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EDITORIAL

Prolonged β-Lactam Infusion in Sepsis Management: An Update

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INTRODUCTION

Sepsis, a severe inflammatory condition driven by a dysregulated immune response to infection, has been identified by the World Health Organization as a top priority, accounting for roughly 20% of all deaths worldwide. [1-3] Critically ill septic patients often experience substantial pathophysiological changes that can drastically affect the antimicrobial pharmacokinetics owing to increased volume of distribution and augmented renal clearance.[4] These changes can result in sub-therapeutic drug exposure of renally cleared antibiotics, especially the beta-lactams which follow time-dependent kinetics.[5,6]

β-Lactam antibiotics, especially piperacillin-tazobactam and meropenem, recognized for their broad-spectrum efficacy, are among the most commonly administered empirical antibiotics in critically ill septic and septic shock patients, respectively, in Intensive Care Units (ICUs).[7] These antibiotics follow time-dependent pharmacodynamics, where maintaining free drug concentrations above the minimum inhibitory concentration (fT>MIC) of the infective pathogen for at least 40-70% of the dosing interval is essential for optimal therapeutic effect.[8] Thus, not only the right antimicrobial but also the right dose and duration of infusion is crucial in achieving positive outcomes in critically ill septic patients.[9]

Traditionally, β-lactams were delivered through intermittent dosing with 30 minutes to one-hour infusion. However, recent pharmacokinetic studies suggest that extending the infusion duration may help maintain the plasma concentration, thereby increasing the time the drug concentration remains above the MIC, potentially enhancing its efficacy.[10] The evidence suggests that patients administered β-lactams via continuous infusion were tenfold more likely to surpass the target MIC than those given the drug through intermittent infusion.[11]

RECENT PRACTICE-CHANGING UPDATES

Conflicting evidence is available from various studies comparing continuous versus intermittent infusion of beta-lactams, which has added to the controversy surrounding the efficacy of prolonged infusion in critically ill septic patients. The meta-analysis conducted by Kondo *et al.* in 2020 concluded that prolonged β-lactam antibiotic infusion (continuous or extended time) significantly enhanced the achievement of target plasma levels with RR 0.40 [95% CI 0.21-0.75] and clinical cure with RR 0.84 [95% CI 0.73-0.97], without any rise in adverse events as compared to intermittent infusion (within 1 hour). Notably, the subgroup analysis revealed significant benefits in-hospital mortality or clinical outcomes, specifically in studies published from 2015 onwards. However,

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caution is necessary when interpreting this study, as the cut-off for defining prolonged infusion was over 1 hour, potentially affecting the overall results.[12]

Recently, two large randomized controlled trials (RCTs) were published in 2023 and 2024 comparing continuous versus intermittent infusion of beta-lactams. Continuous (3 gm infusion over 24 hours) versus intermittent infusion (over 30-60 minutes infusion) of meropenem in critically ill patients (**MERCY**) trial (n=607) with double-dummy design reported no significant difference in the primary outcome, which was a composite of all-cause mortality and emergence of pan-resistant bacteria at Day 28 (RR 0.96 [95%CI 0.81-1.13], p=0.60).[13]

Another large RCT, **BLING III**, recently published in 2024, compared continuous (over 24 hours) versus intermittent (over 30 minutes) infusion of piperacillin-tazobactam and meropenem in critically ill septic patients. There was no significant difference in all causes of 90-day mortality, with an absolute difference of -1.9 (95% CI -4.9 to 1.1). However, clinical cure at day 14 was significantly higher in the continuous versus intermittent infusion group, with an absolute difference of 5.7 (95% CI 2.4 to 9.1).[14]

The point that needs to be considered in the interpretation of the results is the stability of meropenem for more than 3 hours at room temperature in a continuous infusion, which could influence the applicability in ICUs.[15]

A recent meta-analysis by Zhao *et al. (2024)* included 15 studies, including 2130 patients in sepsis/ septic shock, with 11/15 studies evaluating predominantly Gram-negative infections and 4/15 studies with mixed pathogens. Augmented renal clearance was not noted in the studies. The meta-analysis revealed that prolonged infusion of beta-lactams, as opposed to intermittent administration, significantly reduced all-cause mortality (RR 0.83; 95% CI 0.72-0.97; p=0.02), coupled with enhanced clinical success, without any difference in adverse events.[16] The subgroup analysis further emphasized the importance of loading doses with beta-lactams. The use of loading dose in the prolonged infusion group was associated with a significant reduction in mortality (RR 0.84; 95% CI 0.72-0.97; p=0.02).[16] The statistically significant benefit of prolonged infusion on mortality was seen with the penicillin group of antibiotics on subgroup analysis. The benefit of prolonged infusion was also there for carbapenems on subgroup analysis, but it was not statistically significant, indicating the need for further studies to strengthen the findings. Overall, the results further reinforce the International consensus guidelines that advocate using prolonged infusion in critical patients to lower mortality rates and enhance clinical cure outcomes.[8]

Another recent meta-analysis by Abdul-Aziz *et al. (2024),* which included the two large RCTs with a total of 17 studies with around 9000 patients in ICU patients with sepsis or septic shock, further showed that β-lactam antibiotics administered as prolonged infusion significantly reduced 90-day all cause-mortality as compared to intermittent infusion (RR 0.86; 95% CI 0.72-0.98) in line with the previous meta-analysis findings. The prolonged infusion was also associated with a significantly reduced risk of ICU mortality and a non-significant increased clinical cure rate and microbiological cure.[17]

The highly dynamic pharmacokinetics in critically ill patients often leads to therapeutic failures or toxicities, both of which are closely tied to fluctuations in drug concentration. The choice between conventional intermittent dosing and prolonged infusion can significantly influence the drug's pharmacokinetic profile, necessitating careful consideration of dosing strategies to optimize therapeutic outcomes. However, practical considerations of continuous infusion with pumps must be considered, especially in resource-constrained settings such as India. Most studies come from high-income countries, and a dedicated infusion pump/portal poses additional pragmatic challenges in resource-constraint settings. Secondly, the continuous infusion of carbapenem, especially meropenem, might require multiple infusions owing to stability issues of more than 3 hours, adding to additional interruptions and work of the nursing team.

CONCLUSIONS

The extrapolation of results and feasibility of continuous infusion should be carefully considered in our setting, both within and outside the ICUs. In addition, instead of constant infusion, extended/prolonged infusion of 2-3 hours duration could be a pragmatic solution and should be considered to achieve therapeutic concentration for beta-lactams. It also takes care of the stability issues of the meropenem. The evidence supporting this comes from a meta-analysis of 8 studies, indicating 24% lower all-cause mortality in prolonged infusion of meropenem compared to intermittent infusion in patients with sepsis.[18] However, there were a limited number of studies and heterogeneity in treatment and drug dosages used in various studies. Well-conducted RCTs are needed from our settings to confirm these findings and to establish the optimal dosing and administration, especially in critically ill septic patients, to provide

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better clarity and feasible solutions to achieve target fT>MIC for beta-lactams.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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