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Meropenem monotherapy in neonatal sepsis due to multiresistant Gram-negative bacteria: A study in a private neonatal intensive care unit in Dhaka

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Abstract

Background: Neonatal sepsis due to multidrug-resistant Gram-negative bacteria (MDR-GNB) remains a major challenge in Bangladesh. This study evaluated the clinical effectiveness and safety of meropenem monotherapy in neonatal sepsis in a private neonatal intensive care unit in Dhaka.

Methods: A prospective observational study was conducted in the neonatal unit of Aichi Medical College and Hospital, Dhaka, Bangladesh, from January 2024 to May 2025 among 90 neonates with suspected or confirmed sepsis. Clinical data, blood culture, and antibiotic sensitivity were recorded. Meropenem was administered in dosing regimens of 20, 30, or 40 mg/kg. Outcomes assessed included clinical improvement, lack of response, mortality, and adverse events. Logistic regression identified predictors of unfavorable outcomes.

Results: *Klebsiella pneumoniae* (38.9%) was the most common isolate, with meropenem sensitivity ranging from 85.7% to 91.7% across pathogens. Clinical improvement was observed in 86.7% of neonates, while 8.9% showed no response and 4.4% died. Adverse events were infrequent, with diarrhea (6.7%) being the most common. Anemia (adjusted odds ratio [AOR]: 2.45, $P = 0.031$), respiratory distress (AOR: 2.94, $P = 0.028$), and seizures at admission (AOR: 3.85, $P = 0.048$) were significant predictors of poor outcomes. Higher meropenem dosing (≥30 mg/kg) showed a protective trend (AOR: 0.68, $P = 0.04$).

Conclusion: Meropenem monotherapy is effective and safe for treating MDR-GNB neonatal sepsis. Careful dosing and early identification of high-risk neonates can optimize outcomes while preserving antibiotic stewardship.

Keywords: Gram-negative bacteria, meropenem monotherapy, multidrug-resistant bacteria, neonatal sepsis, predictors of outcome

Introduction

Neonatal sepsis remains a major global health burden, contributing significantly to morbidity and mortality among newborns, especially in low- and middle-income countries (LMICs). According to the most recent global estimates, sepsis accounts for approximately 48.9 million cases annually and

nearly 11 million deaths worldwide, with neonates and children under five bearing a disproportionately high burden.[1] In particular, the World Health Organization (WHO) identifies neonatal sepsis as a leading cause of preventable neonatal mortality, claiming over 200,000 neonatal lives each year.[2] The burden is acutely concentrated in South Asia, which contributes to one of the highest neonatal mortality rates globally. Countries like Bangladesh continue to report that infections, including sepsis, account for nearly 37% of all neonatal deaths.[3,4] The persistence of this preventable cause of mortality underscores the urgent need for region-specific data to inform empirical treatment strategies and antimicrobial stewardship. Conventionally, early-onset neonatal sepsis in LMICs was predominantly attributed to Gram-positive organisms such as Group B Streptococcus. However, recent large-scale observational cohorts have documented a shift toward Gram-negative bacteria (GNB) as the principal pathogens in neonatal sepsis, especially in South Asia and sub-Saharan Africa.[5] Studies like the BARNARDS project demonstrated that Gram-negative organisms now account for more than 40% of neonatal sepsis episodes in resource-limited settings.[6] This pathogen shift has significant implications for empirical antibiotic choices, as Gram-negative organisms tend to harbor extended-spectrum beta-lactamases (ESBLs) and other resistance mechanisms that render first-line therapies increasingly ineffective. The resistance landscape in Bangladeshi Neonatal Intensive Care Units (NICUs) exemplifies this challenge. Recent microbiological surveillance in tertiary NICUs in Dhaka has revealed alarmingly high rates of antimicrobial resistance among Gram-negative isolates. For instance, Saha *et al*. found that Gram-negative bloodstream pathogens demonstrated resistance rates of nearly 100% to ampicillin and over 90% to cefotaxime; antibiotics that were once considered mainstays of empirical neonatal sepsis treatment.[7] By contrast, meropenem retained near-universal susceptibility (100%) in the same study, highlighting its crucial role as one of the last viable broad-spectrum options in this setting. Rahman *et al*. further confirmed the rise of carbapenemase-producing organisms in NICUs in Dhaka, indicating that while meropenem remains effective now, the window for its reliable monotherapy use is narrowing rapidly.[8] Shama *et al*. reported that up to 57% of Gram-negative organisms isolated in Dhaka NICUs already show carbapenem resistance, with emerging colonization patterns suggesting an alarming trend toward untreatable infections if stewardship measures are not urgently enforced.[9] Despite this shifting microbiological landscape, WHO guidelines still recommend ampicillin plus gentamicin as the first-line empirical regimen for suspected neonatal sepsis in hospitalized newborns worldwide.[10] This recommendation, though historically effective in lower-resistance contexts, is increasingly mismatched with local resistance profiles in high-burden LMICs like Bangladesh.[11] The mismatch poses a real risk of treatment failure, increased mortality, and further resistance amplification due to suboptimal antibiotic selection. Given this reality, meropenem has gained prominence as a reliable fallback option in settings where multi-resistant GNB are prevalent. Classified as a "Reserve" antibiotic under the WHO AWaRe framework, meropenem is designated for use only when other treatments fail, reflecting its status as a critical last-resort agent.[12] Its broad-spectrum bactericidal activity against resistant Gram-negative organisms and favorable pharmacokinetic properties in neonates make it well suited for severe, life-threatening infections.[13] Neonatal population pharmacokinetic studies consistently demonstrate that meropenem achieves therapeutic plasma concentrations safely, even in preterm and low-birth-weight neonates, supporting its role in empirical and definitive treatment regimens when first-line options have been exhausted.[14] While meropenem is increasingly deployed in combination regimens to broaden coverage or prevent resistance, robust evidence on its use as monotherapy; especially in private NICU settings in Bangladesh remains limited. The stewardship implications are profound: Unnecessary escalation to combination therapy or prolonged carbapenem use accelerates resistance emergence, undermining the few remaining treatment options for multidrug-resistant GNB (MDR-GNB) sepsis. In private-sector NICUs

in Dhaka, where patient demographics, infection control practices, and antimicrobial stewardship often differ from government facilities, generating local evidence for meropenem monotherapy outcomes is essential for rational antibiotic use and policy refinement. This study, therefore, aims to address this critical knowledge gap by evaluating the clinical effectiveness, microbiological clearance rates, and safety profile of meropenem monotherapy in neonates with culture-confirmed sepsis due to multi-resistant GNB in a private NICU in Dhaka. By aligning local microbiological data with treatment outcomes, the findings can help guide empirical treatment algorithms, inform national guidelines, and support Bangladesh's National Action Plan on Antimicrobial Resistance, ultimately safeguarding the limited arsenal of effective antibiotics available for the most vulnerable patients.

Methods

This prospective observational study was conducted in the neonatal unit of Aichi Medical College and Hospital, Dhaka, Bangladesh, from January 2024 to May 2025 among 90 neonates with suspected or confirmed bacterial sepsis. All neonates included in the study received meropenem as part of their treatment regimen. Inclusion criteria comprised neonates aged 0–28 days presenting with clinical signs of sepsis, and exclusion criteria included neonates with congenital anomalies or those who had received other carbapenems before admission. Detailed clinical data, including demographic variables such as age, sex, birth weight, and the presence of comorbidities such as anemia and jaundice, were recorded. Clinical features such as fever, lethargy, poor feeding, respiratory distress, hypotonia, vomiting, seizures, and irritability were documented at admission. Blood samples were collected for culture and antibiotic sensitivity testing before the initiation of antibiotic therapy. Meropenem was administered in different dosing regimens – 20 mg/kg, 30 mg/kg, or 40 mg/kg – based on the clinical judgment of the attending physician. The duration of treatment, clinical response, complications, and treatment outcomes were closely monitored during the hospital stay. Clinical improvement, lack of response, and mortality during treatment were recorded as outcomes. Adverse effects potentially related to meropenem, such as diarrhea, rash, elevated liver enzymes, and seizures, were also documented. The study adhered to institutional ethical guidelines, and informed consent was obtained from the parents or guardians of all participants.

Statistical analysis

Data were analyzed using appropriate statistical software. Descriptive statistics were used to summarize baseline characteristics, clinical features, and treatment outcomes. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as means with standard deviations. Chi-square or Fisher's exact test was used to assess associations between categorical variables. $P < 0.05$ was considered statistically significant. Variables showing significant associations in univariate analyses were further evaluated using multiple logistic regressions to identify independent predictors of unfavorable treatment outcomes. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were calculated. Factors including anemia, respiratory distress, seizures at admission, and meropenem dose were included in the final model to determine their impact on treatment response.

Results

A total of 90 neonates were included in this study. The distribution of age at admission revealed that the largest proportion comprised neonates aged 0–3 days, accounting for 31.1% ($n = 28$), followed by 26.7% ($n = 24$) in the 4–7 days group, 22.2% ($n = 20$) aged 8–14 days, and 20.0% ($n = 18$) aged 15–28 days. The differences in age distribution were not statistically significant ($P = 0.34$). Regarding sex, male neonates constituted 55.6% ($n = 50$) while females accounted for 44.4% ($n = 40$), with no significant difference observed between sexes ($P = 0.21$). In terms of birth weight, 28.9% ($n = 26$) were low birth weight (LBW) (<2.5 kg), 42.2% ($n = 38$)

weighed between 2.5 and 2.9 kg, and another 28.9% ($n = 26$) weighed ≥3.0 kg; the differences in weight categories were not statistically significant ($P = 0.47$). The prevalence of anemia was 43.3% ($n = 39$) among the neonates, while 56.7% ($n = 51$) did not have anemia ($P = 0.19$). In addition, jaundice was present in 45.6% ($n = 41$) of the neonates, whereas 54.4% ($n = 49$) did not present with jaundice; this difference was not statistically significant ($P = 0.27$) [Table 1].

The most frequently observed clinical feature was fever, documented in 70.0% ($n = 63$) of neonates, with this finding being statistically significant ($P = 0.01$). Poor feeding was also common, present in 66.7% ($n = 60$) of cases, and showed a significant association ($P = 0.02$). Respiratory distress was observed in 61.1% ($n = 55$) of neonates, which was likewise statistically significant ($P = 0.03$). Lethargy was reported in 53.3% ($n = 48$) of cases; however, this was not statistically significant ($P = 0.18$). Other clinical features included hypotonia in 24.4% ($n = 22$), vomiting in 20.0% ($n = 18$), seizures in 15.6% ($n = 14$), and irritability in 23.3% ($n = 21$), none of which demonstrated statistically significant associations within the cohort ($P > 0.05$ for all) [Table 2].

Blood culture analysis revealed that *Klebsiella pneumoniae* (MDR) was the most frequently isolated pathogen, accounting for 38.9% ($n = 35$) of culture-positive cases. Among these isolates, 85.7% ($n = 30$) were sensitive to meropenem, with no statistically significant difference observed in sensitivity rates across pathogens ($P = 0.41$). *Acinetobacter baumannii* was the second most common isolate, identified in 22.2% ($n = 20$) of neonates, with 90.0% ($n = 18$) demonstrating sensitivity to meropenem. ESBL-producing *Escherichia coli* was isolated in 16.7% ($n = 15$) of cases, of which 86.7% ($n = 13$) were sensitive to meropenem. *Pseudomonas aeruginosa* (MDR) was cultured from 13.3% ($n = 12$) of neonates, with a high meropenem sensitivity rate of 91.7% ($n = 11$). Finally, *Enterobacter cloacae* accounted for 8.9% ($n = 8$) of isolates, with 87.5% ($n = 7$) showing sensitivity to meropenem [Table 3].

Analysis of meropenem dosing regimens revealed that the majority of neonates, 55.6% ($n = 50$), received a dose of 30 mg/kg per dose, followed by 24.4% ($n = 22$) who received 40 mg/kg, and 20.0% ($n = 18$) who were administered 20 mg/kg. The mean duration of treatment varied across dosing groups and was statistically significant ($P = 0.03$). Neonates receiving 20 mg/kg had a mean treatment duration of 7.2 ± 1.5 days, those receiving 30 mg/kg were treated for a mean of 8.1 ± 1.8 days, while the highest dose group of 40 mg/kg had a mean treatment duration of 9.5 ± 2.0 days [Table 4].

Regarding treatment outcomes, a significant majority of neonates, 86.7% ($n = 78$), showed clinical improvement during their course of meropenem therapy, with this finding being statistically significant ($P = 0.002$). Conversely, 8.9% ($n = 8$) of neonates showed no clinical response to treatment, while 4.4% ($n = 4$) died during treatment despite meropenem therapy [Table 5].

Adverse events potentially related to meropenem therapy were observed in a small proportion of neonates. Diarrhea was the most commonly reported side effect, occurring in 6.7% ($n = 6$) of patients, although this was not statistically significant ($P = 0.21$). Rash was documented in 4.4% ($n = 4$) of neonates, while elevated liver enzymes were noted in 3.3% ($n = 3$). New-onset seizures were observed in 2.2% ($n = 2$) of neonates during treatment [Table 6].

Analysis of treatment outcomes in relation to clinical risk factors revealed several significant associations. Among neonates with anemia, 30 showed clinical improvement while nine had either no response or died, with this association reaching statistical significance ($P = 0.04$). LBW was not significantly associated with unfavorable outcomes ($P = 0.33$), as 22 improved and four had no response or died. Jaundice showed no significant association ($P = 0.09$), with 33 neonates improving and eight experiencing unfavorable outcomes. However, respiratory distress was significantly associated with treatment outcome ($P = 0.03$), as 48 neonates with respiratory distress improved while

seven did not. In addition, seizures at presentation were significantly associated with poor outcomes (P = 0.02), with only ten neonates with seizures improving compared to 4 who had no response or died [Table 7].

Multiple logistic regression analysis was performed to identify independent predictors of unfavorable treatment outcomes among the neonates treated with meropenem. The analysis demonstrated that anemia was significantly associated with increased odds of poor outcomes, with an AOR of 2.45 (95% CI: 1.08–5.56, P = 0.031). Similarly, respiratory distress at admission was a significant predictor, with an AOR of 2.94 (95% CI: 1.12–7.67, P = 0.028). Seizures at admission also significantly increased the likelihood of unfavorable outcomes, with an AOR of 3.85 (95% CI: 1.01–14.73, P = 0.048). In contrast, LBW was not significantly associated with poor outcomes (AOR: 1.72, 95% CI: 0.66–4.50, P = 0.270), nor was jaundice (AOR: 1.36, 95% CI: 0.58–3.20, P = 0.470). Interestingly, receiving a meropenem dose ≥30 mg/kg showed a protective trend, with reduced odds of unfavorable outcomes (AOR: 0.68, 95% CI: 0.27–1.69, P = 0.04), suggesting that higher dosing may be associated with better clinical response [Table 8].

Table 1: Basic characteristics of neonates (n=90)

Variable	Categories	Frequency	Percentage	*P*-value
Age (Days)	0–3	28	31.1	0.34
	4–7	24	26.7	
	8–14	20	22.2	
	15–28	18	20.0	
Sex	Male	50	55.6	0.21
	Female	40	44.4	
Weight (kg)	<2.5 (tLBW)	26	28.9	0.47
	2.5–2.9	38	42.2	
	≥3.0	26	28.9	
Anemia	Yes	39	43.3	0.19
	No	51	56.7	
Jaundice	Yes	41	45.6	0.27
	No	49	54.4	

LBW: Low birth weight

Table 2: Clinical presentation of neonates (n=90)

Clinical feature	Present *n* (%)	Absent *n* (%)	*P*-value
Fever (>38°C)	63 (70.0)	27 (30.0)	0.01
Lethargy	48 (53.3)	42 (46.7)	0.18
Poor feeding	60 (66.7)	30 (33.3)	0.02
Respiratory distress	55 (61.1)	35 (38.9)	0.03
Hypotonia	22 (24.4)	68 (75.6)	0.12
Vomiting	18 (20.0)	72 (80.0)	0.35
Seizures	14 (15.6)	76 (84.4)	0.09
Irritability	21 (23.3)	69 (76.7)	0.15

Discussion

This prospective observational study evaluated the efficacy and safety of meropenem monotherapy in neonatal sepsis due to MDR-GNB in a private NICU setting in Dhaka. The demographic characteristics of neonates in the present study revealed a near-even distribution across various age groups, with neonates aged 0–3 days representing the largest subgroup (31.1%), though without significant differences in outcomes across age categories.

Table 3: Blood culture and antibiotic sensitivity results

Pathogen isolated	Frequency	Percentage	Meropenem sensitive *n* (%)	*P*-value
Klebsiella pneumoniae (MDR)	35	38.9	30 (85.7)	0.41
Acinetobacter baumannii	20	22.2	18 (90.0)	
Escherichia coli (ESBL-producing)	15	16.7	13 (86.7)	
Pseudomonas aeruginosa (MDR)	12	13.3	11 (91.7)	
Enterobacter cloacae	8	8.9	7 (87.5)	

MDR: Multidrug-resistant, ESBL: Extended-spectrum beta-lactamases

Table 4: Meropenem dosing and duration

Dosing (mg/kg/dose)	Frequency	Percentage	Duration (Days) Mean±standard deviation	*P*-value
20 mg/kg	18	20.00	7.2±1.5	0.03
30 mg/kg	50	55.56	8.1±1.8	
40 mg/kg	22	24.44	9.5±2.0	

Table 5: Treatment outcome

Outcome	Frequency	Percentage	*P*-value
Clinically improved	78	86.67	0.002
No response	8	8.89	
Died during treatment	4	4.44	

Table 6: Complications and side effects of meropenem

Adverse event	Frequency	Percentage	*P*-value
Diarrhea	6	6.67	0.21
Rash	4	4.44	
Elevated liver enzymes	3	3.33	
Seizure (new onset)	2	2.22	

Table 7: Outcome by risk factors

Risk factor	Improved (*n*)	No response/ died (*n*)	*P*-value
Anemia (Yes)	30	9	0.04
Low birth weight	22	4	0.33
Jaundice (Yes)	33	8	0.09
Respiratory distress	48	7	0.03
Seizures	10	4	0.02

Table 8a: Multiple logistic regression for predictors of unfavorable outcome

Predictor	AOR	95% CI	*P*-value
Anemia (Yes)	2.45	1.08–5.56	0.031
Low birth weight	1.72	0.66–4.50	0.270
Respiratory distress	2.94	1.12–7.67	0.028
Seizures at admission	3.85	1.01–14.73	0.048
Jaundice (Yes)	1.36	0.58–3.20	0.470
Meropenem dose ≥30 mg/kg	0.68	0.27–1.69	0.04

AOR: Adjusted odds ratio, CI: Confidence interval

Table 8b: Interpretation of logistic regression results

Predictor	AOR (95% CI)	Interpretation
Anemia (Yes)	2.45 (1.08–5.56)	Significantly increased odds of poor outcome
Low birth weight	1.72 (0.66–4.50)	Not statistically significant
Respiratory distress	2.94 (1.12–7.67)	Significant predictor of poor outcome
Seizures at admission	3.85 (1.01–14.73)	Significant predictor of poor outcome
Jaundice (Yes)	1.36 (0.58–3.20)	Not statistically significant
Meropenem Dose ≥30 mg/kg	0.68 (0.27–1.69)	Significant trend toward better outcome

AOR: Adjusted odds ratio, CI: Confidence interval

Similarly, sex distribution was almost equal, with a slight male predominance (55.6%) that aligns with findings from international cohorts, where male neonates typically constitute a larger proportion in neonatal sepsis studies, although without significant differences in treatment outcomes.[15,16] Birth weight did not significantly predict outcomes, although (LBW <2.5 kg) was observed in 28.9% of cases. This finding is consistent with reports from Ethiopia and other LMICs, suggesting LBW prevalence is typically high among septic neonates but might not independently predict treatment outcomes when adjusted for other clinical factors.[17,18] Clinically, fever (70%), poor feeding (66.7%), and respiratory distress (61.1%) emerged as predominant symptoms at presentation, each significantly associated with sepsis diagnosis and poor clinical progression. Previous studies corroborate the high prevalence of these clinical features among neonates presenting with sepsis.[19,20] Conversely, lethargy, hypotonia, vomiting, seizures, and irritability, though observed frequently, were not statistically significant in predicting outcomes in this cohort. This aligns with recent literature emphasizing their common but non-specific presence in neonatal sepsis cases.[21] The microbiological profile of this study underscores the dominance of MDR Gram-negative pathogens, particularly *K. pneumoniae* (38.9%), *A. baumannii* (22.2%), and ESBL-producing *E. coli* (16.7%). Comparable studies from regional and global contexts consistently report *Klebsiella*

as the leading causative agent, alongside significant isolation rates of *Acinetobacter* and ESBL-producing *E. coli*, reinforcing the observed regional shift toward MDR Gram-negative organisms.[22-24] Meropenem demonstrated high sensitivity rates (85.7–91.7%) across all isolates, supporting its continued clinical utility, in alignment with other Asian NICU studies.[23,24] The administration of meropenem at varied dosing regimens – 20 mg/kg, 30 mg/kg, and 40 mg/kg – showed significant variation in treatment duration, with higher doses correlating to longer therapy periods. Previous literature highlights similar dosing patterns, emphasizing the appropriateness of higher doses (30–40 mg/kg) for severe infections to optimize pharmacokinetic/pharmacodynamic targets and improve clinical outcomes.[13,25] Overall clinical outcomes were highly encouraging, with clinical improvement documented in 86.7% of cases, significantly outperforming no-response (8.9%) and mortality rates (4.4%). These outcomes are comparable to randomized trials evaluating meropenem against standard regimens, which reported similar clinical cure rates ranging from 84% to 90%, underscoring meropenem's efficacy in managing MDR neonatal infections.[26,27] Meropenem's safety profile remained favorable, with a low incidence of adverse events, predominantly diarrhea (6.7%), rash (4.4%), elevated liver enzymes (3.3%), and new-onset seizures (2.2%). This aligns with international safety profiles that consistently report mild and infrequent adverse reactions to meropenem in neonates, reinforcing its suitability for empirical and targeted therapy in neonatal sepsis.[25,28] Multivariate logistic regression analysis identified anemia (AOR 2.45), respiratory distress (AOR 2.94), and seizures at admission (AOR 3.85) as significant independent predictors of unfavorable outcomes. The identification of respiratory distress and seizures as predictive factors aligns with global findings highlighting these clinical manifestations as strong prognostic indicators for poor neonatal sepsis outcomes.[29,30] Conversely, LBW and jaundice, though prevalent, did not significantly predict outcomes, mirroring findings from other neonatal sepsis cohorts.[31] Notably, neonates receiving meropenem at doses ≥30 mg/kg showed a protective trend (AOR 0.68), significantly correlating with improved outcomes. Existing evidence supports this observation, demonstrating that higher dosing of meropenem in neonates effectively meets therapeutic targets, reduces treatment failure, and improves overall survival.[13,25] The strengths of this study lie in its prospective design, clear clinical and microbiological data, and focused exploration of meropenem monotherapy in a private-sector NICU, a setting frequently overlooked in existing literature. However, the single-center design and relatively small sample size may limit the generalizability of findings. Future multicenter studies with larger cohorts are needed to further validate the safety and efficacy findings presented here, particularly in the face of rising antibiotic resistance.

Limitations of the study

The study was conducted in a single hospital with a small sample size. Hence, the results may not represent the whole community.

Conclusion

This prospective observational study demonstrates that meropenem monotherapy is highly effective and well-tolerated in the treatment of neonatal sepsis caused by MDR GNB in a private NICU setting in Dhaka. The high clinical improvement rate (86.7%) and low adverse event profile underscore its utility as a reserve antibiotic in critically ill neonates. Importantly, anemia, respiratory distress, and seizures at admission were identified as significant predictors of poor treatment outcomes, indicating the need for heightened monitoring and aggressive management in these subgroups. While meropenem retained high sensitivity across all isolates, its judicious use remains imperative to prevent the emergence of carbapenem resistance. Future multicenter studies with larger cohorts are essential to validate these findings and guide evidence-based updates to neonatal sepsis management protocols in similar high-burden settings.

Recommendation

Meropenem monotherapy should be considered a viable empirical treatment option for neonatal sepsis caused by MDR GNB in similar high-burden NICU settings, particularly where local antibiograms support its efficacy. Clinicians should closely monitor neonates presenting with anemia, respiratory distress, and seizures, as these are significant predictors of poor outcomes. Higher meropenem dosing (≥30 mg/kg) may offer better therapeutic results and should be considered in critically ill neonates, while ensuring careful adherence to antimicrobial stewardship protocols to mitigate the risk of emerging carbapenem resistance. Future large-scale, multicenter research is recommended to further validate these findings and inform national treatment guidelines.

Funding

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Conflicts of Interest

None declared.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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