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Continuous Infusion of Beta-Lactams in the Critically Ill: Considerations for Global Implementation

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Abstract

β-lactam antibiotics are the most commonly used antibiotics for the empiric and targeted treatment of infection in the critically ill. Timely administration of an effective dose of β-lactams is critical to reduce infection-associated morbidity and mortality.

Continuous infusion (CI) of β-lactam antibiotics is now an evidence-based strategy to optimise treatment in critically ill patients with infection. However, the widespread implementation of CI of β-lactams requires consideration of various practical and pharmaceutical related factors.

The following addresses barriers to the implementation of CI of β-lactam antibiotics, including specific considerations for low resource settings, and aims to provide practical solutions for the translation of evidence into practice.

Key words: Sepsis, Infection, Antibiotics, Intensive Care Unit, β-lactam, Implementation, Continuous Infusion

Highlights

- Continuous infusion (CI) of β-lactams reduces mortality in critically ill patients with infection
- Practical and pharmaceutic hurdles need to be addressed to ensure CI is effective beyond clinical trials
- Implementation barriers to CI of β-lactams are likely to differ between poor- and well-resourced settings
- An evidence-based response is needed for the global implementation of CI of β-lactams

1. Introduction

Sepsis, defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection, is a global health problem associated with a high burden of mortality and, in survivors, long-term morbidity [1-3]. Early and appropriate antibiotic administration is central to the treatment of sepsis, and β-lactam antibiotics are a commonly utilised empiric treatment [4, 5].

β-lactam antibiotics demonstrate time-dependent bacterial killing with maximal bacterial kill associated with the time that the unbound concentration of the antibiotic exceeds the minimum inhibitory concentration (MIC) [6, 7]. There is therefore a pharmacological rationale that, following a loading dose, continuous infusion (CI) of β-lactam antibiotics, defined as infusion of a daily dose over a 24 hour period, may be more effective than short intermittent infusions [7, 8]. This rationale has recently been tested in the setting of two large, multi-centre randomised clinical trials, the Continuous Infusion versus Intermittent Administration of Meropenem in Critically Ill Patients (MERCY) and the β-lactam Infusion Group (BLING) III trials [9, 10].

In a recent systematic review and meta-analysis of these and other trials, that additionally included trials of other β-lactam antibiotics (e.g. cephalosporins), the use of prolonged β-lactam antibiotic infusions was associated with a reduced risk of 90-day mortality compared to intermittent administration with a number needed to treat of 26 to prevent 1 death [11]. These results have been further verified by a recent trial sequential analysis [12]. Notably, the individual trials have also consistently demonstrated safety of a CI strategy, with similar adverse event rates between intermittent and prolonged infusions of β-lactam antibiotics [9-11, 13-15].

Given the weight of the evidence, with a high certainty of significant patient-centred benefit and low risk of harm, there is a strong imperative to implement prolonged ($\geq$ 3 hours) and/or continuous β-lactam antibiotic infusions into intensive care practice. However, translating the evidence to bedside clinical practice may be associated with specific challenges and barriers. Further, the implementation considerations are likely to differ across critical care settings worldwide due to variability in available resources.

This review aims to explore some of the real and perceived barriers to the global implementation of CI of β-lactam antibiotics in critically ill patients, including pharmaceutical, equipment, intravenous access, environmental, system and staffing considerations.

2. Sepsis in Resource Poor Settings

The burden of sepsis disproportionately affects populations in resource poor settings, with 80 percent of the global mortality caused by infections occurring in under-resourced settings [16]. Therefore, the impact of effective sepsis interventions in resource poor settings is likely to be particularly beneficial. Extrapolating data from studies conducted predominately in high-resource settings is challenging despite a consistent biological rationale for the effectiveness of CI of β-lactam antibiotics.

While the quality of microbiological data is variable, the burden of antimicrobial resistance (AMR) is higher in under resourced settings [17, 18]. There is therefore an additional theoretical benefit that CI may help reduce resistance rates by optimising the pharmacokinetic/pharmacodynamic (PK/PD) properties of antibiotics with low ecological impact, increasing efficacy against less resistant strains and preventing bacterial regrowth during the dosing interval [19]. The BLING III trial did not demonstrate a significant difference in the new acquisition of multidrug resistance organisms (MDROs) associated with the use of CIs [9]. However, the impact in resource-constrained environments with high rates of AMR is unknown.

Whilst CI may confer significant benefits, particularly in resource poor settings, there are specific implementation challenges that need to be considered.

3. System and Staff Considerations

The process of translating health-related research findings into clinical practice can be slow due to system and staff-associated barriers [20-22]. System barriers and facilitators include environmental context, organisational culture, communication processes, and documentation requirements, including local antibiotic guidelines and reporting requirements. Staff barriers

and facilitators include staff attitude, skills, ability and confidence, role identification, and understanding and awareness [20, 22].

The successful global implementation of CI for β-lactam antibiotics requires engagement of multiple stakeholders. Local practice should be defined by the multidisciplinary team, including intensivists, nursing staff, microbiologists and clinical pharmacists. Some implementation barriers that may affect uptake of CI of β-lactam antibiotics disproportionately in resource-poor areas include higher patient-to-staff ratios, lack of availability of clinical pharmacists, infectious disease physicians, and microbiologists, and lack of intensive care specialist practitioners.

Beyond staffing, there are additional resource and quality of care considerations. In the recently published African Critical Illness Outcomes Study which included data from 180 hospitals in 22 African countries, it was shown that the majority of critically ill patients were cared for in general wards rather than a dedicated intensive care unit (ICU) [23]. Similarly, mismatch between the need for and allocation of resources for patients presenting to the emergency department with sepsis is also common in Brazil, with a point prevalence study revealing adequate allocation occurring in only 52.8% of patients [24]. Thus, institutional protocols in resource limited settings may also need to consider CI of β-lactam antibiotics for critically ill patients who remain in emergency departments or who are admitted to the general wards.

Educational barriers may be addressed somewhat through the provision of freely available educational material, such as open-access web-based education. Where available, barriers to safe and effective implementation of CI of β-lactam antibiotics may be mitigated at the point of prescribing through updating electronic prescribing systems with the use of pre-populated prescriptions and clinical decision support. Representation from researchers and clinicians from resource poor settings is necessary to ensure implementation programmes are adaptable to a diverse range of settings [25].

4. Drug Stability

Drug stability refers to the extent that the active pharmaceutical ingredient remains viable during a specified storage period with >90% being a commonly (but not universally)

accepted value required from the time of drug reconstitution to administration completion [26]. The stability of a drug can be influenced by drug concentration, the container, diluents, temperature, pH changes, and duration of infusion. Resultant administration of sub-optimal drug concentrations may risk clinical failure and increase the risk of MDRO acquisition.

Specific considerations relating to the stability of β-lactam antibiotics have recently been summarised by Barton and colleagues [26]. Briefly, piperacillin/tazobactam is stable when diluted in 0.9% sodium chloride or 5% glucose for 24 hours at a temperature of 25 degrees. This enables only one bag change over a 24-hour period for CI. On the other hand, meropenem is more sensitive to changes in concentration, temperature, and the type of diluent, such that shorter infusions (e.g. over 6-12 hours) and dilutions in 0.9% sodium chloride are recommended [27, 28]. In the MERCY trial, infusion bags were changed every 8 hours for a generic version of meropenem with the longest documented stability after reconstitution was administered [10]. Similarly, drug preparation and infusion bag change every 8 hours was recommended in the BLING III trial for meropenem infusions prepared in 0.9% sodium chloride, although changes every 12 hours were considered appropriate in one region [9].

Notably, lower concentrations of meropenem (10 and 20mg/mL) are more stable than higher concentrations (40mg/mL), with one study testing four commercially available preparations of meropenem demonstrating 10 and 20mg/mL solutions were stable for 12 hours in 0.9% sodium chloride at 25°C [29]. While lower concentrations of β-lactam antibiotics necessitate a need for a greater volume of fluid administration, the increased stability of lower concentrations may confer advantages (e.g. reduced workload, less frequent line disconnection) in certain settings.

Packet insert instructions may preclude administration of extended infusions due to fear of litigation related to off label administration. Partnerships with pharmaceutical companies are thus crucial, as are collaborative efforts to conduct the pharmacokinetic studies that may lead to improvements in product stability and labelling.

Drug stability may also be a particular challenge in resource-limited settings, especially for meropenem. Many under resourced health systems are in tropical regions, where higher ambient temperatures can compromise drug stability [28]. If more frequent back-to-back infusions are required, some of the practical benefits of CI (e.g., reduced nursing workload) may be lost and, depending on drug preparation, there is the risk of drug wastage.

5. Intravenous Access, Equipment and Sustainability Considerations

5.1 Intravenous Access

Whether given as a short intermittent infusion or CI, β-lactam antibiotics can be given via central or peripheral intravenous access. Consideration should be given to: (i) the specific line utilised in relation to line deadspace, with more line flushing required when smaller infusion volumes are utilised and/or long intravenous lines are utilised; (ii) the expected duration of intravenous therapy; and (iii) drug compatibility with concomitant therapies.

When drug stability enables 24 hourly CI (e.g. for piperacillin/tazobactam) the reduced frequency of line disconnection may reduce the risk of infection. On the other hand, inserting additional intravenous lines or placing central venous lines with more lumens increases the incidence of line-associated infection and thrombosis [26]. The additional complexity, cost, and infection risk are likely to be disproportionately challenging in resource-limited environments. Notably, the International Nosocomial Infection Control Consortium measured and reported markedly higher central line associated blood stream infection rates in under resourced settings [30, 31].

Therefore, to avoid unnecessary additional lines or lumens and the consequent risks, co-infusion of β-lactams with compatible drugs should be considered, which can be facilitated with evidence-based guidelines.

If additional access or rationalisation of other infusions is not possible, disconnection of lines may need to occur. In non-urgent scenarios, this should be performed by waiting for the current syringe or bag of β-lactams to finish, flushing the line, administering the other medication, and then flushing the line again prior to commencing the next of β-lactam syringe or bag. In urgent scenarios, a new β-lactam bag or syringe will be required to reduce the risk of infection. In this scenario, it is important to ensure the full daily dose of antibiotic is given in the 24-hour window, which may require the remaining dose to be given more quickly.

5.2 Infusion Pumps

Infusion pumps enable controlled administration of a continuous drug. Furthermore, newer "smart" pumps are equipped with dose error reduction software and drug libraries aimed at reducing the incidence of medication errors and consequent patient harm [32]. In the United States, most hospitals are now using smart infusion pumps [33]. However, as with all new technologies, the translation to patient benefit is dependent on addressing institutional and human factors that contribute to implementation failure.

In severely constrained or remote areas, a lack of infusion pumps precludes controlled administration. In these settings, gravity-driven systems are often used, although the implications of the resultant plasma level fluctuations are uncertain. In other settings, infusion pumps may be available but financial costs may be a significant barrier. Scarcity of pumps may lead to prioritisation of other infusions, and healthcare insurance companies may not routinely cover the added costs associated with continuous antimicrobial infusions. However, these increased costs may be offset by other potential savings associated with increased rates of clinical cure associated with CI of β-lactam antibiotics. Further, CI of β-lactam antibiotics may also reduce nursing workload, enhancing equitable access to care and/or potentially reducing cost, although further time and motion studies are needed. Cost effectiveness analyses of the CI of β-lactam antibiotics in critical ill patients are required to further evaluate these hypotheses.

5.3 Environmental Sustainability Considerations

Reducing the ecological footprint of ICU, while maintaining high-quality patient care, is a responsibility of all ICU stakeholders, and has been endorsed by the European Society of Intensive Care Medicine though publication of the Green Paper [34]. The BLING III trial has recently been used as an illustrative example of how clinicians and researchers can factor in the environmental impact of interventions [35].

Klasen and colleagues found that CI of piperacillin/tazobactam, but not meropenem, when given as 8-hourly back-to-back infusions, resulted in less waste due to the use of fewer materials utilised during drug preparation and administration [35]. However, the additional electricity consumption that may be required for syringe pumps also needs to be considered,

particularly in settings that don't use renewable energy sources [35]. The use of gravity-driven systems utilised in some settings is likely more environmentally friendly, albeit with the aforementioned safety and pharmacokinetic caveats mentioned previously (*see section 5.2*).

Using antibiotic brands with longer stability and infusion bags rather than syringes is likely to result in a reduced environmental burden, whilst reducing the risk of death through the use of CI.

6. Renal Replacement Therapy

Renal replacement therapy (RRT) is a common intervention in the ICU. Optimising antimicrobial dosing in the critically ill patients requiring RRT is an additional challenge, particularly in the context of both individual patient variability, such as residual renal function and fluid removal requirements, and institutional variability of practice, such as the mode and effluent flow rate of RRT and characteristics of the available hemofilter [36]. Notably, the BLING III trial specifically excluded patients receiving RRT prior to enrolment limiting the generalisability of the results to this cohort of critically ill patients [9]. If RRT was subsequently required after enrolment in the trial, doses were adjusted according to medical orders.

Piperacillin/tazobactam and meropenem clearance is reliably predicted by effluent flow rate in continuous renal replacement therapy (CRRT), with increased clearance predicted by higher effluent flow rates [36, 37]. Intermittent modes of haemodialysis rather than CRRT is widely used in low-resource settings. The use of intermittent modes of RRT adds additional complexity to antimicrobial dosing during RRT, particularly in the absence of availability of therapeutic drug monitoring (TDM) [38]. Further trials are required to determine the optimal empiric dosing strategy for various β-lactam antibiotics for intermittent modes of haemodialysis. In the meantime, prescribing support tools, many of which are available as online resources, for patients with renal impairment and/or who require RRT may be helpful to determine dosing adjustments.

7. Therapeutic Drug Monitoring (TDM) and Model Informed Precision Dosing (MIPD)

Although CI of β-lactam antibiotics improves outcomes in critically ill patients with sepsis, there remains an ongoing risk of inappropriate dosing due to pharmacokinetic/pharmacodynamic variability [39]. For example, whilst CI is likely a superior strategy for patients with augmented renal clearance compared to intermittent dosing [40], TDM guided adjustment of CIs, which may be combined with pharmacometrics modelling software [i.e. Model Informed Precision Dosing (MIPD)], can further improve pharmacokinetic target attainment in this population of critically ill patients [41]. However, whether routine TDM and/or TDM or MIPD for select subpopulations of critically ill patients receiving CI of β-lactam antibiotics translates to improved clinical outcomes remains uncertain [42-44].

Access to timely TDM for β-lactam antibiotics is limited, and rarely available in resource-poor settings [39]. This accessibility barrier needs to be addressed, especially if emerging evidence supports a role for TDM for CI of β-lactam antibiotics. In settings where TDM is not available, the using of dosing software that incorporates patient-specific parameters (e.g. weight, renal function) may assist in individualised empirical β-lactam antibiotic dosing.

8. Guidelines

Whilst there is strong evidence for the use of CI of β-lactam antibiotics to reduce morbidity and mortality in the critically ill, there are multiple implementation hurdles that need to be overcome to ensure clinical effectiveness outside of the walls of a clinical trial.

There is a need to establish or update accessible guidelines on the use of CI of β-lactam antibiotics relevant to a diverse range of settings. Guidelines assist in standardisation of practice, with the aim of minimising errors and maximising compliance. Table 1 outlines key considerations for guidelines on CI for β-lactam antibiotics that can be adapted to different settings.

Implementation also requires plans to evaluate the success of various interventions, including audits and monitoring of guideline compliance, interruptions to therapy, and adverse incident reporting. Key actions required for successful global implementation of CI of β-lactam antibiotics are summarised in Figure 1.

9. Conclusion

The global implementation of CI of β-lactam antibiotics in critically ill patients with infection requires addressing clinical efficacy, infrastructure and economic considerations. While CIs have clear advantages in the setting of clinical trials, its impact in real-world settings will be underpinned by health system readiness. A strategic approach incorporating clinical evidence, implementation science, and availability of local resources is necessary for widespread and sustained adoption.

Overcoming implementation barriers associated with the CI of β-lactam antibiotics has the potential to have significant positive impacts on infection and sepsis management, with disproportionate clinical impact in resource limited healthcare settings.

Headings	Rationale	Points to consider
Location of intervention	To define clinical areas where the guideline will be utilised	Will initiation of CI of β-lactams occur in the ED or ward prior to ICU admission?
Inclusion/exclusion criteria	To define the correct administration method is applied to the correct patient	Which patients will be treated by β-lactam CI as opposed to intermittent dosing?
Line availability and compatibility	To avoid placing unnecessary additional lines that increase the risk of infections and thrombosis	Include a compatibility chart with common medications utilised in the specific healthcare setting
Loading doses	To rapidly achieve plasma target concentrations	Specify loading doses to be given immediately before initiating the β-lactam CI – including in what circumstances to reload or when not to give a loading dose
Administration	To assist nursing staff in having information readily available	Details on dose reconstitution, dilution, duration of administration and infusion change intervals. Highlight importance of flushing the intravenous line at the end of each infusion.
Managing interruptions in treatment	Interruptions (e.g. during transfers) may cause drug concentrations to decrease rapidly, which may lead to therapeutic failure if adjustments aren't made	Depending on how long the β-lactam CI is held, what is the strategy to ensure the full dose is given within the dosing interval: Can the CI be restarted at the same rate? Can the remaining dose be given at a faster rate and how can this be calculated? Is a re-loading dose required and at what dose?
Dosing in renal impairment, while on RRT or in the setting of augmented renal clearance	To maintain therapeutic efficacy while minimising adverse effects	When should the dose of a CI be adjusted for alterations in renal clearance and how should this be done?
Discharge planning	To prevent medication errors and therapeutic failure	If transition areas that do not administer CI of β-lactams:

		Who is responsible for prescribing the intermittent dosing schedule? When will the next dose be due after stopping the CI? A process for handover is required

Table 1. Key considerations for guidelines on continuous infusions (CI) for β-lactam antibiotics. ED: Emergency Department, ICU: Intensive Care Unit, RRT: Renal Replacement Therapy

Key Actions Required for Successful Global Implementation of CI of β-lactam Antibiotics

1. **Establishing Global Consensus and Implementation Guidelines**

   Develop or update standardised CI guidelines with clear recommendations on drug stability, vascular access requirements, and dose optimisation

   Align guidelines with antimicrobial stewardship programs to ensure responsible use of antibiotics

   Create resource-stratified guidelines that accommodate both high-resource and resource-limited settings

2. **Scaling Infrastructure and Decision Support Tools**

   Prioritise enhancing equitable access to care (e.g. increasing availability of critical care staffing, infrastructure and equipment in low resource settings)

   Invest in **nursing and pharmacy training and decision support tools** to facilitate safe and effective administration of CI

3. **Conducting Pragmatic, Multicentre Implementation Studies**

   Evaluate **real-world effectiveness** of CI across different healthcare settings

   Assess **impact on clinical outcomes, antimicrobial resistance, the environment, and healthcare costs**

   Identify **context-specific barriers and facilitators** to refine implementation strategies

Figure 1. Recommendations for global implementation of continuous infusion (CI) of β-lactam antibiotics

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