Continuous vs Intermittent Meropenem Administration in Critically Ill Patients With Sepsis
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<table>
<tr><th colspan="3">BACKGROUND AND OVERVIEW</th></tr>
<tr><td>Article Citation</td><td colspan="2">Published in JAMA
https://jamanetwork.com/journals/jama/fullarticle/2806400</td></tr>
<tr><td>Background</td><td colspan="2">Previous Research
Other meta analysis and systematic reviews looking at smaller studies showed that continuous or extended infusion meropenem may decrease all-cause mortality. No adequately powered RCT that focuses on meropenem administration in critically ill patients with sepsis.
Relevant Guidelines
IDSA guidelines on Gram Negative Infections
Important to consider as current recommendations only mention intermittent meropenem infusion regimen
Meropenem Mechanism of Action and Side Effects
MOA: Exerts its bactericidal action by binding to penicillin-binding proteins (PBPs) in the bacterial cell wall and inhibiting peptidoglycan cross-linking associated with cell wall synthesis, which ultimately leads to cell death
Displays time-dependent killing - reason why continuous or extended dosing seems promising
SE: seizures, renal issues, some B-lactam cross sensitivity</td></tr>
<tr><td>Study Objective</td><td colspan="2">To determine if continuous administration of meropenem reduces mortality and emergence of drug-resistant bacteria among critically ill patients with sepsis compared with intermittent administration</td></tr>
<tr><th colspan="3">METHODS</th></tr>
<tr><td>Study Design</td><td colspan="2">Design
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).
Web-based randomization by ICU physician
Pharmacist and ICU nurse not blinded
Pharmacy would have to compound and know what each contains
Data collector and physician are blinded though
Double-dummy bags - each patient received both types of infusion
One bag contained meropenem while the other did not
Follow up Duration
Primary outcome at 28 days and secondary at 90 days. Lost none to follow up.
Timeline of Study
Conducted between June 5, 2018 and August 9, 2022. Final 90 day data collected in November 2022.
Location of Study
Across 4 countries - Croatia, Italy, Kazakhstan, and Russia
Dosing Regimens Used
Standard: 3 g over course of day
CrCl <50 ml/min: 2 g daily
4 or 6 g daily: Used in patients with high minimal inhibitory concentrations on the infection culture result or for meningitis
Treatment diagnosis
All patients received treatment for sepsis according to international guidelines and protocols available at each study center.
Baseline Characteristics
Baseline characteristics and comorbidities, vital signs, history of previously administered antibiotics, SAPS II, SOFA score, Glasgow Coma Scale score, mechanical ventilation status and settings, urine output, and site of infection.</td></tr>
<tr><td rowspan="2">Patient Criteria</td><td>Inclusion:</td><td>Exclusion</td></tr>
<tr><td>18 years or older
Admitted to the ICU
Required new antibiotic treatment with meropenem by clinician assessment
Had sepsis or septic shock.
The definitions used for sepsis and septic shock were a hybrid of Sepsis-321 and traditional sepsis definitions.</td><td>Refusal of consent
Previous therapy with carbapenem antibiotics
Very low probability of survival assessed using the Simplified Acute Physiology Score II (SAPS II) (score ≥65 points)
Severe immunosuppression (eg, AIDS or long-term corticosteroid therapy [>0.5 mg/kg/d of methylprednisolone for >30 days])</td></tr>
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	○ 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.	
Outcomes	Primary endpoint ● 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. ○ Extensively drug-resistant bacteria were defined as organisms resistant to all except 1 or 2 antimicrobial classes. Secondary endpoints ● 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. ○ 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. ○ Adverse event data were collected for seizures, allergic reactions related to the study drug, and mortality	
RESULTS		
Enrollment and Baseline Characteristics	Amount of People Enrolled ● 607 total patients were randomized ○ 303 in continuous infusion group ○ 304 in intermittent group Comparison Between Groups ● Groups fairly similar ○ Extended group had more identified causes of infection ○ Generally have comparable severity score results	
Outcome Summary	Primary Endpoint Outcomes ● Not significantly significant ● RR (95% CI) - 0.96 (0.81 to 1.13) Significant Outcomes ● Nor primary or any secondary outcomes found to be significant	
DISCUSSION		
Authors' Main Points in the Discussion	● No significant difference in primary or secondary outcomes ● Significant effects had only been found before in small trials ● Subgroup analysis done but no groups identified as showing statistical significance in regard to primary outcome ● This study included patients with hospital onset sepsis vs community that most others did not ○ Hospital acquired infections have higher mortality risk as compared to community (31% vs. 23%, respectively)	
Strengths	Strengths ● Guidance on meropenem dosage was provided to facilities ● Largest RCT on this topic ● Rigorous assessment of data ● Strict inclusion criteria - avoided inclusion of low risk patients that may falsely elevate study ● Antibiotic resistance reviewed ● Power was met	

	● Intention to treat and per protocol analysis used
Limitations	Limitations ● Clinicians could change meropenem dose based on kidney function or individual clinical decision ● Treatment could be interrupted based on clinical judgment ● Patient safety was guiding therapy but not strictly enforced ● Focused only on meropenem, which has unique effects, so cannot be extrapolated to other beta lactams. ○ Acts bactericidal originally then later inhibits bacterial growth at subinhibitory concentrations ○ Post antibiotic effect unlike other beta lactams ● Concurrent therapy with other antimicrobials was common and might have offered protection during low meropenem concentration periods ● Data not presented on microbiological cure of baseline infection after randomization because does not always reflect clinical cure
Personal Conclusions	The authors are aware of the weaknesses of the trial. Although statistical significance was not found, the outcomes covered in this study were appropriate. The addition of an outcome looking at the emergence of resistant bacteria was unique yet important as this displays a concern for public health and the effects on clinical outcomes this has. Clinical practice will not change based on this study but looking into studies that compared extended interval vs intermittent infusions could reveal interesting results. Overall, a well thought-out study but did not prove statistically significant.