Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis

The BLING III Randomized Trial *Joel M. Dulhunty et al, JAMA (2024)*

RESEARCH AIM

To investigate the effect of continuous vs. intermittent infusion of β-lactam antibiotics on all-cause 90-day mortality in patients with sepsis hospitalized in critical care.

BACKGROUND

- β-lactam antibiotics are commonly administered through repeated short-term intravenous infusions.
- The time-dependent efficacy of β-lactam antibiotics provides a clinical rationale for using continuous infusion instead of intermittent administration.
- Results of previous trials are inconclusive regarding the effect of continuous β-lactam infusion on outcomes.

METHODS

Design: Prospective, randomized trial conducted in 104 ICUs in Australia, Belgium, France, Malaysia, New-Zealand, Sweden and the United Kingdom.

Population:

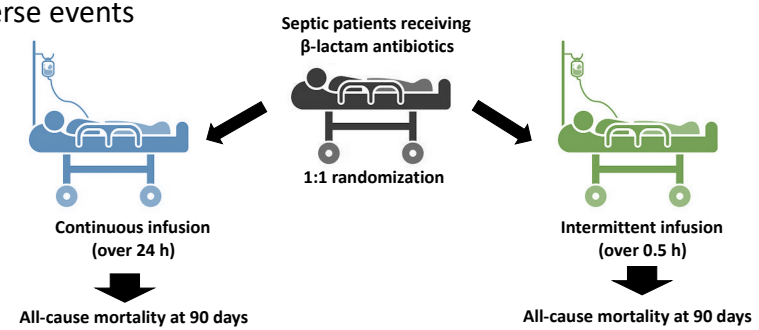
- ICU patients ≥18 years of age
- Documented or suspected side of infection
- Treatment with piperacillin-tazobactam or meropenem initiated within the previous 24 h
- ≥ 1 organ dysfunction criteria

Intervention:

Continuous (over 24h) or intermittent (over 30 min) infusion of piperacillin-tazobactam or meropenem

Outcome Parameters:

1) All-cause mortality at 90 days
2) Clinical cure, defined as the completion of β-lactam antibiotics by day 14 without recommencement of antibiotic therapy within 48 h of cessation.
3) New acquisition, colonization or infection with a multidrug resistant organism or C. difficile.
4) All-cause ICU and hospital mortality.
5) Days free of ICU, hospital, mechanical ventilation and renal replacement therapy up to 90 days.
6) Adverse events



Statistical Analysis:

- Intention-to-treat analysis with logistic regression models adjusted for sex, APACHE II score and type of β-lactam antibiotic used before randomization.
- Linear- and Cox models were used to investigate duration outcomes and the effect of interventions, respectively.

RESULTS

- Of 7202 randomized patients, 3498 were included in the final analysis for the continuous and 3533 for the intermittent infusion group. 171 were excluded after randomization due to a lack of consent to use any data.

Outcome	Continuous infusion	Intermittent Infusion	Odds ratio (95% CI)	P
Mortality at 90 days	864/3474 (24.9 %)	939/3507 (26.8 %)	0.91 (0.81-1.01)	.08
Adjusted 90-days Mortality			0.89 (0.79-0.99)	**.04**
Clinical cure at day 14	1930/3467 (55.7 %)	1744/3491 (50.0 %)	1.26 (1.15-1.38)	**<.001**

- There were **no differences** between groups in the new acquisition, colonization or infection with **multiresistant organisms or C. difficile, ICU mortality, or** hospital mortality.
- **No differences** between groups **in days a**live and **free of ICU** stay, **hospital stay**, **mechanical ventilation or renal replacement therapy**.
- **10 (0.3%)** and **6 (0.2%) adverse events** were reported in the continuous and intermittent infusion group, respectively.

SIS COMMENTS

This study is an exemplary prospective interventional trial conducted in 104 ICUs located in 8 countries on 3 different continents, investigating the effect of continuous compared to intermittent β-lactam infusion on 90-day mortality.[1] The trial identified no statistically significant difference for the primary endpoint but attributed a relevant difference of 2.2% and reducing the odds to reach the primary endpoint by 0.89 (95% CI: 0.79-0.99, p = .04) after adjustment for sex, APACHE II score, and type of β-lactam antibiotics used. Additionally, a higher incidence of clinical cure at day 14 in patients receiving continuous replacement therapy was found.

This is particularly vital in the context of escalating multidrug resistance, where achieving optimal eradication of pathogens is crucial to prevent the development of resistance. Since Alexander Fleming discovered penicillin in 1928, β-lactam antibiotics have served as foundational treatments for severe infection and sepsis, yet knowledge about the optimal administration of these drugs remains limited. The time-dependent bactericidal properties of β-lactams have prompted numerous studies, exploring the benefits of their prolonged or continuous over intermittent use in the care of infected patients.

While many studies have explored pharmacokinetic aspects, this study by Dulhunty's et al. is distinctively focused on 90-day mortality, providing crucial insights into clinically relevant implications for patients. Although the study did not meet the predetermined significance threshold for this hard primary endpoint, adjustment suggests a clinical benefit of continuous infusion strategies.
This is in line with a recent meta-analysis conducted by Abdul-Aziz and colleagues, which reviewed 17 trials involving 9014 participants.[2] Using a Bayesian framework, the authors identified a risk ratio of 0.86 (95% credible interval 0.72-0.98), favouring prolonged infusion for reducing all-cause 90-day mortality.

Although results from individual trials may vary, the aggregate evidence supports the benefits of prolonged infusions of β-lactam antibiotics, suggesting the consideration for broader implementation of these practices.

1. Dulhunty et al. JAMA, 2024.
2. Abdul-Aziz et al. JAMA, 2024.