration are key to achieving therapeutic success.

Notably, treatment failure was observed in 14% of patients, all of whom received a dose of 15,000 IU/kg/day. This low dosage may have been insufficient to reach therapeutic drug levels needed for bacterial eradication. A similar conclusion was reached by Ismail et al. (2018), who identified lower doses (≤15,000 IU/kg/day) as an independent predictor of treatment failure. Given that Polymyxin B's bactericidal action is concentration-dependent (Nang et al., 2021), suboptimal dosing could allow bacteria to survive and contribute to resistance, thereby compounding the challenges posed by multidrug-resistant infections.

Incidence of Polymyxin B Nephrotoxicity

The incidence of acute kidney injury (AKI) in this study was 48%, with hypomagnesemia occurring in 67% of these cases. This suggests a potential link between Polymyxin B therapy and hypomagnesemia, although other electrolytes remained unaffected. John et al. (2018) observed a comparable AKI incidence of 47%, while studies in China by Chang et al. (2022) and Wu et al. (2022) reported lower incidences of 33.5% and 28.6%, respectively. Discrepancies in nephrotoxicity rates might be influenced by differences in patient renal status, Polymyxin B dosing, and varying methodologies in defining kidney injury.

Higher doses of Polymyxin B, such as those used in this study, may contribute to increased nephrotoxicity, as supported by Manchandani et al. (2017), who found that elevated renal exposure to Polymyxin B was associated with faster onset of nephrotoxicity. The nephrotoxic mechanisms of Polymyxin B involve cellular oxidative stress, apoptosis, impaired cell cycle progression, and autophagy, leading to tubular injury and renal dysfunction (Avedissian et al., 2019).

The occurrence of hypomagnesemia alongside AKI indicates that Polymyxin B therapy may impair renal magnesium handling, contributing to

electrolyte imbalances (Manchandani et al., 2017). Hypomagnesemia can have severe consequences, including arrhythmias and increased mortality in critically ill patients (Hansen & Bruserud, 2018). Therefore, monitoring magnesium levels during Polymyxin B therapy is crucial to mitigate these risks and improve patient outcomes.

CONCLUSIONS

Polymyxin B demonstrated good clinical response in treating infections caused by multidrug-resistant gram-negative bacteria, with successful bacterial eradication at doses of 20,000 and 25,000 IU/Kg/day. However, its use is associated with a significantly higher incidence of nephrotoxicity compared to global averages for drug-induced nephrotoxicity. Therefore, close monitoring of serum creatinine and electrolyte levels is crucial to mitigate the risk of nephrotoxicity during therapy and ensuring safer administration of Polymyxin B.

RECOMMENDATIONS

Polymyxin B at doses of between 20,000-25,000IU/Kg/day should be considered as a starting dose due to the association with good clinical response in MTRH ICUs and confirmation of bacterial eradication done through post-treatment cultures after treatment cessation. Alternate-day monitoring of serum creatinine levels should be done for early detection of nephrotoxicity.

DECLARATION

Competing Interests

The authors declare that they have no competing interests in this study.

Authors' Contribution

The main author conceived the study, designed the methodology, and performed data collection and analysis. The co-authors contributed to the interpretation of the results and provided critical revisions to the manuscript. All authors have read and approved the final manuscript.

Source of Funding

This research was self-funded by the primary author, with no external funding sources.

Availability of Data and Materials

The data and materials supporting the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

Aggarwal, R., & Dewan, A. (2018). Comparison of nephrotoxicity of Colistin with Polymyxin B administered in currently recommended doses: a prospective study. *Annals of clinical microbiology and antimicrobials*, 17(1), 1-8.

Apondi, O. E., Oduor, O. C., Gye, B. K., & Kipkoech, M. K. (2016). High prevalence of multi-drug resistant klebsiella pneumoniae in a tertiary teaching hospital in Western Kenya. *African journal of infectious diseases*, 10(2), 89–95. https://doi.org/10.21010/ajid.v10i2.3

Cai, Y., Lee, W., & Kwa, A. L. (2015). Polymyxin B versus colistin: an update. Expert review of anti-infective therapy, 13(12), 1481-1497.

Chang, K., Wang, H., Zhao, J., Yang, X., Wu, B., Sun, W., ... & Cao, B. (2022). Risk factors for polymyxin B-associated acute kidney injury. *International Journal of Infectious Diseases*, 117, 37-44.

European Antimicrobial Resistance Surveillance Network (EARS-Net). (2022). *Antimicrobial resistance surveillance in Europe: Annual report of the European Antimicrobial Resistance Surveillance Network.* Retrieved from https://iris.who.int/bitstream/handle/10665/351141/9789289056687-eng.pdf?sequence=1&isAllowed=y

Fulop, T., Larbi, A., Dupuis, G., Le Page, A., Frost, E. H., Cohen, A. A., ... & Franceschi, C. (2018). Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes?. *Frontiers in immunology*, 8, 1960.

Gales, A. C., Jones, R. N., Forward, K. R., Linares, J., Sader, H. S., & Verhoef, J. (2001). Emerging importance of multidrug-resistant Acinetobacter species and Stenotrophomonas maltophilia as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY Antimicrobial Surveillance

Program (1997–1999). *Clinical Infectious Diseases*, 32(Supplement_2), S104-S113.

Hansen, B. A., & Bruserud, Ø. (2018). Hypomagnesemia in critically ill patients. *Journal of intensive care*, *6*, 1-11.

Ismail, B., Shafei, M. N., Harun, A., Ali, S., Omar, M., & Deris, Z. Z. (2018). Predictors of polymyxin B treatment failure in Gram-negative healthcare-associated infections among critically ill patients. *Journal of Microbiology, Immunology and Infection*, 51(6), 763-769.

John, J. F., Falci, D. R., Rigatto, M. H., Oliveira, R. D., Kremer, T. G., & Zavascki, A. P. (2018). Severe infusion-related adverse events and renal failure in patients receiving high-dose intravenous polymyxin B. *Antimicrobial Agents and Chemotherapy*, 62(1), 10-1128.

Justo, J. A., & Bosso, J. A. (2015). Adverse reactions associated with systemic Polymyxin therapy. Pharmacotherapy: *The Journal of Human Pharmacology and Drug Therapy*, 35(1), 28-33.

Klein, E. Y., Van Boeckel, T. P., Martinez, E. M., Pant, S., Gandra, S., Levin, S. A., ... & Laxminarayan, R. (2018). Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences*, 115(15), E3463-E3470.

Langat, C. K. D. (2018). *Antimicrobial susceptibility and management of bacterial skin and soft tissue infections at Moi Teaching and Referral Hospital, Eldoret, Kenya* (Doctoral dissertation, Moi University).

Manchandani, P., Zhou, J., Babic, J. T., Ledesma, K. R., Truong, L. D., & Tam, V. H. (2017). Role of renal drug exposure in Polymyxin B-induced nephrotoxicity. *Antimicrobial Agents and Chemotherapy*, 61(4).

Mattos, K. P. H., Gouvêa, I. R., Quintanilha, J. C., Cursino, M. A., Vasconcelos, P. E., & Moriel, P. (2019). Polymyxin B clinical outcomes: A prospective study of patients undergoing intravenous treatment. *Journal of clinical pharmacy and therapeutics*, 44(3), 415-419.

Ministry of Health. (2019). *Kenya Essential Medicines List 2019*. Retrieved March 8, 2021, from https://khf.co.ke/wp-content/uploads/2020/03/KEML-2019.pdf

Nang, S. C., Azad, M. A., Velkov, T., Zhou, Q. T., & Li, J. (2021). Rescuing the last-line polymyxins: achievements and challenges. *Pharmacological reviews*, 73(2), 679-728.

Ngamprasertchai, T., Boonyasiri, A., Charoenpong, L., Nimitvilai, S., Lorchirachoonkul, N., Wattanamongkonsil, L., & Thamlikitkul, V. (2018). Effectiveness and safety of Polymyxin B for the treatment of infections caused by extensively drug-resistant Gram-negative bacteria in Thailand. *Infection and drug resistance*, 11, 1219.

Onyango, O. S. (2018). *Antibacterial susceptibility patterns and risk factors for surgical site infections at Moi Teaching and Referral Hospital, Eldoret-Kenya* (Doctoral dissertation, Moi University).

Ramasubban, S., Majumdar, A., & Das, P. S. (2008). Safety and efficacy of Polymyxin B in multidrug resistant Gram-negative severe sepsis and septic shock. *Indian journal of critical care medicine*, 12(4), 153.

Rice, L. B. (2008). Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis.*, 197(8):1079-81. doi: 10.1086/533452. PMID: 18419525.

Rodrigues, A. C. S., Santos, I. C. D. O., Campos, C. C., Rezende, I. N., Ferreira, Y. M., Chaves, C. E. V., ... & Chang, M. R. (2019). Non-clonal occurrence of pmrB mutations associated with polymyxin resistance in carbapenem-resistant Klebsiella pneumoniae in Brazil. *Memórias do Instituto Oswaldo Cruz*, 114.

Shaw, A. C., Goldstein, D. R., & Montgomery, R. R. (2013). Age-dependent dysregulation of innate immunity. *Nature Reviews Immunology*, 13(12), 875-887.

World Health Organization. (2021). *Global antimicrobial resistance and use surveillance system (GLASS) report: 2021*. https://iris.who.int/bitstream/hand

le/10665/341666/9789240027336-eng.pdf?sequence=1

World Health Organization. (2017). *WHO publishes list of bacteria for which new antibiotics are urgently needed*. Retrieved from https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

Wu, X. L., Long, W. M., Lu, Q., Teng, X. Q., Qi, T. T., Qu, Q., ... & Qu, J. (2022). Polymyxin B-associated nephrotoxicity and its predictors: a retrospective study in carbapenem-resistant gram-negative bacterial infections. Frontiers in Pharmacology, 13, 672543.

Ye, Q., Wang, Q., Chen, Z., Chen, W., Zhan, Q., & Wang, C. (2022). Effectiveness, nephrotoxicity, and therapeutic drug monitoring of polymyxin B in nosocomial pneumonia among critically ill patients. *The Clinical Respiratory Journal*, 16(5), 402-412.

Zeng, H., Zeng, Z., Kong, X., Zhang, H., Chen, P., Luo, H., & Chen, Y. (2021). Effectiveness and nephrotoxicity of intravenous polymyxin B in Chinese patients with MDR and XDR nosocomial pneumonia. Frontiers in Pharmacology, 11, 579069.

Zhang, X., Qi, S., Duan, X., Han, B., Zhang, S., Liu, S., ... & Sun, T. (2021). Clinical outcomes and safety of polymyxin B in the treatment of carbapenem-resistant Gram-negative bacterial infections: a real-world multicenter study. Journal of Translational Medicine, 19(1), 1-10.