

Efficacy of prolonged versus standard infusion meropenem in critically ill pediatric patients with sepsis: A randomized controlled trial

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ABSTRACT

Background: This study compared meropenem administered for a longer duration with its standard duration in suspected and confirmed bacterial sepsis. This study aims assess the efficacy of prolonged infusion meropenem versus standard infusion in critically ill patients admitted to the pediatric ICU.

Material and Methods: This randomized controlled trial included 150 critically ill pediatric patients and was conducted in the Pediatric Intensive Care Unit of PNS Shifa Hospital, Karachi, from 01 January 2025 to 30 June 2025. The trial was registered at ClinicalTrials.gov (NCT07122596). Children (1 month to 16 years) with suspected or proven bacterial sepsis who required meropenem intravenously were selected. Independent samples t-test or Mann–Whitney U test was used to compare continuous variables, and chi-square or Fisher's exact test was used to compare categorical variables. The relative risks with 95% confidence intervals were used to express the effects of treatment.

Results: Baseline characteristics were comparable between groups. The mean age was 7.7 ± 2.04 years in the prolonged infusion group and 7.6 ± 1.98 years in the standard infusion group. Day-7 clinical success was significantly higher with prolonged infusion (92.0% vs. 73.3%; RR 1.25, 95% CI 1.08–1.46; $p=0.003$), with greater microbiological eradication among culture-positive patients (91.4% vs. 75.4%; $p=0.012$). Prolonged infusion also reduced time to clinical improvement and PICU stay, while in-hospital mortality was lower but not statistically significant.

Conclusion: Prolonged infusion of meropenem improved clinical success and shortened PICU stay.

Keywords: Anti-bacterial agents, Critical illness, Infusions, Intravenous, Intensive care units, Meropenem, Pediatrics, Sepsis.

BACKGROUND

Severe infections are still a major cause of morbidity and mortality in critically ill children and need timely and effective treatment with antimicrobials. Meropenem is a broad-spectrum carbapenem antibiotic that is used to treat severe bacterial infections in neonates and children due to its strong antimicrobial activity and good safety profile.¹ It is time dependent and is related to the time the free drug concentrations are above the minimum inhibitory concentration ($fT>MIC$). Physiological changes in critically ill patients can affect drug pharmacokinetics and could impact target attainment by classical pharmacokinetic/

pharmacodynamic (PK/PD) principles.^{2,3} A prolonged infusion may increase $fT>MIC$ while keeping the total daily dose the same and thus may improve therapeutic response.^{4,5}

Critically ill children are where this approach is relevant in view of significant inter-individual pharmacokinetic variability. Systematic reviews have demonstrated an association of longer β -lactam infusion duration with better eradication and clinical outcome⁷ and paediatric studies have recommended individualized antimicrobial therapy.⁶ Precision-dosing and population pharmacokinetic studies also suggest that standard meropenem dosing can be inadequate in critically ill children.⁸⁻¹⁰

These factors have become more significant in light of global antimicrobial resistance. Carbapenems should be used judiciously and the meropenem is a Watch antibiotic per the World Health Organization AWARe classification which highlights appropriate use and monitoring.^{11,12} Thus, pediatric antimicrobial stewardship will help ensure that a child is exposed to indicated carbapenem use instead of increasing the dose or unnecessarily expanding the spectrum. WHO defines AWARe as a framework to monitor the impact of

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antibiotic stewardship policies and antimicrobial resistance (AMR) and reports that global surveillance is ongoing, with high rates of AMR reported.

Comparative data on the use of prolonged meropenem infusion versus standard infusion in critically ill children is limited, and is especially scarce in the local intensive-care environment. Thus, this study aimed to evaluate the outcomes of extended infusion and standard infusion meropenem therapy in critically ill children with suspected and confirmed bacterial sepsis.

MATERIAL AND METHODS

The study was conducted in Pediatric Intensive Care Unit (PICU) Department of Paediatrics, PNS Shifa Hospital, Karachi from 01 January 2025 to 30 June 2025, after receiving approval from the Institutional Ethical Review Committee (ERC/2024/PAEDS/81-A) and registration at ClinicalTrials.gov (NCT07122596). Written informed consent was obtained from parents or legal guardians. Eligible children were those aged 1 month to 16 years who had suspected or proven bacterial sepsis who needed intravenous meropenem as part of standard PICU care. Suspected sepsis was considered to be one or more age-based SIRS criteria and confirmed sepsis was based on microbiological data from blood, urine, CSF or tracheal aspirate cultures. Patients with carbapenem hypersensitivity, glomerular filtration rate (GFR) < 30 mL/min/1.73 m², receiving another investigational antimicrobial agent, and do-not-attempt-for-withdrawal (DAFWA) were excluded.

One hundred and fifty participants were randomly assigned in a 1:1 ratio with computer-generated permuted block randomisation with variable block sizes of four and six. Sequentially-numbered, opaque, sealed envelopes prepared by an independent investigator were used to insure allocation concealment. A total of 75 children were assigned to the prolonged-infusion group and 75 were assigned to the standard-infusion group. Randomization was done at the start of meropenem treatment according to clinical judgment of possible bacterial sepsis and microbiological culture results were subsequently collected for identification of pathogens and optimization of antibiotic treatment.

The infusion times varied between treatment groups, and no blinding was undertaken for treating physicians and nursing staff, but outcome assessors and statisticians were blinded to treatment allocation. In septic shock, healthcare-associated infection or

suspected multidrug-resistant infection of Gram-negative bacteria, meropenem was started empirically. After culture and susceptibility data were made available, antimicrobial use was continued, escalated or adjusted based on the microbiological results and clinical response. There was no exclusion of participants after randomization and all randomized participants were included in the intention to treat analysis.

Meropenem was given every 8 hours for 4 or 30 minutes (standard- or prolonged-infusion, respectively) over a 4-h period in the prolonged-infusion group and for 30 min in the standard-infusion group. Doses of meropenem were administered according to weight and the institutional Pediatric Intensive Care Unit (PICU) guidelines, with renal dose adjustment if needed. The exact dose, maximum dose limits and loading-dose policy were detailed in the original study protocol. The severity of disease was measured with Pediatric Risk of Mortality III (PRISM III) within 24 hours of admission to the PICU. Under observation for 24 hours a day during their hospital stay.

The primary outcome was clinical success on Day 7, which included continued clinical improvement with a temperature <38°C for ≥24 hours without the use of antipyretics, hemodynamic stability without the need to escalate vasoactive medication, and no worsening of respiratory support due to infection, and no change or escalation in antibiotic therapy because of therapeutic failure. Secondary outcomes were microbiological eradication, time to clinical improvement, length of stay in the PICU, and in-hospital mortality.

Data were analyzed with SPSS version 26, which was analyzed on an intention-to-treat basis. The independent-samples t-test and the Mann-Whitney U test were used for comparing continuous variables, and the chi-square test or Fisher's exact test were used for categorical variables, as appropriate. Treatment effects have been reported as relative risk (RR) with 95% confidence interval (CI), absolute risk difference (ARD), and number needed to treat (NNT). The p value of <0.05 was set as a statistically significant level.

RESULTS

A total of 150 patients were randomized equally to the prolonged infusion group (PIG) and standard infusion group (SIG), with all participants completing follow-up and included in the final analysis (Figure-I). Baseline demographic and clinical characteristics, infection sites,

PRISM III scores, septic shock, and mechanical ventilation were comparable between groups (Table-I). Clinical success at Day 7 was significantly higher in the PIG than SIG (92.0% vs. 73.3%; RR 1.25, 95% CI 1.08–1.46; $p=0.003$), with an absolute benefit of 18.7% and NNT of 6. Time to clinical improvement and PICU stay were significantly shorter in the PIG, whereas mortality was lower but not statistically significant (Table-II). Culture positivity and distributions of *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas*

aeruginosa, *Acinetobacter baumannii*, ESBL-producing, multidrug-resistant, and carbapenem-resistant isolates were comparable between groups (Table-III). Adverse events were infrequent and similar between groups, with no serious meropenem-related adverse events. Exploratory subgroup analyses generally favored prolonged infusion without significant treatment-by-subgroup interactions (Table-IV).

Table-I. Baseline demographics and clinical characteristics of critically ill pediatric patients with sepsis (N=150).

Characteristic	Total (N=150)	Prolonged Infusion Group (PIG) (n=75)	Standard Infusion Group (SIG) (n=75)	p-value
Age (years), mean $\pm$ SD	7.65 $\pm$ 2.01	7.7 $\pm$ 2.04	7.6 $\pm$ 1.98	0.761
Male, n (%)	82 (54.7)	40 (53.3)	42 (56.0)	0.743
Female, n (%)	68 (45.3)	35 (46.7)	33 (44.0)	—
Weight (kg), mean $\pm$ SD	24.1 $\pm$ 3.9	24.4 $\pm$ 3.9	23.8 $\pm$ 3.9	0.348
PRISM III score, mean $\pm$ SD	10.9 $\pm$ 1.4	11.1 $\pm$ 1.4	10.8 $\pm$ 1.4	0.191
Lower respiratory tract infection, n (%)	60 (40.0)	29 (38.7)	31 (41.3)	0.739
Bloodstream infection/sepsis, n (%)	35 (23.3)	18 (24.0)	17 (22.7)	0.847
Urinary tract infection, n (%)	23 (15.3)	12 (16.0)	11 (14.7)	0.821
CNS infection/meningitis, n (%)	16 (10.7)	8 (10.7)	8 (10.7)	1.000
Intra-abdominal infection, n (%)	10 (6.7)	5 (6.7)	5 (6.7)	1.000
Other infection, n (%)	6 (4.0)	3 (4.0)	3 (4.0)	>0.999
Septic shock, n (%)	49 (32.7)	24 (32.0)	25 (33.3)	0.862
Mechanical ventilation, n (%)	61 (40.7)	30 (40.0)	31 (41.3)	0.868

Other infections: CNS: Central nervous system; **PRISM III:** Pediatric Risk of Mortality III; **PIG:** Prolonged infusion group; **SIG:** Standard infusion group.

Table-II: Primary, microbiological, and secondary clinical outcomes among critically ill pediatric patients with sepsis (N=150).

Outcome	Total (N=150)	Prolonged Infusion Group (PIG) (n=75)	Standard Infusion Group (SIG) (n=75)	Relative Risk (95% CI)	p-value
Clinical success at Day 7, n (%)	124 (82.7)	69/75 (92.0)	55/75 (73.3)	1.25 (1.08–1.46)	0.003
Absolute increase in clinical success	—	—	—	18.7% (6.9–30.4)	—
Number needed to treat (NNT)	—	—	—	6	—
Microbiological eradication*, n (%)	113/135 (83.7)	64/70 (91.4)	49/65 (75.4)	1.21 (1.04–1.42)	0.012
Time to clinical improvement (days), mean $\pm$ SD	—	4.0 $\pm$ 1.2	5.3 $\pm$ 1.6	MD -1.30 (-1.76 to -0.84)	<0.001
PICU stay (days), mean $\pm$ SD	—	6.8 $\pm$ 2.1	8.1 $\pm$ 2.5	MD -1.30 (-2.05 to -0.55)	0.001
In-hospital mortality, n (%)	10 (6.7)	3 (4.0)	7 (9.3)	0.43 (0.12–1.59)	0.327

*Among patients with positive baseline cultures.

Abbreviations: RR: Relative Risk; CI: Confidence Interval; MD: Mean Difference; NNT: Number Needed to Treat; PICU: Pediatric Intensive Care Unit; PIG: Prolonged Infusion Group; SIG: Standard Infusion Group.

Table-III: Baseline Microbiological Characteristics and Resistance Profile Among Critically Ill Pediatric Patients with Sepsis (N=150)

Characteristic	Total (N=150)	Prolonged Infusion Group (PIG) (n=75)	Standard Infusion Group (SIG) (n=75)	p-value
Culture-positive infection, n (%)	135 (90.0)	70 (93.3)	65 (86.7)	0.174
Blood culture positive, n (%)	44 (29.3)	23 (30.7)	21 (28.0)	0.720
Urine culture positive, n (%)	25 (16.7)	13 (17.3)	12 (16.0)	0.827

Respiratory/ tracheal culture	50 (33.3)	26 (34.7)	24 (32.0)	0.729
positive, n (%)				
CSF/other sterile-site culture	16 (10.7)	8 (10.7)	8 (10.7)	>0.999
positive, n (%)				
<i>Klebsiella pneumoniae</i> , n (%)	42 (28.0)	22 (29.3)	20 (26.7)	0.716
<i>Escherichia coli</i> , n (%)	29 (19.3)	15 (20.0)	14 (18.7)	0.836
<i>Pseudomonas aeruginosa</i> , n (%)	27 (18.0)	14 (18.7)	13 (17.3)	0.832
<i>Acinetobacter baumannii</i> , n (%)	23 (15.3)	12 (16.0)	11 (14.7)	0.821
Other Gram-negative organisms, n (%)	14 (9.3)	7 (9.3)	7 (9.3)	>0.999
ESBL-producing isolates, n (%)	52 (34.7)	27 (36.0)	25 (33.3)	0.731
Multidrug-resistant isolates, n (%)	69 (46.0)	35 (46.7)	34 (45.3)	0.870
Carbapenem-resistant isolates, n (%)	11 (7.3)	5 (6.7)	6 (8.0)	0.754

CSF: Cerebrospinal fluid; ESBL: Extended-spectrum β -lactamase; PIG: Prolonged infusion group; SIG: Standard infusion group.

Table-IV: Safety outcomes and exploratory subgroup analysis of day-7 clinical success (N=150).

Outcome/ Subgroup	PIG	SIG	RR (95% CI)	p-value
Safety outcomes				
Any adverse event, n (%)	7 (9.3)	8 (10.7)	0.88 (0.34–2.27)	1.000
Seizure, n (%)	1 (1.3)	2 (2.7)	0.50 (0.05–5.43)	1.000
New/worsening renal dysfunction, n (%)	2 (2.7)	2 (2.7)	1.00 (0.14–7.10)	1.000
Hypersensitivity/rash, n (%)	1 (1.3)	1 (1.3)	1.00 (0.06–15.70)	1.000
Gastrointestinal adverse event, n (%)	3 (4.0)	3 (4.0)	1.00 (0.21–4.76)	1.000
Meropenem discontinued due to adverse event, n (%)	0 (0.0)	1 (1.3)	0.33 (0.01–8.05)	1.000
Serious drug-related adverse event, n (%)	0 (0.0)	0 (0.0)	—	—
Exploratory subgroup analysis				
Culture-positive	65/70 (92.9)	48/65 (73.8)	1.26 (1.07–1.47)	0.487
Mechanically ventilated	26/30 (86.7)	20/31 (64.5)	1.34 (1.00–1.81)	0.677
Not mechanically ventilated	43/45 (95.6)	35/44 (79.5)	1.20 (1.02–1.41)	—
Septic shock	20/24 (83.3)	16/25 (64.0)	1.30 (0.92–1.84)	0.394
No septic shock	49/51 (96.1)	39/50 (78.0)	1.23 (1.05–1.44)	—
Age 1–12 months	5/6 (83.3)	3/5 (60.0)	1.39 (0.62–3.09)	0.852
Age >12 months	64/69 (92.8)	52/70 (74.3)	1.25 (1.07–1.45)	—

CI: confidence interval; PIG: prolonged infusion group; RR: relative risk; SIG: standard infusion group.

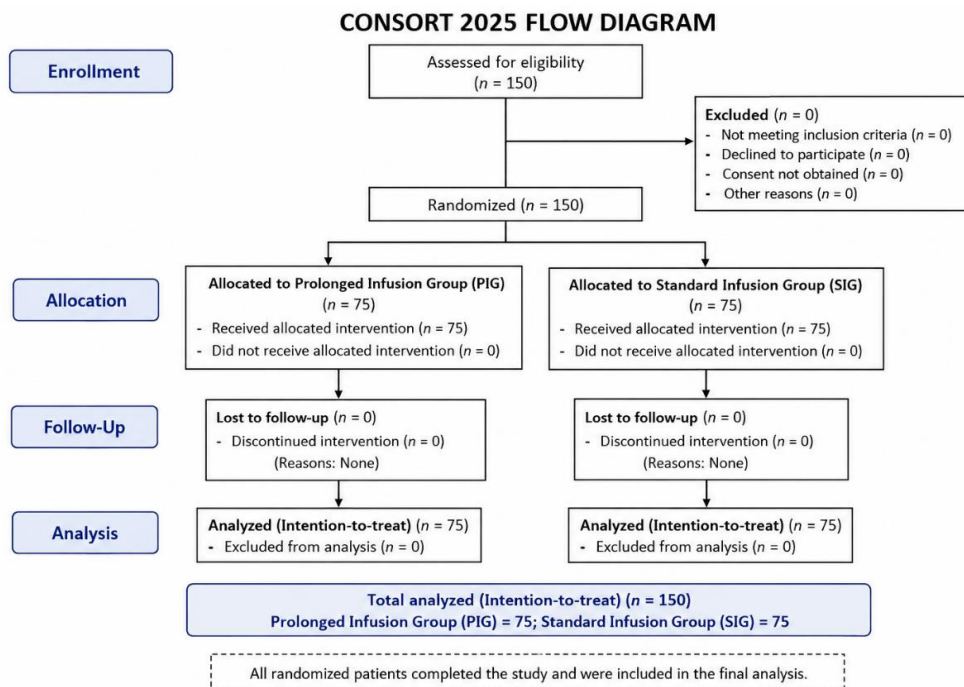


Figure-1: CONSORT flow diagram showing participant enrollment, randomization, allocation, follow-up, and intention-to-treat analysis in the prolonged infusion and standard infusion groups.

DISCUSSION

The results of this randomized controlled study of 150 children at high risk for bacterial sepsis showed that meropenem given as a longer infusion was superior to meropenem given as a standard infusion. The primary outcome, Day-7 clinical success, was significantly higher in the prolonged-infusion group (92.0% vs. 73.3%; RR 1.25, 95% CI 1.08–1.46; $p=0.003$). No difference in adverse events was observed, but prolonged infusion was also linked to better microbiological clearance in culture-positive patients and decreased time to clinical improvement as well as decreased length of stay in the PICU.

The observed benefit could be due to the pharmacodynamic properties of meropenem, a β -lactam antibiotic that requires free drug levels above the minimum inhibitory concentration ($fT>MIC$) to kill bacteria. Altered pharmacokinetics is common in critically ill pediatric patients and can be caused by altered renal clearance, volume of distribution, fluid therapy, and organ dysfunction, leading to suboptimal exposure to an antimicrobial with traditional infusion regimens. Target attainment with meropenem has been shown to be sub-optimal with standard dosing intervals in critically ill children, but longer infusion durations are more likely to reach pharmacodynamic targets.¹¹

Our findings suggest some clinical implications for the consideration of prolonged meropenem infusion as an optimization strategy in severely ill children with severe infection. Aldaz *et al.* showed that pharmacokinetics/pharmacodynamics-based meropenem dosing had a beneficial impact on the degree of antimicrobial exposure in the critically ill population, and that individual dosing strategies are important to consider in this population.¹² Likewise, research comparing extended or continuous infusion has indicated that this longer duration of effective drug levels may lead to better target attainment.¹³

The results of our study are in agreement with the previous evidence assessing the use of prolonged β -lactam administration. In another study, Luque *et al.* found that extended or continuous meropenem infusion achieved better pharmacokinetic/pharmacodynamic exposure in patients with low body weight in the critical care setting and suggested that longer infusion durations may be beneficial in patients with altered physiological states.¹⁴ In children, Zembles *et al.* noted positive results for extended-infusion β -lactams for Gram-negative

bloodstream infection, but the observational study design may be a limitation for making causal interpretation.¹⁵ In addition, extended and continuous β -lactam therapy in children has been reviewed and recommended as being associated with better pharmacodynamic target achievement and clinical potential benefits with a call for more robust randomized evidence.¹⁶

Our trial has some key differences to previous trials. Many previous studies were observational, pharmacokinetic or involved in studies of mixed critically ill patients while the present study involved a randomized pediatric sepsis group of patients treated with meropenem in a controlled treatment allocation study. Also, age distribution, severity of infection, prevalence of infection, antimicrobial resistance and intensive care practices could account for some of the differences in treatment effects when comparing studies.¹⁷

In addition, there has been recent systematic evidence suggesting that extended duration of beta-lactam therapy could be clinically beneficial in children, but there is significant heterogeneity in antibiotic choice, infusion regimens, patient demographics and outcome criteria. Although extended infusion is an attractive option, additional quality pediatric randomized controlled trials are needed to provide clear clinical guidelines, Burch *et al.* stressed.¹⁸ The same applies to febrile neutropenic children, where extended-infusion β -lactams appear to be safe, although the benefit might vary depending on the characteristics of the underlying disease, the susceptibility of the pathogens and the variability of β -lactam pharmacokinetics.¹⁹

This enhanced clinical response in our study may thus be due to greater pharmacodynamic exposure afforded by prolonged infusion, especially in the critically ill child whose drug clearance is variable. The current study did not have the necessary information for meropenem plasma levels, therapeutic drug monitoring, and organism-specific MIC values, so it was not possible to directly assess pharmacokinetic/pharmacodynamic target attainment. Further multicenter randomized trials that include therapeutic drug monitoring, MIC analysis and customized dosing are needed to validate these.

CONCLUSION

This single-center, pediatric study found that prolonged-infusion meropenem was associated with better clinical

and microbiological outcomes with no apparent increase in adverse events. But, due to the small sample size, single-center design and lack of direct pharmacokinetic/pharmacodynamic measurements, it is not advised to use prolonged infusion routinely. Therefore, prolonged-infusion meropenem might be a viable treatment option that should be validated in multicenter randomized trials including more patients prior to widespread adoption.

DISCLOSURES

None

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Nadia Iqbal: Substantial contributions to study conception, design, and data collection, Drafting of manuscript and critical review for important intellectual content, final approval, accountable for all aspects of publication

Khurram Fayyaz: Substantial contributions to study supervision and overall design, critical review of manuscript for important intellectual content, final approval, accountable for all aspects of publication

Sadia Karim: Substantial contributions to data analysis and interpretation of results, manuscript revision and critical intellectual input, final approval, accountable for all aspects of publication

Khadija Yasmin: Substantial contributions to data analysis and drafting support, manuscript reviewing for intellectual content, final approval, accountable for all aspects of publication

Nadeem Sadiq: Substantial contributions through clinical input and patient management, manuscript reviewing for important intellectual content, final approval, accountable for all aspects of publication

Hajra Begum: Substantial contributions to literature review and data collection, Proofreading and critical revision of the manuscript, final approval, accountable for all aspects of publication

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