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ORIGINAL RESEARCH

A Pharmacist-Driven Closed-Loop Stewardship Model of Meropenem: Impact on Stability and Efficacy in Neurosurgery Patients

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Purpose: To evaluate the impact of a pharmacist-driven closed-loop stewardship model on meropenem stability and therapeutic efficacy in neurosurgical patients with hospital-acquired pneumonia (HAP).

Patients and Methods: An interrupted time series study enrolled neurosurgical patients treated with meropenem for HAP. The patients from October 2019 to December 2021 were retrospectively collected as the control group, whereas the patients were prospectively enrolled from January 2022 to March 2025 as the intervention group. The intervention featured optimized drug preparation, prioritized administration, rapid specimen processing, real-time therapeutic drug monitoring and dynamic dose adjustments. Steady-state trough concentrations (C_{min}) and open-ring metabolite (ORM) levels in serum and cerebrospinal fluid (CSF), and clinical outcomes were analyzed.

Results: A total of 227 patients was included (control group: n = 102; intervention group: n = 125). The intervention group demonstrated a significantly higher median C_{min} [3.75 (1.45, 8.64) mg/L vs 0.78 (0.25, 2.74) mg/L, $P < 0.001$] and lower subtherapeutic exposure rate (35.48% vs 70.59%, $P < 0.0001$) compared to control group. The ratio of ORM/C_{min} in serum [0.83 (0.62, 1.24) vs 1.97 (1.42, 2.65), $P < 0.0001$] and CSF [1.21 (0.84, 1.90) vs 2.05 (1.27, 2.81), $P < 0.05$] were also lower in the intervention group, indicating mitigated degradation. There were no significant differences in clinical response rates (72.5% vs 61.3%, $P = 0.157$) or bacterial eradication rates (68.1% vs 59.4%, $P = 0.160$). However, the bacterial eradication rates improved for Gram-negative isolates with Minimum inhibitory concentration (MIC) ≤8 mg/L in the intervention group than the control group (84.4% vs 69.1%, $P < 0.05$).

Conclusion: The closed-loop stewardship model effectively improved meropenem target concentration attainment by systematically reducing drug loss through degradation and metabolism. This optimized exposure profile correlated with improved eradication rates of Gram-negative sensitive bacteria.

Keywords: meropenem, closed-loop management of precision medication, concentration, open-ring metabolite, hospital-acquired pneumonia, acute brain injury

Introduction

Hospital-acquired pneumonia (HAP) is a common and severe complication in patients with acute brain injury (ABI), affecting disease recovery and prognosis.[1] Meropenem is the first-line therapeutic agent for severe HAP and central nervous system infections due to its potent antimicrobial activity against multidrug-resistant Gram-negative organisms. However, characteristic pathophysiological alterations in neurosurgery patients-including disrupted blood-brain barrier

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(BBB) integrity, cerebrospinal fluid (CSF) drainage, diabetes insipidus, osmotic diuresis for cerebral edema, and augmented renal clearance-collectively accelerate meropenem elimination. These pharmacokinetic changes result in subtherapeutic plasma concentrations and compromising antimicrobial efficacy while promoting resistance.[2,3] Our previous research identified craniocerebral injury as a significant risk factor of meropenem underexposure.[4] While many studies have reported on the BBB permeability of meropenem in patients with central nervous system infections, there is limited research on its permeability in patients with HAP complicating traumatic brain injury. Critically, for neurosurgery patients with ABI, the efficacy of meropenem is not solely dependent on plasma concentrations—as CSF concentration emerges as a pivotal determinant of therapeutic success. Furthermore, the BBB permeability of meropenem in neurosurgery patients with ABI may be different with central nervous system infections. Therefore, there is an urgent need to optimize the dosing regimen of meropenem for neurosurgery patients with HAP.

Furthermore, meropenem demonstrates limited stability in aqueous solutions, maintaining therapeutic integrity for only 3–4 hours at room temperature (20–25°C) when reconstituted in 0.9% sodium chloride or 5% dextrose.[5,6] Higher pH and temperature could accelerate the degradation, at temperatures exceeding 25°C, it degrades by more than 10% within 3.5 hours.[5–7] The core mechanism underlying meropenem degradation lies in the irreversible cleavage of its pharmacologically active β-lactam ring. Specifically, in aqueous environments, water molecules act as nucleophiles to attack the electrophilic carbonyl carbon of the β-lactam ring's amide bond, leading to irreversible ring opening and conversion to its sole inactive metabolite, the open-ring metabolite (ORM) (Supplementary Figure 1).[8] This degradation process exhibits concentration dependence: more than 15% of meropenem is converted to ORM when stored for 12 or 24 hours at 4°C.[9] Meanwhile, meropenem degradation persists across biological matrices, with plasma samples demonstrating progressive decomposition even at −20°C, necessitating long-term storage at −80°C for analytical validity.[10] Current stabilization strategies involve incorporating 3-(N-morpholino) propane sulfonic acid (MOPS) buffer systems during sample processing, which enhances short-term stability.[11] Meropenem showed higher stability at −80°C, and addition of MOPS might increase the short-term and extracted samples stability. However, meropenem still has the problem of degradation in the stages of intravenous infusion preparation, transportation and clinical infusion, especially for continuous infusion.[7]

The combined challenges of meropenem underexposure and inherent drug instability necessitate meticulous quality control throughout the therapeutic chain. Suboptimal handling during drug dissolution, intravenous administration, biological sampling, specimen storage, or analytical processing can further exacerbate meropenem degradation, ultimately diminishing antimicrobial effectiveness. Given that pharmacotherapy for these patients extends beyond individual pharmacokinetic adjustments to require systematic management of the entire treatment process, the closed-loop management model—characterized by integrated multidisciplinary collaboration and informatics-driven monitoring, enabling dynamic therapeutic strategy adjustments that significantly reduce antimicrobial medication errors and infection risks. Therefore, this study implemented a pharmacist-driven closed-loop stewardship model of the whole meropenem medication in the neurosurgery department of Suzhou Municipal Hospital and analyzed the in-vivo and in-vitro stability and the clinical efficacy before and after the clinical pharmacist intervention to facilitate the advancement of personalized meropenem dosing strategies.

Materials and Methods

Study Design and Ethics

This prospective intervention study employed an interrupted time series (ITS) design to assess the pharmacist-driven closed-loop stewardship model, with its primary endpoints including: meropenem exposure, the ORM/C_{min} ratio and therapeutic effectiveness.

The intervention protocol received ethical approval from the Ethics Committee of Suzhou Municipal Hospital (Ethics Approval No. K-2021-082-H01) and was prospectively registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR2100053649, Registration Date: November 26, 2021). All study procedures complied with the Declaration of Helsinki principles, with written informed consent obtained from participants or legally authorized representatives prior to data collection and intervention implementation.

Study Population

Neurosurgery patients diagnosed with HAP and treated with meropenem for anti-infective therapy from October 2019 to March 2025 were consecutively enrolled. Inclusion criteria: (1) age ≥18 years; (2) diagnosis of HAP or severe pneumonia based on ATS/IDSA criteria;[12] (3) neurosurgery patients contained of traumatic brain injury (TBI), sub arachnoid hemorrhage, post-neurosurgery, and intracerebral hemorrhage after tracheostomy; (4) targeted or empirical antimicrobial therapy was administered using meropenem (Sumitomo Dainippon Pharma Co., Ltd., Oita Plant, National Drug Approval No. J20140169, 0.5 g per vial) for anti-infective treatment; (5) Availability of measured steady-state C_{min} and ORM concentrations of meropenem. Exclusion criteria: (1) meropenem duration ≤3 days; (2) incomplete medical records or laboratory data; (3) withdrawal of consent.

Study Groups and Data Collection

Control Group: A retrospective case-control cohort analysis was performed on neurosurgical patients receiving meropenem for HAP from October 2019 to December 2021. Data extraction followed STROBE guidelines for observational studies. Intervention Group: Following the implementation of a clinical pharmacist-driven closed-loop stewardship program, we prospectively enrolled neurosurgical patients receiving meropenem for anti-infective treatment at our hospital from January 2022 to March 2025.

From the hospital information system (HIS), we systematically collected six data dimensions: (1) patient demographics: gender, age, weight, height, diagnosis; (2) infection-related indicators: infection site, microbiological culture, drug sensitivity; (3) therapeutic parameters: course of treatment, dosage regimen, combination antimicrobial therapy; (4) administration data: time from meropenem dissolution to the start of intravenous infusion; infusion duration; time from the blood sampling to the laboratory reception; Sample pretreatment and storage conditions; time of concentration determination; time of concentration report issuance; (5) laboratory indicators: blood tests, hepatic and renal function tests, meropenem C_{min} or ORM concentrations; (6) clinical outcomes: microbiological eradication, related adverse reactions, 28-day survival rate and length of hospital stay Dual data entry with cross-validation was implemented. Creatinine clearance (CrCL) was calculated using the Cockcroft-Gault equation, and the equation is defined as:[13]

$$\mathrm{CrCL}(ml/min) = \frac{(140 - Age) \times Weight(kg)}{72 \times Serum\ creatinine(mg/dL)} \times (0.85 if female)$$

Construction of the Closed-Loop Management Precision Medication of Meropenem

This study established a pharmacist-driven closed-loop stewardship model for meropenem precision dosing. Under the leadership and coordination of pharmacists, a dedicated multidisciplinary team was formed, comprising pharmacists from clinical pharmacy department, intravenous admixture services and therapeutic drug monitoring (TDM) laboratory, alongside nurses and clinicians. This pharmacist-driven model integrated eight critical processes into a seamless workflow spanning from drug dispensing to individualized dosage regimen optimization, achieving comprehensive and fine-grained management of meropenem therapy (Figure 1). The processes, strategically designed under pharmacist direction, targeted two primary objectives:

Minimizing in vitro degradation—through pharmacists' direct leadership in (1) developing and implementing optimized drug preparation protocols and (2) establishing prioritized medication administration workflows; and optimizing pharmacokinetic exposure while modulating in vivo metabolism—via pharmacists' core coordination and oversight of (3) standardized TDM sampling procedures, (4) expedited specimen handling protocols, (5) validation of analytical methodologies, (6) delivery of evidence-based clinical decision support, (7) continuous therapeutic monitoring, and (8) dynamic dose optimization strategies. The specific interventions designed, initiated, and supervised by pharmacists at each of the eight stages are detailed in Table 1, which summarizes key process enhancements post-implementation.

Meropenem Dosing Regimen

The initial dosing regimen of meropenem was formulated based on the *Sanford Guide to Antimicrobial Therapy (53rd Edition)*,[5] *ABX Guide (2nd Edition)*,[14] and Manufacturer's prescribing information. Dosage regimens were individualized based on the infection site, infection severity, and renal function stratification. Standard dosing ranged from 0.5 g q12h (mild infections) to 2 g q8h (CNS infections/septic shock), with adjustments based on C_{min}, clinical efficacy, and safety.

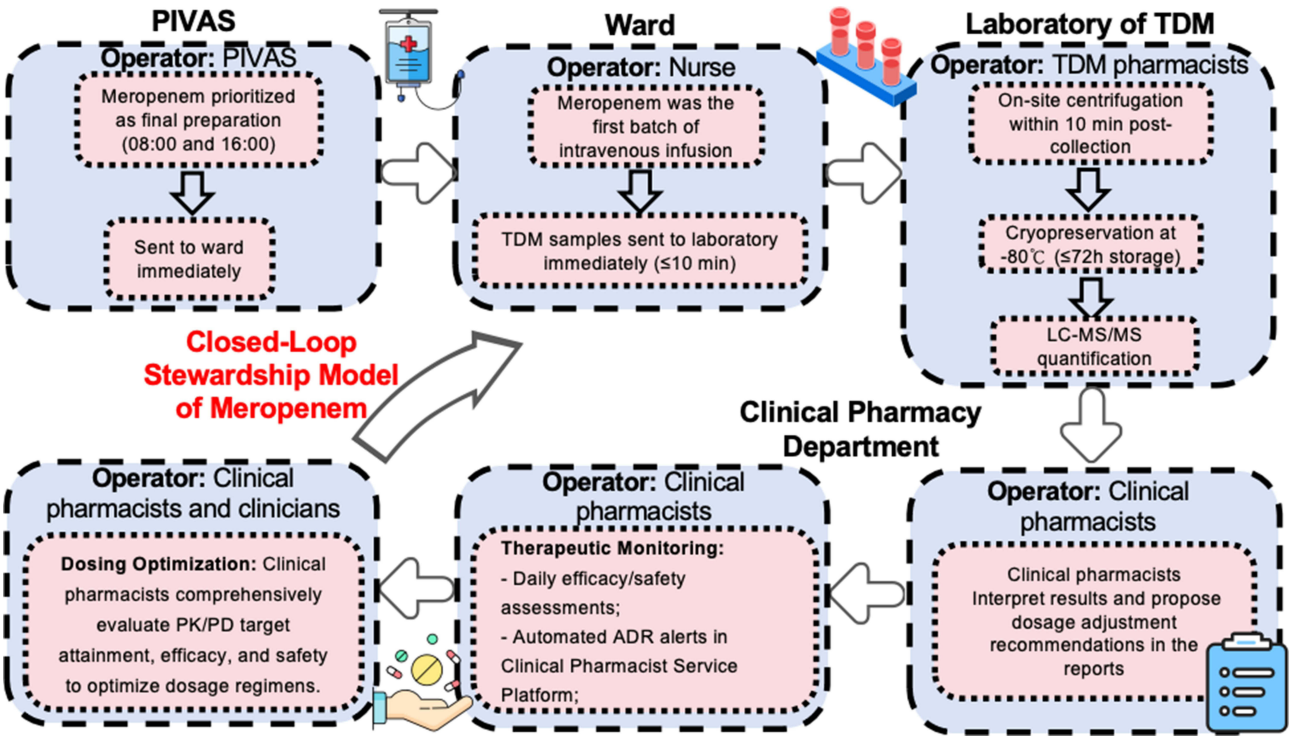

Figure 1 A Pharmacist-driven Closed-loop Stewardship Model Flowchart of Meropenem.

Measurement of Meropenem C_{min} and ORM Concentration

Steady-state C_{min} and ORM samples were collected 30 minutes prior to the fifth meropenem dose administration. Venous blood (2 mL) sample was collected in a yellow-top vacuum tube (containing coagulant and separation gel), the CSF sample was collected in a sealed tube at the same time point of serum in CNS infections patients, centrifuged at 3000 rpm for 10 minutes, and the supernatant (0.5 mL) was stored in −80°C refrigerator for testing within 3 days. Among them, CSF sampling was performed opportunistically and was not mandatory for all patients; samples were collected only from patients with pre-existing clinical indications for lumbar puncture or external ventricular drainage (eg, intracranial pressure monitoring, suspected CNS infection) as part of standard neurosurgical care. No additional invasive procedures were conducted for research purposes.

For serum sample processing, a total volume of 25.0 μL of serum samples was combined with 100.0 μL internal standard solution, comprising a mixed solution containing meropenem-D6 and ORM-D6 at a concentration of 1.00 μg/mL, and vortexed thoroughly to ensure proper mixing. Centrifugation was followed for ten minutes at 13500 rpm, after which 50 μL of the supernatant was collected and diluted with 100 μL water before being vortexed again for uniform distribution. Subsequently, the prepared samples underwent LC-MS/MS analysis.

For CSF sample processing, a total volume of 25.0 μL of serum samples was combined with 100.0 μL internal standard solution, comprising a mixed solution containing meropenem-D6 and ORM-D6 at a concentration of 2.00 μg/mL, and vortexed thoroughly to ensure proper mixing. Centrifugation was followed for ten minutes at 13500 rpm, after which 50 μL of the supernatant was collected and diluted with 100 μL water before being vortexed again for uniform distribution. Subsequently, the prepared samples underwent LC-MS/MS analysis.

The serum and CSF concentrations of meropenem and its ORM were quantified using a validated LC-MS/MS method, comprehensive details regarding the analytical procedures are available in the Supplementary Material 1. The typical multiple reaction monitoring (MRM) chromatograms of meropenem, its ORM, and the internal standards (meropenem-D6 and ORM-D6) in human serum and CSF are presented in Supplementary Figure 2 and Supplementary Figure 3, respectively, illustrating the specificity and separation efficiency of the method. The method demonstrated a linear range of 0.1–100.0 μg/mL for both meropenem C_{min} and its ORM in serum and CSF, with the corresponding standard curve equations provided in Supplementary

Table 1 Comparative Analysis of Meropenem Administration Protocols: Pre- vs Post- Implementation of Closed-Loop Precision Management

Operational Phase	Pre-Intervention Protocol	Post-Intervention Protocol	Operator
Drug Preparation	• Batch preparation initiated at 06:00 and 13:00 in PIVAS; • All medications delivered to wards at 08:00 and 16:00;	• Meropenem prioritized as final preparation at 08:00 and 16:00; • Sent to ward immediately;	Intravenous admixture services pharmacists
Medication Administration	• Sequential administration per prescription receipt timing;	• Meropenem was the first batch of intravenous infusion;	Nurse
TDM Sampling	• The samples were sent to the laboratory together with other blood samples (average waiting time 0.5–2 hours);	• TDM samples sent to laboratory immediately (≤10 min);	Nurse
Specimen Handling	• On-site centrifugation within 10 min post-collection; • Cryopreservation at −80°C (≤72 h storage);	• The same as before;	TDM pharmacists
Analytical Methodology	• LC-MS/MS quantification;	• The same as before;	TDM pharmacists
Clinical Decision Support	• No clinical pharmacist's intervention; • Physician-led empirical adjustments;	• Clinical pharmacists interpret the results and propose; suggestions for adjusting the dosage in the reports;	Clinical pharmacists and clinicians
Therapeutic Monitoring	• Reactive clinician-driven monitoring; • No standardized ADR tracking;	• Systematic monitoring protocol: • Daily efficacy/safety assessments; • Automated ADR alerts in Clinical Pharmacist Service Platform;	Clinical pharmacists
Dosing Optimization	• Static dose adjustments based on isolated results; • No retesting protocol.	• Clinical pharmacists establish a precision medication closed-loop management cycle by comprehensively assessing PK/PD target attainment, optimizing dosing regimens through efficacy-safety evaluation, and iteratively monitoring C_{min}.	Clinical pharmacists and clinicians

Abbreviations: PIVAS, pharmacy intravenous admixture services; TDM, therapeutic drug monitoring; LC-MS/MS, Liquid Chromatography-Tandem Mass Spectrometry; ADR, adverse drug reaction; PK/PD, pharmacokinetic/pharmacodynamic.

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Table 1. Additionally, intra- and inter-assay precision, stability, and reproducibility of the method were all within acceptable limits, and detailed validation results are summarized in Supplementary Material 1. The target range for steady-state C_{min} was set at 2.0–16.0 mg/L (without MIC) or 100% fT > 1-8×MIC (with MIC).[15,16]

Efficacy and Safety Evaluation

Therapeutic outcomes were assessed in compliance with the *Guidelines for Clinical Trials of Antimicrobial Drugs*,[17] the efficacy of anti-infective therapy was evaluated as follows: (1) Clinical efficacy: cure or failure. (2) Microbiological efficacy: eradication, presumed eradication, presumed non-eradication, or non-eradication. (3) Safety: adverse drug reactions (ADRs) were classified per WHO-UMC causality criteria: definite, probable, possible, possibly unrelated, unassessable, or unclassifiable. The first three categories were considered ADRs.[18]

Statistical Analysis

Analyses were conducted using SPSS 27.0 (IBM Corp.) and GraphPad Prism 9.4.1 (GraphPad Software) under a pre-specified $\alpha = 0.05$ (two-tailed). To properly incorporate all concentration data, including beyond the limits of quantification which carry essential exposure information, a likelihood-based approach was employed as the gold standard method for data beyond quantification limits.[19] Continuous variables with normal distribution were expressed as mean ± standard deviation (X ± s), and independent samples *t*-test was used for comparison between groups. Non-normally distributed data were expressed as median (Q_{25}, Q_{75}), and the Mann–Whitney *U*-test was used for comparison. Categorical data were described by frequency and percentage, and the chi-square test or Fisher's exact test was used for comparison. $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

The study cohort comprised 227 neurosurgical patients determined meropenem concentrations, stratified into two groups: historical control cohort (n = 102) and prospective intervention cohort (n = 125). Comparative analysis revealed balanced baseline characteristics between groups, and no significant intergroup differences were observed across these variables, confirming cohort comparability. Comprehensive baseline data are presented in Table 2.

Table 2 Characteristics of Patients in the Control Group and the Intervention Group

Characteristic	Control Group (N = 102)	Intervention Group (N = 125)	Statistical Value	P-value
Male sex, no. (%)	68 (66.7)	75 (60.0)	1.071	0.301
Age (year), [M (Q_{25}, Q_{75})]	68 (57, 78)	70 (58, 79)	−0.722	0.470
Weight (kg), [M (Q_{25}, Q_{75})]	60 (55, 69)	60 (55, 70)	−1.589	0.112
Height (cm), [M (Q_{25}, Q_{75})]	165.0 (160.0, 170.0)	167.0 (160.0, 172.5)	−0.566	0.571
BMI (kg/m^2), [M (Q_{25}, Q_{75})]	22.4 (20.0, 24.2)	22.5 (20.8, 25.0)	−0.906	0.365
Infection site, no. (%)				
Severe pneumonia	40 (39.2)	42 (33.6)	0.876	0.381
Intracranial infection	39 (38.2)	52 (41.6)	0.265	0.607
Bloodstream infection	20 (19.6)	22 (17.6)	0.150	0.698
Urinary tract infection	18 (17.6)	30 (24)	1.360	0.244
Abdominal infection	6 (5.9)	6 (4.8)	0.131	0.717
Skin and soft-tissue infection	5 (4.9)	11 (8.8)	1.303	0.254
More than two infection sites	64 (62.7)	88 (70.4)	1.488	0.223

(*Continued*)

Table 2 (Continued).

Characteristic	Control Group (N = 102)	Intervention Group (N = 125)	Statistical Value	P-value
Type of craniocerebral injury, no. (%)			0.298	0.862
Postoperative intracranial haemorrhage	70 (68.6)	87 (69.6)		
Traumatic brain injury	14 (13.7)	19 (15.2)		
Postoperative brain tumors	18 (17.6)	19 (15.2)		
Complications of infection, no. (%)				
Septic shock	16 (15.7)	23 (18.4)	0.291	0.590
Respiratory failure	30 (29.4)	42 (33.6)	0.455	0.500
MODS	13 (12.7)	25 (24.5)	2.121	0.145
Diabetes insipidus	5 (4.9)	8 (6.4)	0.233	0.629
Hypertension	56 (54.9)	82 (65.6)	2.697	0.101
Laboratory indexes/[M (Q_{25}, Q_{75})]				
WBCs (× 10^9/L)	12.2 (9.7, 15.0)	11.8 (9.2, 15.3)	−0.720	0.471
Haemoglobin (g/L)	109.5 (93.8, 123.0)	106.0 (92.5, 123.5)	−0.387	0.699
Neutrophils (%)	84.7 (79.0, 90.0)	85.7 (80.0, 90.0)	−0.321	0.748
Absolute Neutrophil Count (× 10^9/L)	9.9 (7.7, 12.3)	9.9 (6.7, 13.2)	−0.306	0.760
Platelets (× 10^9/L)	183.5 (142.0, 233.8)	182.0 (138.5, 244.5)	−0.405	0.685
Eosinophils (× 10^9/L)	0.010 (0.000, 0.060)	0.007 (0.000, 0.030)	−0.879	0.380
CRP (mg/L)	81.8 (27.1, 124.2)	68.6 (29.8, 130.1)	−0.311	0.756
PCT (μg/L)	0.28 (0.10, 2.16)	0.21 (0.10, 1.99)	−0.272	0.785
ALT (IU/L)	24.0 (16.0, 41.0)	28.5 (17.0, 53.3)	−1.325	0.185
AST (IU/L)	26.5 (20.0, 44.3)	30.0 (21.0, 49.8)	−1.596	0.110
TBIL (μmol/L)	11.4 (6.8, 16.5)	11.0 (6.6, 18.0)	−0.097	0.923
ALB (g/L)	34.2 (31.0, 38.7)	34.1 (30.1, 37.8)	−1.371	0.170
Creatinine (μmol/L)	65.5 (47.2, 90.3)	66.1 (47.4, 89.5)	−0.288	0.774
Creatinine clearance (mL/min)	74.9 (52.9, 116.4)	77.9 (51.1, 124.7)	−0.655	0.512

Abbreviations: BMI, body mass index; MODS, multiple organ dysfunction syndrome; WBCs, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin.

Infection Site and Etiological Detection

Biological specimens for microbiological diagnosis were collected, with respiratory secretions (69.3%) constituting the primary source, followed by urinary tract (14.7%), bloodstream (9.0%), CSF (4.1%) and drainage fluid (2.9%) samples. The predominant Gram-negative pathogens isolated included Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa. Further analysis revealed Gram-positive bacterial detection rates of 29.2% in the control group versus 36.2% in the intervention group, with corresponding fungal isolation rates of 43.3% and 37.7%, respectively. Comparative analysis demonstrated comparable pathogen distributions between cohorts, with no significant intergroup differences in MIC values of meropenem, see Table 3 for detailed antimicrobial susceptibility profiles. However, 35.85% of Gram-negative isolates in the control group and 34.78% in the intervention group exhibited meropenem MIC values ≥16 mg/L.

Distribution and Comparative Analysis of Meropenem C_{min} and ORM Concentrations

A total of 495 valid quantified concentration points were included in the analysis, stratified by analyte (C_{min} and ORM) and sample type (serum/CSF) across the two study groups. Specifically, for C_{min}, 227 serum samples (Control: n = 102; Intervention: n = 125) and 63 CSF samples (Control: n = 20; Intervention: n = 43) were analyzed. For ORM, the analysis included 145 serum concentrations (Control: n = 58; Intervention: n = 87) and 61 CSF concentrations (Control: n = 19; Intervention: n = 42). ORM serum concentrations were measured only in some patients of control group (56.86%) and intervention group (69.60%) due to less volume of blood or the retrospective patients missed collecting blood samples or other patients' subjective factors.

Table 3 Etiological Detection Distribution Results of Two Groups

Variable	Control Group (N = 102)	Intervention Group (N = 125)	Statistical Value	P-value
Distribution of Pathogenic Bacteria, no. (%)	106	138	6.317	0.722
Acinetobacter baumannii	24 (22.6)	37 (26.8)	–	–
Burkholderia cepacia	4 (3.8)	11 (8.0)	–	–
Escherichia coli	9 (8.5)	7 (5.1)	–	–
Klebsiella pneumoniae	32 (30.2)	39 (28.3)	–	–
Pseudomonas aeruginosa	15 (14.2)	18 (13.0)	–	–
Citrobacter	5 (4.7)	8 (5.8)	–	–
Proteus mirabilis	3 (2.8)	5 (3.6)	–	–
Enterobacter aerogenes	3 (2.8)	6 (4.3)	–	–
Enterobacter cloacae	7 (6.6)	5 (3.6)	–	–
Serratia marcescens	4 (3.8)	2 (1.4)	–	–
Gram–positive bacteria	31 (29.2)	50 (36.2)	2.259	0.133
Fungus	46 (43.4)	52 (37.7)	0.280	0.597
Specimen Sources for Gram–negative Bacteria, no. (%)			1.686	0.907
Sputum	73 (68.9)	85 (61.6)	–	–
Blood	9 (8.5)	13 (9.4)	–	–
Urine	13 (12.3)	23 (16.7)	–	–
Cerebrospinal fluid	4 (3.8)	6 (4.3)	–	–
Secretion	4 (3.8)	7 (5.1)	–	–
Drainage fluid	3 (2.8)	4 (2.9)	–	–
MIC of meropenem, no. (%)			0.525	0.988
≤1 mg/L	58 (54.7)	76 (55.1)	–	–
=2 mg/L	3 (2.8)	4 (2.9)	–	–
=4 mg/L	4 (3.8)	7 (5.1)	–	–
=8 mg/L	3 (2.8)	3 (2.2)	–	–
≥16 mg/L	38 (35.8)	48 (34.8)	–	–

Abbreviation: MIC, minimum inhibitory concentration.

There were no statistically significant differences in the initial dosage and administration protocols of meropenem between the two groups ($P > 0.05$, Table 4). However, the C_{min} exhibited a widely range, from 0.20 mg/L to 45.24 mg/L. The intervention group demonstrated significantly higher meropenem serum concentrations compared to the control group (Figure 2). Patients were stratified into three subcategories based on meropenem target attainment: subtherapeutic (C_{min}< 2 mg/L), target exposure (C_{min} at 2–16 mg/L), and supratherapeutic (C_{min}> 16 mg/L). Notably, the control group exhibited a significantly higher proportion of subtherapeutic patients compared to the intervention group (70.59% vs 35.48%, $P < 0.0001$), as shown in Figure 3. Although the proportion of patients achieving the target exposure demonstrated no statistically significant difference between groups, the intervention group exhibited a trend toward higher attainment rates (50.81% vs 26.47%, $P = 0.290$).

Meropenem was degraded to varying degrees in both groups of patients. The distribution of ORM concentration levels was shown in Figure 2. The ratio of ORM to C_{min} in the control group was significantly higher than that in the intervention group, had statistically significant [serum: 1.97 (1,42, 2.65) vs 0.83 (0.62, 1.24), $P < 0.0001$; CSF: 2.05 (1.27, 2.81) vs 1.21 (0.84, 1.90), $P < 0.05$], as shown in Figure 4. The correlation between the serum C_{min} of meropenem and ORM concentrations in the intervention group was lower than that in the control group (0.6603 vs 0.7314, $P < 0.0001$), as shown in Figure 5. There were 39 patients and 52 patients of intracranial infection in the control group and intervention groups, respectively. Among them, the CSF meropenem concentrations and ORM concentrations were simultaneously determined at the same time of serum samples in 19 and 43 patients, respectively. Similar with the results in serum, the C_{min} and ORM concentrations of meropenem in both groups had pretty good correlations (Figure 6), and

Table 4 Medication Information Evaluation of Two Groups of Patients

Evaluation Criteria	Control Group (N = 102)	Intervention Group (N = 125)	Statistical Value	P-value
Medication information				
Treatment course of meropenem (days), [M (Q_{25}, Q_{75})]	12 (8.8, 18.0)	12 (9.0, 17.0)	−0.239	0.811
Initial dose of meropenem (mg/kg), [M (Q_{25}, Q_{75})]	50.0 (40.96, 62.5)	50.0 (40.0, 54.6)	−0.711	0.477
Initial dosage regimen			3.891	0.424
0.5 g q12h	6 (5.9)	3 (2.4)	–	–
0.5 g q8h	4 (3.9)	10 (8.0)	–	–
1 g q12h	6 (5.9)	11 (8.8)	–	–
1 g q8h	67 (65.7)	77 (61.6)	–	–
2 g q8h	19 (18.6)	24 (19.2)	–	–
Initial trough concentration of meropenem (mg/L), [M (Q_{25}, Q_{75})]	0.78 (0.25, 2.74)	3.75 (1.45, 8.64)	3.561	0.001
Combined with other antibiotics, no. (%)	79 (77.5)	93 (74.4)	0.534	0.594
Colistimethate sodium	7 (6.9)	14 (11.2)	–	–
Tigecycline	6 (5.9)	8 (6.4)	–	–
Amikacin sulfate	13 (12.8)	9 (7.2)	–	–
Levofloxacin	3 (2.9)	9 (7.2)	–	–
Anti–gram–positive agents	62 (60.8)	74 (59.2)	–	–
Antifungal agents	22 (21.6)	24 (19.2)	–	–
Adjusted dosage regimen	37 (36.3)	37 (29.6)	0.066	0.797
Increase the dosage or frequency, no. (%)	27 (26.5)	26 (20.8)	–	–
Decrease the dosage or frequency, no. (%)	10 (9.8)	11 (8.8)	–	–
Intrathecal injection of meropenem, no. (%)	11 (10.8)	15 (12.0)	0.082	0.775

the correlation between the C_{min} of meropenem and ORM concentrations in the intervention group was significantly lower than that of the control group (0.9294 and 0.6657, $P < 0.0001$).

Clinical Efficacy and Safety Evaluation

In the control group, physician empirically adjusted the dosage and remeasured C_{min} in 20 patients, only 7 patients had C_{min} in the target range. However, 33 patients adjusted the dosage according to the suggestions of clinical pharmacists (increase or decrease the dosage and/or prolong the infusion time) in the intervention group, the results indicated that the rate of C_{min} in the target range was significantly higher than that of the control group (66.7% vs 35.0%, $P = 0.025$).

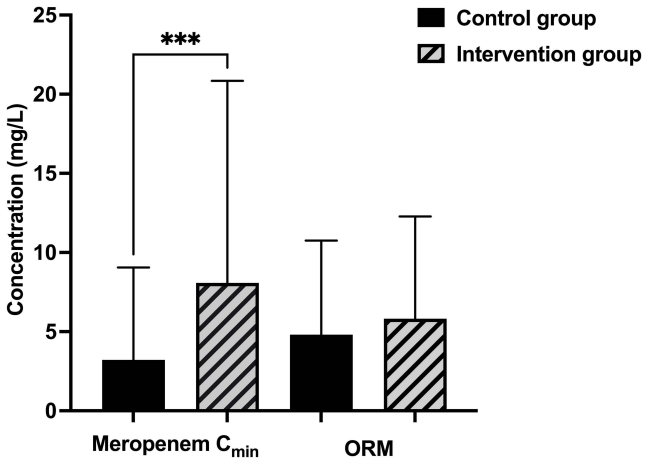

Figure 2 The comparison of meropenem C_{min} and ORM concentration between the two groups.
Note: ***Bonferroni-adjusted $P < 0.001$.

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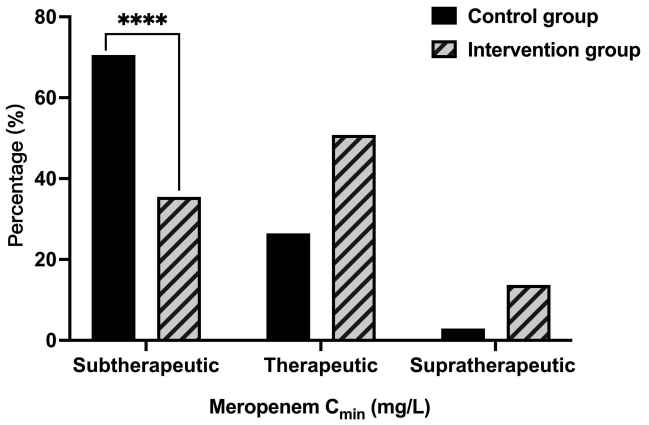

Figure 3 Target attainment of meropenem C_{min} in the two groups.
Notes: Therapeutic exposure is defined as C_{min} of 2–16 mg/L for meropenem. Supratherapeutic exposure is defined as C_{min} above the desired range, whereas subtherapeutic exposure is defined as C_{min} below the desired range. ****Bonferroni-adjusted $P < 0.0001$.

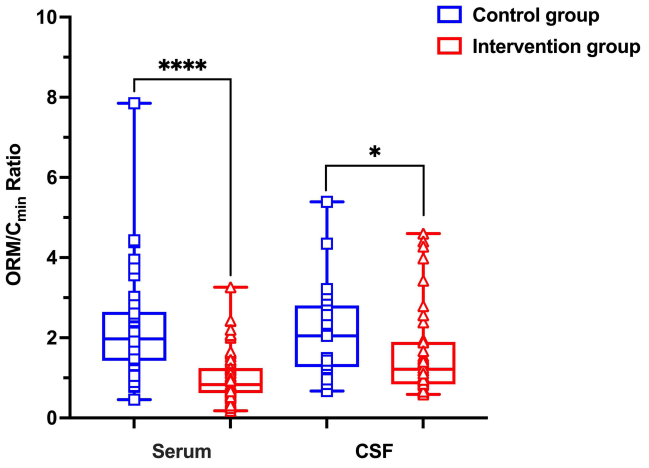

Figure 4 Distribution and comparison of ORM/C_{min} Ratios in Serum and CSF between the two groups.
Notes: ****Bonferroni-adjusted $P < 0.0001$ [serum: 1.97 (1,42, 2.65) vs 0.83 (0.62, 1.24)]; *Bonferroni-adjusted $P < 0.05$ [CSF: 2.05 (1.27, 2.81) vs 1.21 (0.84, 1.90)].

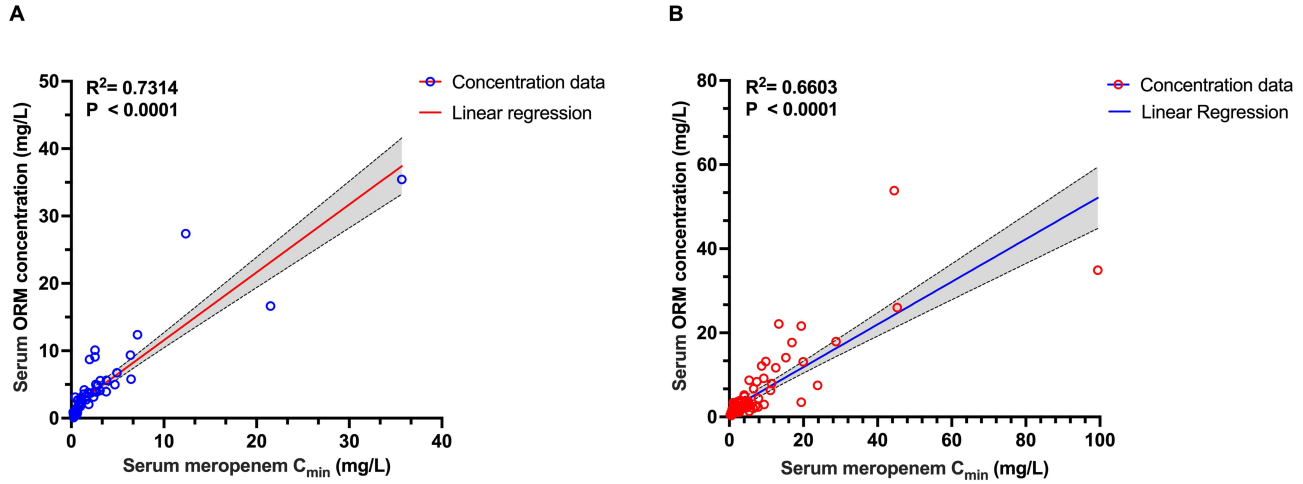

Figure 5 The correlation analysis of (**A**) control group and (**B**) Intervention group between meropenem C_{min} and its ORM concentration in the serum.
Notes: The correlation coefficients (R^2) were 0.7314 and 0.6603 for the meropenem C_{min} in the two groups, respectively ($P < 0.0001$ vs $P < 0.0001$).

https://doi.org/10.2147/DDDT.S569180

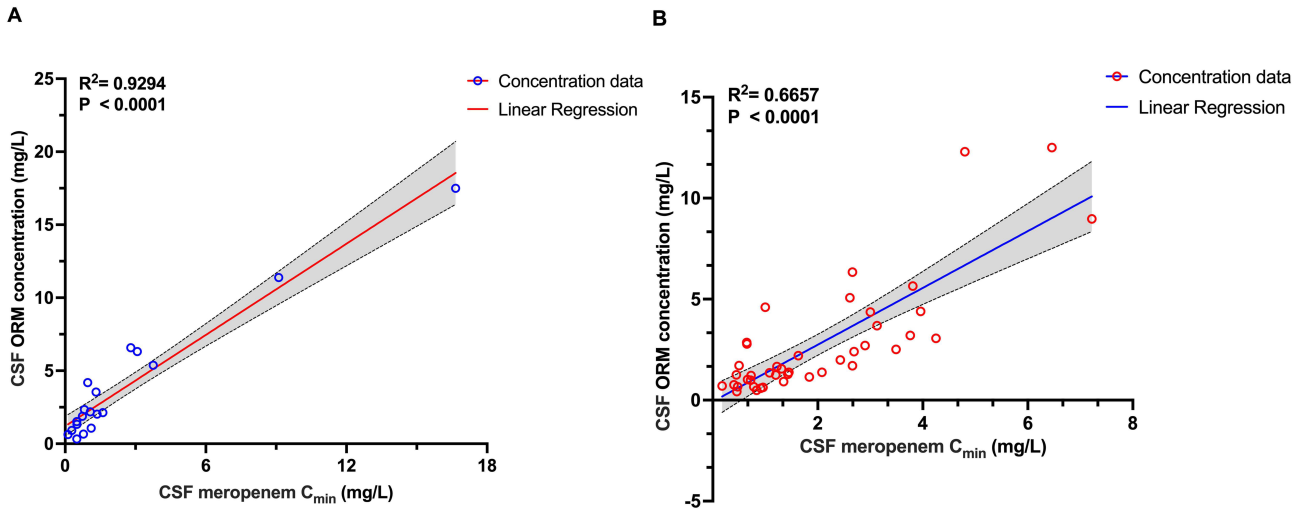

Figure 6 The correlation analysis of (**A**) control group and (**B**) Intervention group between meropenem C_{min} and its ORM concentration in the cerebrospinal fluid.
Notes: The correlation coefficients (R^2) were 0.9294 and 0.6657 for the meropenem C_{min} in the two groups, respectively ($P < 0.0001$ vs $P < 0.0001$).

There were no statistically significant differences between the control and intervention groups in the clinical efficacy rates (61.3% vs 72.5%, $P = 0.157$) or bacterial eradication rates (59.4% vs 68.1%, $P = 0.160$). Notably, subgroup analysis considering the restricted antibacterial activity of meropenem against carbapenem-resistant Gram-negative bacteria revealed that for patients infected with Gram-negative pathogens demonstrating meropenem MIC ≤ 8 mg/L, the intervention group achieved significantly superior pathogen clearance rates (84.4% vs 69.1%, $P = 0.022$). Laboratory analyses revealed statistically significant between-group differences in key inflammatory and hematologic parameters following meropenem therapy: haemoglobin ($P = 0.034$), eosinophils count ($P = 0.016$), CRP ($P = 0.037$), and PCT ($P = 0.048$). There was no statistically significant difference in the incidence of ADR between the two groups ($P = 0.581$). Additionally, although the intervention group exhibited lower 28-day hospital mortality compared to the control group (16.3% vs 21.0%), this difference did not reach statistical significance ($P = 0.471$). See Tables 4 and 5 for details.

Table 5 Clinical Efficacy Evaluation of Two Groups of Patients

Evaluation Criteria	Control Group (N = 102)	Intervention Group (N = 125)	Statistical Value	P-value
Laboratory indexes/[M (Q_{25}, Q_{75})]*				
WBCs (× 10^9/L)	8.1 (6.1, 10.3)	7.3 (5.6, 10.9)	0.986	0.325
Haemoglobin (g/L)	100.5 (87.0, 115.0)	94.0 (82.0, 110.0)	2.132	0.034
Neutrophils (%)	72.8 (65.2, 82.0)	73.4 (65.2, 79.8)	0.608	0.544
Absolute Neutrophil Count (× 10^9/L)	5.9 (4.2, 8.5)	5.5 (4.0, 8.7)	0.252	0.801
Platelets (× 10^9/L)	266.0 (182.0, 328.0)	235.0 (158.0, 328.8)	1.684	0.094
Eosinophils (× 10^9/L)	0.095 (0.025, 0.230)	0.039 (0.016, 0.153)	2.423	0.016
CRP (mg/L)	20.0 (6.2, 48.1)	17.6 (5.7, 39.1)	2.101	0.037
PCT (μg/L)	0.11 (0.07, 0.30)	0.10 (0.05, 0.20)	1.997	0.048
ALT (IU/L)	37.0 (22.5, 57.0)	34.5 (22.8, 49.0)	0.578	0.564
AST (IU/L)	33.0 (22.8, 46.0)	33.0 (24.8, 48.3)	1.451	0.148
TBIL (μmol/L)	9.0 (6.3, 12.2)	7.3 (5.2, 11.1)	0.649	0.517
ALB (g/L)	34.3 (30.8, 38.6)	34.8 (30.6, 38.5)	0.106	0.916
Creatinine (μmol/L)	54.0 (41.7, 74.9)	53.0 (39.0, 71.3)	1.211	0.227
Creatinine clearance (mL/min)	90.5 (66.0, 126.0)	95.6 (64.4, 142.6)	0.711	0.478

(*Continued*)

https://doi.org/10.2147/DDDT.S569180

Table 5 (Continued).

Evaluation Criteria	Control Group (N = 102)	Intervention Group (N = 125)	Statistical Value	P-value
Target number of treatment cases, no. (%)	62 (60.8)	80 (58.0)	0.248	0.619
Gram-negative bacterial eradication, no. (%)	63 (59.4)	94 (68.1)	1.970	0.160
Eradication	49 (46.2)	74 (53.6)	–	–
Presumed eradication	14 (13.2)	20 (14.5)	–	–
Failure of eradication	21 (19.8)	18 (13.0)	–	–
Presumed failure of eradication	13 (12.3)	8 (5.8)	–	–
Emergence of other Gram–negative bacteria	9 (8.5)	18 (13.0)	–	–
Clinical efficacy, no. (%)	38 (61.3)	58 (72.5)	2.004	0.157
Cure	38 (61.3)	58 (72.5)		
Failure	24 (38.7)	22 (27.5)		
Gram–negative bacterial strains clearance rate (MIC ≤ 8 mg/L), no. (%)	47 (69.1)	76 (84.4)	5.276	0.022
ADR incidence rate, no. (%)	13 (12.8)	13 (10.4)	0.305	0.581
Probable,	8 (7.8)	6 (4.8)	–	–
Possible	5 (4.9)	7 (5.6)	–	–
Epilepsy	1 (1.0)	1 (0.8)	–	–
Kidney injury	3 (2.9)	3 (2.4)	–	–
Hepatic injury	4 (3.9)	6 (4.8)	–	–
Pancytopenia	2 (2.0)	1 (0.8)	–	–
Allergic reaction	2 (2.0)	1 (0.8)	–	–
Diarrhea	1 (1.0)	1 (0.8)	–	–
Length of hospital stay (days), [M (Q_{25}, Q_{75})]	24.0 (18.5, 40.0)	29.0 (20.0, 42.0)	1.155	0.250
28-day mortality, no. (%)	13 (21.0)	13 (16.3)	0.520	0.471

Note: * After meropenem anti-infection treatment.
Abbreviations: WBCs, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; MIC, minimum inhibitory concentration.

Discussion

This prospective intervention study implemented a clinical pharmacist-driven closed-loop stewardship model for meropenem precise medication in neurosurgery patients. To the best of our knowledge, this is the first study establishing a clinical pharmacist-driven closed-loop meropenem stewardship program. Compared to traditional empirical dosing, this research represents the first deep integration of TDM technology with the closed-loop management concept. Through multidisciplinary collaboration led by clinical pharmacists, it facilitates a paradigm shift from empirical administration to a dynamic precision therapy model characterized by "monitoring-analysis-intervention-remonitoring", providing a replicable paradigm for individualized antimicrobial therapy in neurosurgical critically ill patients. More importantly, our analysis of serum and CSF concentrations of meropenem C_{min} and ORM demonstrated that this stewardship program effectively reduced meropenem degradation while simultaneously increasing systemic meropenem concentrations, thereby improving anti-infective therapeutic outcomes.

As a quintessential time-dependent antimicrobial agent, meropenem exerts bactericidal effects predominantly through persistent exposure to the parent compound rather than its metabolites.[9] Extensive evidence documents its limited stability across various solvents and plasma, with rapid degradation and oxidative processes necessitating immediate processing or refrigeration/cryopreservation of blood specimens post-collection.[5–7,9,10] Due to the massive dehydration and diuresis, coupled with the inherent instability of meropenem, these factors collectively decrease the meropenem steady-state trough concentration and compromise its anti-infective efficacy. Therefore, studies on patients with intracranial infections have reported that increasing the dosage of meropenem, prolonging the infusion time, or combining intrathecal administration are recommended strategies to increase plasma concentrations and improve anti-infective efficacy.[5,20–24]

Due to the presence of blood-brain barrier and hemodynamic changes in patients with central nervous system infection, meropenem has been recommended as a higher dosage of 2 g q8h or as a continuous infusion of 6 g/day.[20,21] In refractory patients with poor efficacy, intrathecal injection of meropenem and vancomycin may even be required.[22–24] Our preliminary investigations demonstrate that craniocerebral injury significantly accelerates meropenem clearance, resulting in a high incidence of subtherapeutic steady-state trough concentrations in this population, which may compromise clinical therapeutic efficacy.[4] Notably, more than 60% of control group patients exhibited initial trough concentrations below the target ranges. Post-implementation of closed-loop meropenem management, the rate of suboptimal exposure decreased to 32.52%. Nevertheless, approximately 10% of patients failed to achieve therapeutic targets and showed poor therapeutic effect, even with maximal dosing (6g/d) and extended infusions, necessitating intrathecal administration.

Emerging evidence indicates that TDM and model-informed precision dosing (MIPD) can optimize meropenem concentration attainment and clinical outcomes.[25,26] So far, this is the first study implemented the closed-loop intervention which focus on reducing the degradation and metabolism of meropenem. The closed-loop management of precise medication significantly improved meropenem exposure distribution and target attainment rates. Elevated ORM concentrations in control group reflected greater meropenem degradation and metabolism, with substantial interindividual variability, resulting in a weaker correlation between ORM concentrations and C_{min}. The observed decrease in the ORM/C_{min} ratio in the intervention group is likely attributable to the combined result of mitigating in vitro degradation through streamlined drug preparation and prioritized administration, as well as controlling in vivo metabolism via TDM-guided precision dosing. The serum ORM/C_{min} ratio in the intervention group was consistent with the literature values (median 69.1%, range 19.7–186.7%) derived from 35-sample analyses.[9] This study further demonstrated a significant positive correlation between ORM concentrations and C_{min}. Notably, implementation of closed-loop management intervention attenuated this correlation coefficient, while simultaneously resulting in significantly higher C_{min} in the intervention group compared to controls. This paradoxical phenomenon suggests that the closed-loop management system may enhance meropenem's penetration capacity across physiological barriers (eg, blood-brain barrier [BBB]). However, given the substantial interindividual variability in BBB permeability-modulated by factors including P-glycoprotein expression levels and inflammatory status-the precise mechanistic underpinnings warrant further elucidation through large-scale, multicenter prospective studies.

While the closed-loop stewardship model did not yield statistically significant improvements in conventional clinical efficacy endpoints—likely due to the carbapenem- resistant Gram-negative bacteria (CR-GNB) in our cohort, which are intrinsically less susceptible to meropenem. First, in the subgroup analysis confined to infections caused by meropenem-susceptible GNB (MIC $\leq$ 8 mg/L), the intervention group demonstrated a significantly higher bacterial clearance rate ($P < 0.05$), confirming the program's pharmacodynamically effectiveness. Furthermore, the intervention group exhibited accelerated normalization of infection-related inflammatory biomarkers (eg, CRP, PCT). Collectively, these findings position the closed-loop model not merely as a dosing optimization tool, but as a systems-based intervention that transitions meropenem therapy from empirical administration to a metric-driven, precision care paradigm.

Though ORM lacks intrinsic antimicrobial activity, simultaneous quantification of meropenem and ORM is of clinical interest: elevated ORM proportions may indicate (extended time interval between dissolvation of the compound and administration), and from pre-analytical issues (extended time interval between sampling and reception in the laboratory for centrifugation and freezing until analysis), enzymatic degradation by resistant pathogens, or enhanced non-renal clearance. Our prospective intervention confirms that controlling the degradation of meropenem at all stages of clinical application can effectively increase the C_{min} of meropenem, thereby enhancing the clearance rate of Gram-negative sensitive bacteria. The closed-loop precision medication management for meropenem may significantly reduce the concentration variability, attenuating pharmacokinetic heterogeneity and facilitating personalized dosing optimization in clinical practice.

There are several limitations in this study. First, it was not a randomised controlled intervention study, the non-randomized design with retrospective controls introduces potential bias from unmeasured confounders and outcome assessment variability, including temporal changes in antimicrobial use policies, evolving medical technologies, and variations in clinical practice patterns. Second, our study analyzed the effect of clinical pharmacists' intervention on

optimizing the meropenem dosage regimen and all stages of clinical application; however, several clinical factors affected the efficacy, including infection severity, and the presence of co-morbidities. All these factors might have caused deviations in the results. Finally, the single-center design and limited sample size may restrict precise estimation of intervention effects, particularly for CSF concentrations, and precluded meaningful subgroup analyses based on clinically relevant variables such as intracranial infection status or surgery type, etc. Future larger-scale, multicenter studies are warranted to comprehensively verify the intervention effect of management model on the efficacy, safety and economic benefits of meropenem. Notwithstanding these constraints, this intervention study provides clinically meaningful insights for advancing precision antimicrobial management in neurosurgical populations.

Conclusion

Neurosurgery patients treated with meropenem exhibited a higher risk of having trough concentrations below the target range. This study innovatively developed a precision closed-loop management system for meropenem administration, establishing a comprehensive quality control framework through optimized integration of the whole operational phases. The intervention systematically decreased the degradation of meropenem, while concurrently elevating meropenem C_{min} levels. This optimized exposure profile correlated with improved eradication rates of Gram-negative sensitive bacteria, confirming the program's capacity to bridge pharmacological targets with clinical outcomes.

Data Sharing Statement

Deidentified individual participant data will be provided. The datasets generated and/or analyzed during the current study are available from the corresponding author Lian Tang (tanglian716@aliyun.com) upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the Affiliated Suzhou Hospital of Nanjing Medical University (Ethics Approval No. K-2021-082-H01). Written informed consent was obtained from patients or substitute decision makers unless the requirement for informed consent was waived, according to local standards and legislation. A formal data creation and statistical analysis plan was approved for secondary use of the data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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