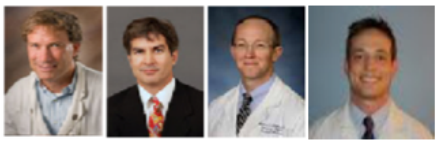
critical care perspectives in emergency medicine



Intermittent or Continuous Antibiotic Infusions for Sepsis?

Key Article

- *Dulhunty JM, Brett SJ, De Waele JJ, et al. Continuous vs Intermittent B-Lactam Antibiotic Infusions in Critically Ill Patients with Sepsis. The BLING III Randomized Clinical Trial. JAMA. Published online June 12, 2024.*

Background

- A cornerstone of sepsis resuscitation is the early administration of antibiotic therapy directed at the likely organism.
- B-lactam antibiotics are an important class of antibiotics used in the treatment of sepsis.
- Piperacillin-tazobactam and meropenem are two of the most common B-lactams empirically given in the early resuscitation of patients with sepsis.
- Typically, B-lactam antibiotics are administered via short (30 min) infusions.
- Recent trials have reported that continuous infusions of B-lactam antibiotics result in higher concentrations and may be more effective than intermittent infusions.
- At present, the data on continuous infusions is not conclusive as it pertains to patient-centered outcomes.

Objective

- To determine whether a continuous infusion of piperacillin-tazobactam or meropenem results in decreased all-cause mortality at 90 days in critically ill patients with sepsis when compared to intermittent infusions.

Methods

- International, open-label, phase 3, randomized clinical trial.
- 104 ICUs in Australia, Belgium, France, Malaysia, New Zealand, Sweden, and the UK
- Patients
    - Included:
        - Adults $\geq$ 18 years
        - Admitted to the ICU
        - A documented site or strong suspicion of infection
        - Treatment with piperacillin-tazobactam or meropenem within the previous 24 hrs.
        - 1 or more organ dysfunction within the previous 24 hours
        - Expected to remain in the ICU for at least the next calendar day.
- Trial procedures
    - Randomized in 1:1 ratio to receive piperacillin-tazobactam or meropenem by either continuous (intervention group) or intermittent (control group) infusion.
    - Interventions
        - The total 24-hour dose of antibiotics were determined by the attending physician.

        - All participants received at least 1 B-lactam antibiotic infusion prior to open-label randomized treatment.
        - Continuous or intermittent infusions were continued for the duration of the treatment course or until ICU discharge.
- Primary outcome
    - All-cause mortality at 90 days
- Secondary outcomes
    - Clinical cure – defined as the completion of the B-lactam antibiotic treatment course by day 14 without need to restart antibiotics within 48 hours of cessation for the same infection.
    - New infection, colonization, infection with an MDR organism, or C.diff up to 14 days after randomization.
    - All-cause ICU mortality
    - All-cause hospital mortality

Results

- A total of 7202 patients were randomized, with 7031 used in the primary analysis.
    - Continuous infusion group: 3498 patients
    - Intermittent infusion group: 3533 patients
    - Similar baseline characteristics
- Most common sites of infection
    - Pulmonary: 60%
    - Intraabdominal: 13%
    - Blood: 8%
    - Urinary: 5.5%
- Median duration of treatment
    - Continuous infusion group: 5.8 days
    - Intermittent infusion group: 5.7 days
    - Daily dose of study drug was similar between groups.
- Primary Outcome
    - Continuous infusion group: 24.9%
    - Intermittent infusion group: 26.8%
    - Absolute difference: -1.9% [95% CI -4.9% to 1.1%]
    - P=0.08
- Secondary outcome
    - Clinical cure at day 14
        - Absolute difference: 5.7% [95% CI 2.4% to 9.1%]
        - Statistically significant
    - No differences in rates of new infection, colonization, infection with an MDR organism, ICU mortality, hospital mortality
- Adverse events
    - Continuous infusion group: 10
    - Intermittent infusion group: 6
    - 1 serious event in continuous infusion group that may have been due to infusion – meropenem – patient developed severe encephalopathy that led to aspiration, cardiac arrest, and death.

Limitations Identified by Authors

- Unblinded, open-label study
- Some patients may have had a noninfectious etiology of organ dysfunction at randomization.
- No adjustment for susceptibility results to the B-lactam
- No assessment of impact of additional antibiotics
- Patients received an intermittent dose of the antibiotic prior to randomization.

Take Home Points

- The use of a continuous infusion of a B-lactam antibiotic did not statistically improve 90-day all-cause mortality when compared to an intermittent infusion in ICU patients with confirmed or presumed sepsis.
- Authors cite that the confidence interval around the effect estimate does include the possibility of a benefit and that they found a statistical improvement in rates of clinical cure with continuous infusion.

Key Article

- *Abdul-Aziz MH, Hammond NE, Brett SJ, et al. Prolonged vs Intermittent Infusions of B-lactam Antibiotics in Adults with Sepsis or Septic Shock. A Systematic Review and Meta-Analysis. JAMA. 2024; Published online June 12, 2024.*

Background

- B-lactams are widely used as first-line antibiotics for treatment of sepsis and septic shock.
- These agents display time-dependent bactericidal activity – optimal when free drug concentration remains above the MIC of the infecting pathogen for at least 40-70% of the dosing interval.
- Biologic rationale that prolonged infusions may be more effective compared with conventional intermittent dosing. Supported by pharmacokinetic-pharmacodynamic studies that demonstrate prolonged infusions achieve B-lactam antibiotic exposures associated with maximal bacterial-killing more consistently than intermittent infusions.

Objective

- To assess whether administration of B-lactam antibiotics by prolonged infusions are associated with reduced 90-day all-cause mortality.

Methods

- Systematic review of RCTs
- RCTs
    - Recruited critically ill adults.
    - With sepsis or septic shock
    - Compared administration of prolonged infusions with intermittent infusions of 1 or more B-lactam antibiotics
        - Prolonged infusions defined as either an extended infusion (2 hours or longer) or a continuous infusion.
        - Intermittent infusion defined as fewer than 2-hour dosing interval.
- Primary outcome

    - All-cause mortality at 90 days
- Secondary outcomes
    - ICU mortality
    - ICU LOS
    - Clinical cure
    - Microbiologic cure
    - Adverse events
- Prespecified subgroups
    - Meropenem vs. piperacillin-tazobactam
    - Culture-positive vs. culture-negative infection
    - Gram-negative vs. gram-positive
    - RRT vs. no RRT
    - Lung vs. other infections
    - Sepsis vs. septic shock
    - Male vs. female patients

Results

- 18 RCTs included totaling 9108 patients.
    - Median of 59 trial participants
    - Median APACHE II score: 20
    - Median SOFA score: 8
    - 17 trials compared continuous infusion vs. intermittent.
    - 1 trial compared extended infusion vs. intermittent.
    - Median duration of treatment 7 days for prolonged infusions vs. 9 days in intermittent infusions
- Primary Outcome
    - 17 trials that evaluated the primary outcome – 9014 patients.
    - Pooled estimated RR for all-cause 90-day mortality for prolonged infusions compared with intermittent infusions was 0.86 (95% CI 0.71 to 0.98)
    - 99% posterior probability that prolonged infusions were associated with lower 90-day mortality.
    - Certainty of evidence was adjudicated as high.
- Bayesian Analysis
    - 14-point relative reduction in risk of mortality at 90 days with prolonged infusions
    - NNT to prevent 1 death was 26 patients.
- Subgroup Analyses
    - No evidence that prolonged infusions compared with intermittent infusions for all-cause 90-day mortality was different between the groups.
- Secondary outcome
    - Continuous infusions compared with intermittent infusions were associated with reduced ICU mortality (RR 0.84, high certainty) and increased clinical cure (RR 1.16, moderate certainty)
    - No differences in microbiologic cure, adverse events, or ICU LOS.

Limitations Identified by Authors

- Included trials used various definitions for sepsis and septic shock.

- Current analysis combined extended and continuous infusions, though only 1 trial looked at an extended infusion.
- Variable definitions of clinical cure across studies.

Take Home Point

- The use of a prolonged infusion of a B-lactam antibiotic was associated with a reduced risk of 90-day all-cause mortality in ICU patients with sepsis or septic shock when compared to an intermittent infusion.