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Continuous vs Intermittent Meropenem Administration in Critically Ill Patients With Sepsis
The MERCY Randomized Clinical Trial

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IMPORTANCE Meropenem is a widely prescribed β-lactam antibiotic. Meropenem exhibits maximum pharmacodynamic efficacy when given by continuous infusion to deliver constant drug levels above the minimal inhibitory concentration. Compared with intermittent administration, continuous administration of meropenem may improve clinical outcomes.

OBJECTIVE To determine whether continuous administration of meropenem reduces a composite of mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria compared with intermittent administration in critically ill patients with sepsis.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, randomized clinical trial enrolling critically ill patients with sepsis or septic shock who had been prescribed meropenem by their treating clinicians at 31 intensive care units of 26 hospitals in 4 countries (Croatia, Italy, Kazakhstan, and Russia). Patients were enrolled between June 5, 2018, and August 9, 2022, and the final 90-day follow-up was completed in November 2022.

INTERVENTIONS Patients were randomized to receive an equal dose of the antibiotic meropenem by either continuous administration (n = 303) or intermittent administration (n = 304).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of all-cause mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28. There were 4 secondary outcomes, including days alive and free from antibiotics at day 28, days alive and free from the intensive care unit at day 28, and all-cause mortality at day 90. Seizures, allergic reactions, and mortality were recorded as adverse events.

RESULTS All 607 patients (mean age, 64 [SD, 15] years; 203 were women [33%]) were included in the measurement of the 28-day primary outcome and completed the 90-day mortality follow-up. The majority (369 patients, 61%) had septic shock. The median time from hospital admission to randomization was 9 days (IQR, 3-17 days) and the median duration of meropenem therapy was 11 days (IQR, 6-17 days). Only 1 crossover event was recorded. The primary outcome occurred in 142 patients (47%) in the continuous administration group and in 149 patients (49%) in the intermittent administration group (relative risk, 0.96 [95% CI, 0.81-1.13], $P = .60$). Of the 4 secondary outcomes, none was statistically significant. No adverse events of seizures or allergic reactions related to the study drug were reported. At 90 days, mortality was 42% both in the continuous administration group (127 of 303 patients) and in the intermittent administration group (127 of 304 patients).

CONCLUSIONS AND RELEVANCE In critically ill patients with sepsis, compared with intermittent administration, the continuous administration of meropenem did not improve the composite outcome of mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28.

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Visual Abstract
Editorial
Supplemental content

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Antibiotic-resistant bacteria caused more than 2.8 million infections in the US in 2019 alone and contribute to 35 900 deaths each year.[1] β-Lactam antibiotics are the most widely used antibacterial drugs, accounting for more than 65% of intravenous antimicrobial prescriptions in the US.[2] β-Lactam antibiotics are time-dependent and their efficacy is related to time spent above the minimal inhibitory concentration.[3]

β-Lactam antibiotics are typically administered intermittently.[4,5] Thus, their plasma concentration initially reaches a high peak level. However, due to their short half-lives, this peak is typically followed by a rapid decrease to below the minimal inhibitory concentration. Prolonged periods below the minimal inhibitory concentration may decrease efficacy, potentially allowing the residual bacterial population to resume growth and promote the selection of resistant bacteria.[3] Pharmacokinetic studies suggested that prolongation of administration time can provide constant serum levels, maximize time above the minimal inhibitory concentration, and potentially improve the efficacy of β-lactam antibiotics.[6-8]

Systematic reviews and meta-analyses showed that continuous or extended administration may decrease mortality in patients with sepsis.[9-12] This resulted in increased use of continuous or extended protocols for administration[13,14] of β-lactam antibiotics and the suggestion of prolonged administration over intermittent administration by the Surviving Sepsis Campaign guidelines.[15] In general, meropenem is administered intermittently to treat several types of infection in critically ill patients.[16-18] However, continuous administration of meropenem may increase bacterial clearance,[19] decrease the emergence of antimicrobial resistance, and may even decrease mortality.[11] To date, no suitably powered double-blind randomized clinical trials (RCTs) focusing on meropenem have been conducted in critically ill patients with sepsis to test this hypothesis.

The Continuous Infusion vs Intermittent Administration of Meropenem in Critically Ill Patients (MERCY) multicenter, double-blind, RCT was designed to test the hypothesis that, in critically ill patients with sepsis, compared with intermittent administration, continuous administration of meropenem would decrease the composite outcome of new antimicrobial resistance and mortality.

Key Points

Question Does continuous administration of meropenem reduce a composite of mortality and emergence of drug-resistant bacteria among critically ill patients with sepsis compared with intermittent administration?

Findings In this randomized clinical trial enrolling 607 critically ill patients with sepsis or septic shock, continuous administration of meropenem, compared with intermittent administration, did not significantly decrease the composite of all-cause mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28 (47% vs 49%, respectively).

Meaning Continuous administration of meropenem, compared with intermittent administration, does not improve clinically relevant outcomes in critically ill patients with sepsis.

Methods

Trial Design

We performed a multicenter, double-blind, RCT with a 1:1 allocation at 31 intensive care units (ICUs) of 26 hospitals in 4 countries (Croatia, Italy, Kazakhstan, and Russia). The trial protocol appears in Supplement 1 and was approved by the ethics committees of all participating centers. Details of the trial methods were published together with the statistical analysis plan[20] (appears in Supplement 2). Additional information appears in the eMethods in Supplement 3.

Patients

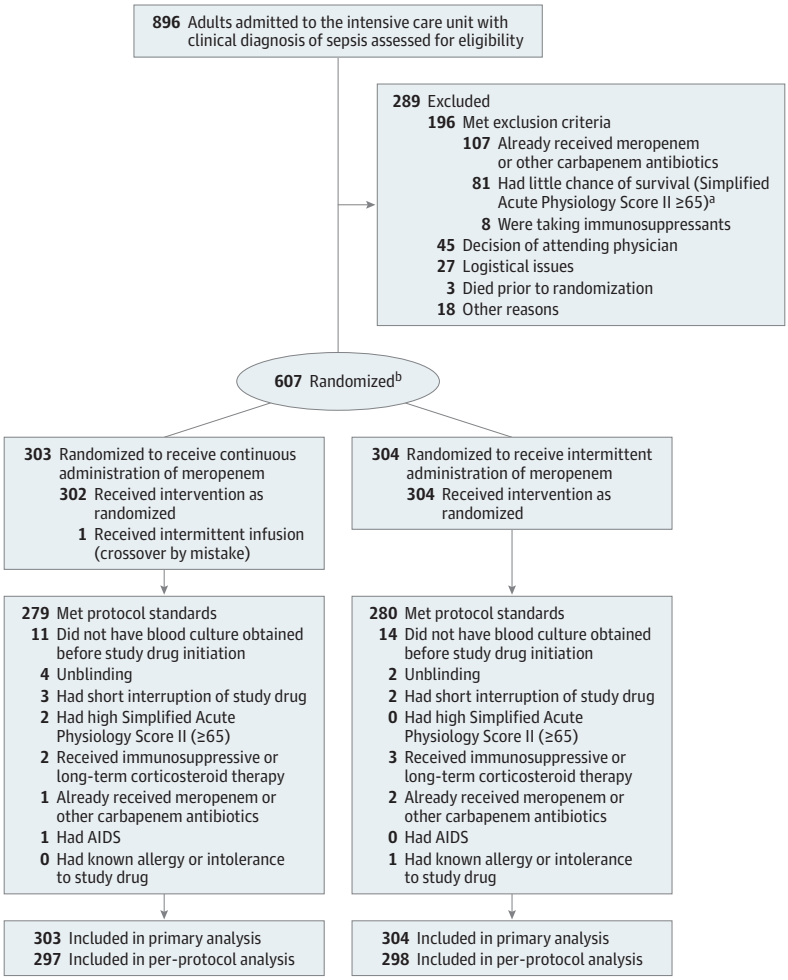
All patients prescribed meropenem according to clinical judgment were screened for eligibility. Eligible patients were aged 18 years or older, admitted to the ICU, required new antibiotic treatment with meropenem by clinician assessment, and had sepsis or septic shock. The definitions used for sepsis and septic shock were a hybrid of Sepsis-3[21] and traditional sepsis definitions.[22,23] Sepsis was defined as the presence of systemic inflammatory response syndrome, suspected or documented infection, and Sequential Organ Failure Assessment (SOFA) score of 2 or greater. Septic shock was defined as persistent hypotension requiring vasoconstrictors to maintain mean arterial pressure of 65 mm Hg or greater and a serum lactate level greater than 2 mmol/L after adequate resuscitation in addition to the presence of sepsis. The diagnosis of sepsis or septic shock was based on clinician assessment. Patients provided consent or consent was obtained according to instructions from the local ethical committee when patients were initially unable to provide it.

The exclusion criteria included refusal of consent, previous therapy with carbapenem antibiotics, very low probability of survival assessed using the Simplified Acute Physiology Score II (SAPS II)[24] (score ≥65 points), and severe immunosuppression (eg, AIDS or long-term corticosteroid therapy [>0.5 mg/kg/d of methylprednisolone for >30 days]). Details of the inclusion and exclusion criteria appear in eTables 1-2 in Supplement 3. Given that patients with different races and ethnicities may be affected by differential pre-ICU admission health literacy and care, we collected race and ethnicity information. Race and ethnicity were determined by the clinicians and were not self-reported.

Randomization

Web-based, centralized randomization was performed by the attending ICU physician. A randomization list was created with the use of computer-generated, permuted-block sequences. Randomization was stratified according to study center. Immediately after randomization (**Figure 1**), pharmacists and ICU trial nurses automatically received an email containing treatment allocation. Patients, physicians, and study investigators were blinded to treatment allocation. Pharmacists and ICU trial nurses were aware of treatment allocation, but were not involved in the data collection or data analysis. The data collection was performed by trained personnel who did not participate in patient care and were blinded to group allocation.

Figure 1. Assessment, Exclusions, and Randomization for the MERCY Randomized Clinical Trial



MERCY indicates Continuous Infusion vs Intermittent Administration of Meropenem in Critically Ill Patients. Randomization was stratified according to study center.

[a] Calculated based on the patient characteristics, reason for intensive care admission, and physiological abnormalities. The score range is from 0 to 163; a higher score indicates higher severity of disease and higher risk of death.

[b] After randomization, it was discovered that 12 patients actually met the exclusion criteria (were already receiving carbapenem antibiotics, had previous allergy to carbapenem antibiotics, had high Simplified Acute Physiology Score II [≥65], were taking immunosuppressants or chronic corticosteroid therapy, or had AIDS). A per-protocol analysis was performed excluding these 12 patients.

Interventions

Immediately after the clinical decision to prescribe meropenem and independent of group assignment or kidney function, patients received a loading dose of 1 g of meropenem to promptly achieve bactericidal concentration. Before administration of the loading dose (if not already performed during the preceding 48 hours), blood samples and suspected site of infection cultures were obtained. The respiratory cultures included distal, protected samples (bronchoalveolar lavage or similar). Three samples of blood cultures were obtained with at least 1 sample not drawn from an indwelling intravascular catheter.

After collection of the microbiological specimens, patients were randomized to receive continuous administration of meropenem (a generic version produced by Aurobindo Pharma, which has the longest documented stability after reconstitution) as a dose of 3 g over 24 hours or intermittent administration (over 30 to 60 minutes) of an equal dose that was divided into 3 daily boluses (ie, 1 g every 8 hours). To maintain blinding, each patient experienced both types of administration methods using a double-dummy technique according to randomization group assignment in which 1 of the 2 administration methods was placebo (0.9% solution of sodium chloride) and the other was the study drug (meropenem).

Following international consensus, the meropenem dose was reduced to 2 g/d if a patient's creatinine clearance was less than 50 mL/min/1.73 m^2. In special circumstances and based on clinical judgment, the total amount of study drug could be doubled (eg, in patients with high minimal inhibitory concentrations on the infection culture results or in those with meningitis; additional details appear in the eMethods in Supplement 3) while maintaining the interval of administration.

The study assessment lasted up to 28 days after administration of the first bolus of study drug. Patients were monitored for efficacy and safety. Duration of treatment and its interruption were according to clinical judgment, but recommendations were provided to guide such clinical decisions (eTables 3-4 in Supplement 3).

All patients received treatment for sepsis according to international guidelines[25] and protocols available at each study center.

Data and Study Management

We collected data on baseline characteristics and comorbidities, vital signs, history of previously administered antibiotics, SAPS II,[24] SOFA score,[26] Glasgow Coma Scale score, mechanical ventilation status and settings, urine output, and site of infection.

From day 1 to day 28, we collected daily data on vital status, SOFA score, emergence of new drug-resistant bacteria, and ongoing antibiotic treatment. In addition, microbiological samples (blood and suspected site of infection) were collected from every patient in a predetermined fashion.

Primary and Secondary Outcomes

The primary outcome was a composite of all-cause mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28. Pandrug-resistant bacteria were defined as organisms resistant to all classes of antimicrobial agents available and intrinsically active against the respective species.[27] Extensively drug-resistant bacteria were defined as organisms resistant to all except 1 or 2 antimicrobial classes. Further details on the definitions of pandrug-resistant and extensively drug-resistant bacteria appear in the eMethods (under the definitions of trial outcomes) in Supplement 3.

We selected emergence of new pandrug-resistant or extensively drug-resistant bacteria as a component of the composite primary outcome because antimicrobial resistance represents a globally prioritized public health issue[28] and has huge effects on clinical outcomes and clinical practice.[29] Additional information appears in the eMethods (under the definitions of trial outcomes) in Supplement 3.

The prespecified secondary outcomes included days alive and free from antibiotics at day 28, days alive and free from the ICU at day 28, and all-cause mortality at day 90. Cumulative SOFA score at day 28 also was a prespecified secondary outcome, but there was poor data collection for this outcome after day 7.

The post hoc exploratory outcomes included all-cause mortality at day 28, emergence of new pandrug-resistant or extensively drug-resistant bacteria at day 28, length of ICU stay, length of hospital stay, and readmission to the ICU. Days alive and free from antibiotics at day 28 were defined as the number of days without antibiotics during the initial 28 days after randomization. Deaths within the initial 28 days were assigned 0 days alive and free from antibiotics at day 28. Days alive and free from the ICU at day 28 were defined analogously. Additional details appear in the eMethods in Supplement 3. Adverse event data were collected for seizures, allergic reactions related to the study drug, and mortality.

A blinded investigator performed telephone follow-up with the patients or caregivers at 28 days and 90 days from randomization, focusing on hospital readmissions and survival. If follow-up with the patient or caregiver was unsuccessful, contact was made with the patient's general practitioner, the local office of vital statistics, or through a letter sent to the home address of the patient. If a randomized patient died before informed consent could be obtained, data were collected if allowed by local regulations and approved by the local ethical committee. For the other outcomes, we performed daily contact until hospital discharge and censored their occurrence at 28 days after randomization.

Statistical Analysis

Based on published literature,[30-33] we hypothesized the primary outcome (composite outcome of all-cause mortality and emergence of new pandrug-resistant or extensively drug-resistant bacteria at day 28) would occur in 52% of patients in the intermittent administration group and that the continuous administration of meropenem would lead to an absolute risk reduction of 12% (40% of patients would have composite outcome in continuous administration group).[20]

We estimated that a sample size of 300 patients per group would achieve greater than 80% power to detect such a difference at an α level of .05. An independent data and safety monitoring board oversaw and reviewed the results of 3 planned interim analyses after 150, 300, and 450 patients had completed 28-day follow-up for the primary outcome.

The composite primary outcome was analyzed using the 2-tailed χ^2 test based on the intention-to-treat principle. Descriptions of the prespecified subgroup analyses appear in the eMethods in Supplement 3. Data were also analyzed using a per-protocol analysis based on the modified intention-to-treat principle (patients with evidence of multidrug-resistant bacteria but sensitive to meropenem on cultures). Missing data were not imputed. The statistical analysis plan was published prior to its conduct[20] and appears in Supplement 2.

We compared dichotomous data using the 2-tailed χ^2 test when the number of variables was more than 5 and using the Fisher exact test when the number of variables was equal to or less than 5. We calculated relative risks and 95% CIs using the 2 × 2 table method with log-linear regression and a normal approximation for the SE.

For continuous variables with nonparametric distribution, the data are expressed as medians and IQRs and the Mann-Whitney test was used to compare outcomes. For variables with normal distribution, the data are expressed as means and SDs and the *t* test was used to compare outcomes. The between-group differences are reported as mean differences with 95% CIs. Two-sided significance tests were applied to all analyses.

We performed prespecified subgroup analyses as reported in the trial protocol (bacteria with high minimal inhibitory concentration to carbapenem, bacteria expected to develop carbapenem resistance, acute kidney injury, and SAPS II) and post hoc subgroup analyses (eMethods in Supplement 3). A prespecified logistic regression model with stepwise selection was used to identify predictors of the primary outcome as a sensitivity analysis with the aim of identifying residual baseline imbalances that could have masked the effect of the intervention itself.[34]

Clinical data collected before randomization were entered into the model if they had a univariate $P<.10$. We then repeated the analysis using a less conservative entry ($P = .20$). Treatment allocation was forced into the multivariate model. Collinearity and overfitting were assessed with the use of a stepwise regression model and a Pearson correlation test. In the

multivariate analyses, variables are expressed as odds ratios with 95% CIs.

A post hoc time-to-event analysis of death from any cause was performed, and the hazard ratio and corresponding 95% CI were calculated and used for a stratified log-rank test. We used the following models to account for the competing risk of death: the cause-specific hazard model of emergence of new pandrug-resistant or extensively drug-resistant bacteria and death at day 28 and the Fine-Gray subdistribution hazard model. In addition, we described microbiological and antibiotic data for secondary infections.

We did not adjust the 95% CIs for the prespecified secondary, post hoc exploratory, or adverse outcomes for multiplicity. Thus, any inferences drawn from these outcomes are only hypothesis-generating. Data were stored electronically and analyzed using Stata software, version 16 (StataCorp). A 2-sided $P < .05$ was used as the statistical significance threshold.

Results

Patients

Between June 5, 2018, and August 9, 2022, 607 patients were randomized (303 to receive meropenem by continuous administration and 304 to receive meropenem by intermittent administration; mean age, 64 years [SD, 15 years]; 203 were women [33%]; Figure 1). All 607 patients were included in the measurement of the 28-day primary outcome. No patient was lost to follow-up to assess survival at 90 days. The final 90-day follow-up was completed in November 2022. Baseline characteristics of the study patients were balanced between groups (**Table 1**). All patients were admitted to ICUs and most patients underwent invasive mechanical ventilation. Septic shock was present in 369 patients (61%), and the remaining 238 (39%) had sepsis. The median time from hospital admission to randomization was 9 days (IQR, 3-17 days) and the median duration of meropenem therapy was 11 days (IQR, 6-17 days).

Infection site (mostly lower respiratory tract, gastrointestinal, and genitourinary tract) was definitely identified in 70% of patients in the continuous administration group and in 64% of patients in the intermittent administration group.

During the enrollment period (between June 2018 and August 2022), there were several months with low recruitment due to the COVID-19 pandemic (eMethods in Supplement 3).

Study Drug Administration

Patients received a median overall dose of 24 g of meropenem in the continuous administration group and 21 g in the intermittent administration group. Interruption of the administration and interruption of blinding was uncommon even during the period of the COVID-19 pandemic (Figure 1 and eTable 5 in Supplement 3).

Concurrent Antibiotic Treatment and Type of Identified Bacteria

Immediately before randomization, 443 patients (74%) received additional antibiotics (**Table 2**). Glycopeptides were the most prescribed additional antibacterial agents.

In 28% of patients in the continuous administration group and in 30% of patients in the intermittent administration group, a causative pathogen was never identified. The most frequently identified gram-negative bacterial species were *Klebsiella*, *Pseudomonas*, and *Escherichia coli* (Table 2). Microbiological and antibiotic data of primary and secondary infection appear in eTables 6-14 in Supplement 3. The daily SOFA score, C-reactive protein, and body temperature appear in eFigures 1-2 in Supplement 3.

Primary Outcome

At 28 days, there was no statistically significant difference in the primary outcome: 142 (47%) patients in the continuous administration group and 149 (49%) in the intermittent administration group had either died or experienced emergence of pandrug-resistant or extensively drug-resistant bacteria (relative risk, 0.96 [95% CI, 0.81 to 1.13], $P = .60$) (**Table 3**).

Secondary Outcomes

At day 28, there was a median of 3 antibiotic-free days (IQR, 0 to 15 days) in the continuous administration group and a median of 2 antibiotic-free days (IQR, 0 to 15 days) in the intermittent administration group (mean difference, 0.4 days [95% CI, −0.9 to 1.7 days], $P = .57$) and there was a median of 0 ICU free-days (IQR, 0-19 days) in both groups (mean difference, 0.6 days [95% CI, −1.0 to 2.2 days], $P = .40$). At 28 days, overall mortality was not significantly different (30% in the continuous administration group vs 33% in the intermittent administration group; relative risk, 0.92 [95% CI, 0.73 to 1.17], $P = .50$).

At 90 days, there was no significant between-group difference in mortality (42% in both groups; relative risk, 1.00 [95% CI, 0.83 to 1.21], $P = .97$). Time to mortality showed no difference between groups (**Figure 2**B and eFigure 3 in Supplement 3). Emergence of new pandrug-resistant or extensively drug-resistant bacteria at day 28 was 24% in the continuous administration and 25% in the intermittent administration group (relative risk, 0.94 [95% CI, 0.71 to 1.26], $P = .70$). No adverse events of seizures or allergic reactions related to the study drug were reported.

Sensitivity Analyses for the Primary Outcome

The results of the subgroup analyses showed no significant between-group differences and are reported in eFigure 4A, 4B, and 4C and eTable 15 in Supplement 3. The analysis of the primary outcome with stratification according to trial center did not identify a significant interaction. The results of the modified intention-to-treat and per-protocol analyses, which also showed no significant between-group differences, are reported in eTables 16-18 in Supplement 3. The results of the univariate and multivariate analyses for the association of baseline variables with the primary outcome confirmed the lack of significant effect for continuous administration (eTables 19-21 in Supplement 3). A Fine-Gray competing risk analysis also found no significant effect on the primary outcome for continuous administration (eTable 22 and eFigure 5 in Supplement 3).

Table 1. Baseline Characteristics[a]

	Continuous administration (n = 303)	Intermittent administration (n = 304)
Age, mean (SD), y	65.5 (14.0)	63.4 (15.0)
Sex, No. (%)		
Female	108 (36)	95 (31)
Male	195 (64)	209 (69)
Race and ethnicity, No. (%)	(n = 292)	(n = 295)
Asian	8 (2.7)	8 (2.7)
Black	2 (0.7)	1 (0.3)
Hispanic or Latino	7 (2.4)	8 (2.7)
White	275 (94)	278 (95)
Comorbidities, No. (%)[b]		
Diabetes	68 (23)	83 (28)
Chronic kidney disease[c]	57 (19)	49 (16)
Active cancer	27 (9)	38 (13)
Antibiotic therapy within 3 mo before randomization, No. (%)	202 (67)	199 (65)
Body mass index, median (IQR)[d]	26 (23-30)	26 (23-30)
Tracheal tube or tracheostomy, No. (%)[b]	221 (74)	221 (74)
Sepsis, No. (%)[e]	116 (38)	122 (40)
Septic shock, No. (%)[f]	187 (62)	182 (60)
Known infection site, No. (%)[b]	205 (70)	189 (64)
Respiratory tract	96 (33)	99 (33)
Gastrointestinal tract	28 (9.6)	24 (8.1)
Catheter-related bloodstream	28 (9.6)	15 (5.1)
Genitourinary tract	16 (5.5)	12 (4.1)
Other	33 (11)	35 (12)
SARS-CoV-2 infection, No. (%)	33 (11)	40 (13)
Clinical severity, median (IQR)		
Simplified Acute Physiology Score II[g]	44 (35-55)	43 (34-53)
Sequential Organ Failure Assessment score[h]	9 (6-11)	9 (6-11)
Time from hospital admission to randomization, median (IQR), d	9 (4-18)	8 (3-17)
Time from intensive care unit admission to randomization, median (IQR), d	5 (1-11)	5 (1-10)

[a] The percentages may not sum to 100 because of rounding. There were no significant between-group differences.

[b] The proportion of missing values was less than 5%.

[c] Defined as abnormalities of kidney structure or function that were present for longer than 3 months and had implications for health. The markers (≥1) of kidney damage included: albuminuria; urine sediment abnormalities; electrolyte; and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, and history of kidney transplantation. Impaired kidney function defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Defined as the presence of systemic inflammatory response syndrome, suspected or documented infection, and Sequential Organ Failure Assessment score.

[f] Defined as the presence of sepsis plus required use of a vasopressor to maintain a mean arterial pressure of 65 mm Hg and serum lactate level greater than 2 mmol/L in the absence of hypovolemia.

[g] Calculated based on the patient characteristics, reason for intensive care admission, and physiological abnormalities. The score range is from 0 to 163; a higher score indicates higher severity of disease and higher risk of death.

[h] Based on the dysfunction of 6 organs. The score range is from 0 to 24; a higher score indicates higher severity of disease and higher risk of death.

Discussion

In this double-blind, international, RCT of critically ill patients with sepsis, there was no significant difference in the composite outcome of all-cause mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at 28 days for continuous administration vs intermittent administration of meropenem. No significant difference was observed for any of the 4 secondary outcomes or for the individual elements of the composite primary outcome.

Before this study, several investigations suggested that continuous administration or extended administration of β-lactam antibiotics would be superior to intermittent administration. Several meta-analyses found reduced mortality[9,35-37] or increased clinical cure[12] in patients receiving continuous or extended administration of β-lactam antibiotics; however, RCTs have reported inconsistent findings. The beneficial effect of

Table 2. Study Drug Doses, Use of Concurrent Antibiotics, and Microbiological Characteristics

	Continuous administration (n = 303)	Intermittent administration (n = 304)
Not susceptible to carbapenem antibiotics at baseline, No./total (%)[a]	84/239 (35)	64/216 (30)
Initial meropenem dose, No. (%)[b]		
2 g/d (low dose when creatinine clearance was <50 mL/min)	70 (24)	84 (28)
3 g/d (standard dose)	180 (62)	166 (56)
4 g/d (high dose when creatinine clearance was <50 mL/min)[c]	11 (3.8)	13 (4.3)
6 g/d (high dose)[d]	31 (11)	34 (11)
8 g/d (high dose)[d]	0	1 (0.3)
Meropenem dose, median (IQR)		
Daily, g	3 (3-3)	3 (2-3)
Corrected for body weight, g/kg/d	0.04 (0.03-0.05)	0.04 (0.03-0.05)
Meropenem dose changes, No. (%)[e]	25 (8.9)	22 (7.5)
Duration of meropenem treatment, median (IQR), d		
Overall	11 (6-18)	11 (6-17)
Among those who survived to 28 d	13 (8-21)	13 (8-21)
Meropenem dose, median (IQR)		
Overall, g	24 (9-37)	21 (6-36)
Corrected for body weight, g/kg	0.29 (0.11-0.49)	0.27 (0.11-0.49)
Concurrent antibiotic therapy, No. (%)[b]	218 (73)	225 (74)
Class of concurrent antibiotic therapy, No. (%)[b]		
Glycopeptides	89 (30)	86 (28)
Cephalosporins (third and fourth generation)	63 (21)	63 (21)
Oxazolidinones (eg, linezolid)	51 (17)	60 (20)
Lipopeptides (eg, daptomycin)	19 (6.4)	32 (11)
Quinolones	15 (5.0)	17 (5.6)
Tigecycline	17 (5.7)	14 (4.6)
Aminoglycosides	12 (4.0)	16 (5.3)
Macrolides	1 (0.3)	5 (1.7)
Rifampicin	3 (1.0)	3 (1.0)
Other	18 (6.0)	18 (5.9)
Microbiological characteristics, No./total (%)[f]		
Gram-negative[g]		
Klebsiella species	72/246 (29)	59/222 (27)
Pseudomonas species	48/246 (20)	44/222 (20)
Escherichia coli	44/246 (18)	44/222 (20)
Acinetobacter species	28/246 (11)	22/222 (9.9)
Enterobacter	13/246 (5.3)	15/222 (6.8)
Other	41/246 (17)	38/222 (17)
Gram-positive[g]		
Coagulase-negative Staphylococci	58/116 (50)	49/103 (48)
Staphylococcus aureus	16/116 (14)	25/103 (24)
Enterococcus faecium	18/116 (16)	12/103 (12)
Enterococcus faecalis	14/116 (12)	6/103 (5.8)
Other	10/116 (8.6)	13/103 (13)
Anaerobes	0	0
Polymicrobial[h]		
Gram-negative infection	59/303 (20)	51/304 (17)
Gram-negative and gram-positive infection	65/303 (22)	44/304 (15)
Unidentified pathogen[h]	84/303 (28)	90/304 (30)

[a] The denominators were the number of isolated gram-negative bacteria that were microbiologically tested for carbapenem antibiotics.

[b] The proportion of missing values was less than 5%.

[c] Mistake in an overweight patient who should have received 6 g/d.

[d] Patients with an infection involving the central nervous system (eg, meningitis) could receive a high dose.

[e] The proportion of missing values was 5.6% (34/607 patients).

[f] Causative pathogens were identified through the results of blood cultures and microbiological specimens collected from the suspected site of infection.

[g] The denominators were the number of the culprit culture of the primary infection site.

[h] The denominators were the total number of patients in each group.

Table 3. Primary Outcome, Secondary Outcomes, and Post Hoc Exploratory Outcomes[a]

	Continuous administration (n = 303)	Intermittent administration (n = 304)	Difference (95% CI)	Unadjusted relative risk (95% CI)	*P* value
Primary outcome, No. (%)					
Composite of all-cause mortality and emergence of pandrug-resistant[b] or extensively drug-resistant[c] bacteria at 28 d	142 (47)	149 (49)	Absolute, −2.1 (−10.1 to 5.8)	0.96 (0.81 to 1.13)	.60
Components of the primary outcome					
All-cause mortality at 28 d	91 (30)	99 (33)	Absolute, −2.5 (−9.9 to 4.8)	0.92 (0.73 to 1.17)	.50
Emergence of pandrug-resistant[b] or extensively drug-resistant[c] bacteria at 28 d	68/288 (24)[d]	70/280 (25)[d]	Absolute, −1.4 (−8.4 to 5.7)	0.94 (0.71 to 1.26)	.70
Secondary outcomes					
90-d mortality, No. (%)	127 (42)	127 (42)	Absolute, 0.1 (−7.7 to 8.0)	1.00 (0.83 to 1.21)	.97
Alive and free from antibiotics at 28 d, median (IQR), d[e]	3 (0 to 15)	2 (0 to 15)	Mean, 0.4 (−0.9 to 1.7)		.57
Alive and free from intensive care unit at 28 d, median (IQR), d[f]	0 (0 to 19)	0 (0 to 19)	Mean, 0.6 (−1.0 to 2.2)		.40
Post hoc exploratory outcomes					
Length of intensive care unit stay, median (IQR), d	11 (5 to 22)	11 (5 to 23)	Mean, −0.2 (−3.2 to 2.8)		.93
Length of intensive care unit stay among those who survived to 28 d, median (IQR), d	12 (6 to 23)	12 (7 to 27)	Mean, −1.0 (−3.0 to 1.0)		.42
Length of hospital stay, median (IQR), d	21 (12 to 38)	22 (10 to 40)	Mean, −0.3 (−4.3 to 3.6)		.99
Length of hospital stay among those who survived to 28 d, median (IQR), d	26 (16 to 45)	30 (17 to 56)	Mean, −3.6 (−9.0 to 1.8)		.14
Readmission to intensive care unit, No. (%)	27/215 (13)[g]	18/199 (9.0)[g]	Absolute, 3.5 (−2.4 to 9.5)	1.39 (0.79 to 2.44)	.25

[a] The proportion of missing values was less than 5%. Antimicrobial resistance was assessed not only by blood culture but also by all the other culture information collected between randomization and day 28. Although the cumulative Sequential Organ Failure Assessment score at day 28 was prespecified as a secondary outcome, it was excluded from the analysis because there were numerous missing data, especially after intensive care unit discharge.

[b] Defined as an organism resistant to all classes of antimicrobial agents available and intrinsically active against the respective species.

[c] Defined as an organism resistant to all except 1 or 2 antimicrobial classes.

[d] Patients who died within 48 hours after randomization were excluded from the denominator (15 patients in the continuous administration group and 24 patients in the intermittent administration group).

[e] Defined as the number of calendar days within 28 days after randomization on which the patient was alive and did not receive any antibiotic treatments.

[f] Defined as the number of calendar days within 28 days after randomization on which the patient was alive and not admitted to the intensive care unit.

[g] The denominators reflect the number of patients who were previously discharged alive from the intensive care unit.

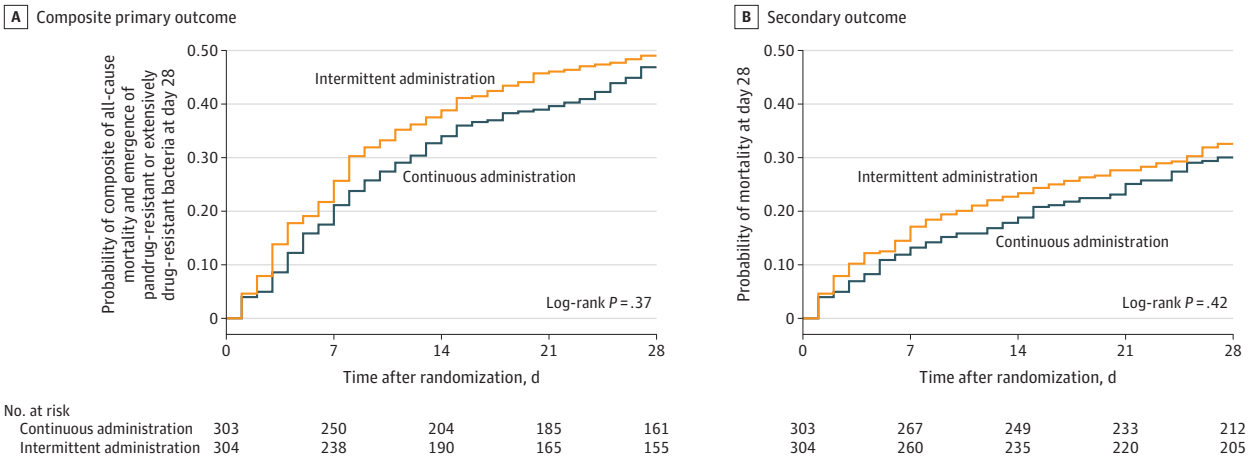
extended administration was seen in a small, randomized trial[38] and in some studies,[19,38,39] while another trial found no difference.[40] Pharmacological studies also supported continuous or prolonged administration of meropenem with higher plasma and subcutaneous concentrations and, for resistant pathogens (*Acinetobacter* species and *Pseudomonas aeruginosa*), the delivery of greater exposure to target the minimal inhibitory concentration.[7] In addition, expert opinions supported continuous administration of β-lactam antibiotics, highlighting the pharmacokinetic and pharmacodynamic advantages of continuous infusion, the feasibility of the technique, and the likely maximal benefit in critically ill patients infected by resistant organisms.[41-44]

The results of the current study suggest that continuous administration of meropenem does not improve clinically relevant outcomes in critically ill patients with sepsis, including long-term mortality. Previous studies found short-term survival benefits, whereas 1 study reporting 90-day mortality showed a nonsignificant difference (26% in the continuous group vs 28% in the intermittent group, $P = .67$),[40] which is consistent with the current study (42% in both groups, $P = .97$). Experts further suggested the method of meropenem administration should take into account other factors such as feasibility, intravenous line availability, issues with stability of the drug, costs, and logistical issues.[45] In addition, the experts indicated that no specific subgroups could be identified in whom continuous administration might be the target of future RCTs.

Infection was microbiologically documented in 70% of patients. The trial protocol relied on rigorous assessment, timed blood cultures, and specimen collection paired with additional blood or specimen cultures performed when deemed necessary by the attending clinicians. The current study relied on strict inclusion criteria, enrolling a population of critically ill patients with sepsis,[21] and avoiding inclusion of low-risk patients. Combined with higher minimal inhibitory concentrations in the commonly identified pathogens, the current study population was a suitable candidate to test continuous administration.[46]

Moreover, comprehensive subgroup analysis was performed in populations that theoretically might have greater

Figure 2. Kaplan-Meier Analysis for the Composite Primary Outcome and the Secondary Outcome of Probability of Mortality at Day 28



No. at risk

Continuous administration	303	250	204	185	161	303	267	249	233	212
Intermittent administration	304	238	190	165	155	304	260	235	220	205

Emergence of pandrug-resistant bacteria or extensively drug-resistant bacteria is shown as occurring on the day the positive culture was sent to the laboratory. All patients were followed up to death or emergence of resistant bacteria or through day 28.

benefit from continuous administration due to pharmacokinetic or pharmacodynamic differences or because of the microbiological characteristics of the isolated pathogen in both severely ill patients infected by gram-negative pathogens and those with high minimal inhibitory concentrations. These patient characteristics might explain the different findings between the current study and previous randomized evidence.[9,10] Unlike previous studies enrolling patients in the very early stages of sepsis,[10] most patients in the current study experienced hospital-onset sepsis, which often results in a poor prognosis with a limited modifiable clinical course compared with community-onset sepsis.[47] In fact, mortality at 1 month was higher in the current study (31%) than reported in previous studies (23%).[10] In addition, the current study is a multinational, double-blind, large, pragmatic trial, and all of these features led to less biased results.[48]

The current study chose antibiotic resistance as a component of the composite primary outcome. In addition to the controversy about mortality as the sole primary outcome,[49] and an increased risk of death and morbidity related to antimicrobial resistance,[29] a consensus statement supported the use of composite outcomes in clinical trials of severe infection.[50]

Limitations

This study has several limitations. First, clinicians could change the dose of meropenem throughout the study period (by doubling or reducing doses) based on kidney function or individual clinician decision. The treatment also could be interrupted based on clinician judgment. Patient safety and access to the best therapy were the guiding principles, but were not enforced by strict protocols. However, guidance on meropenem dosage was provided to the participating centers. Thus, the decision to change therapy was seldom used and the mean duration of therapy was similar in both groups.

Second, this study focused on 1 molecule, meropenem. Meropenem first exerts its bactericidal action and later inhibits its bacterial regrowth at subinhibitory concentrations. This postantibiotic effect[16] is associated with a delayed regrowth of bacteria following exposure. Postantibiotic effects have been identified for *E coli* strains, *Klebsiella* pneumonia, and *P aeruginosa* and range from 0.7 hours to 2.5 hours and may have contributed to the study findings. Therefore, the observations of this study cannot be extrapolated to other β-lactam antibiotics.

Third, routine therapeutic monitoring of meropenem was not performed in this study because at the starting time of trial no clear recommendation had been issued on therapeutic drug monitoring of β-lactam antibiotics. In addition, lack of data on efficacy and cost-effectiveness is still a major barrier for the incorporation of therapeutic drug monitoring into routine clinical practice.[51,52] As a result, such measurements are not part of usual care.

Fourth, concurrent therapy with other antimicrobials was common and might have offered protection during low meropenem concentration periods. Fifth, it might be possible that this study was underpowered to detect a smaller treatment effect than expected. However, this study achieved the estimated sample size and power, being the largest RCT to date for this research question. A lack of interaction in any of the subgroup analyses supported the robustness of the study findings.

Sixth, we did not collect detailed data about the microbiological cure of the baseline infection after randomization because it does not always reflect clinical cure,[50] but we presented the data about clearance of the primary infection and etiology and the management of the secondary infections.

Conclusions

In critically ill patients with sepsis, compared with intermittent administration, the continuous administration of meropenem did not improve the composite outcome of mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28.

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