Intensive Care Med (2016) 42:1604–1606
DOI 10.1007/s00134-016-4241-7

EDITORIAL

Continuous infusion of β-lactam antibiotics for all critically ill patients?

Fabio S. Taccone[1*], Kevin B. Laupland[2] and Philippe Montravers[3]

Infections are common in critically ill patients and are associated with a significant increase in ICU mortality and total costs related to patient management [1]. One of the main therapeutic interventions in severe infections is the administration of antibiotics; however, the prescription of adequate antimicrobial therapy still represents a complex challenge for clinicians because of the late identification of microorganisms and the increasing spread of multidrug-resistant pathogens [2]. International guidelines recommend an early and broad-spectrum antibiotic therapy, typically given as combination therapy, for life-threatening infections [3]. Nevertheless, optimizing antibiotic therapy in critically ill patients also needs to consider the changes in drug pharmacokinetics (PKs), in particular an increased volume of distribution associated with either augmented or impaired renal clearance, which are responsible for variations in circulating antibiotic levels and, potentially, for therapeutic failure [4]. β-lactam antibiotics, which are the first-line therapy for severe infections, are the most effective when drug concentrations exceed the minimal inhibitory concentration (MIC) of the pathogen for an extended period of time between different administrations (T > MIC) [4]. Because of significant and unpredictable changes in drug PKs during critical illness when standard intermittent administrations (IA) are given [4], a continuous infusion (CI) of β-lactam antibiotics could rapidly obtain prolonged T > MIC in almost all patients and even for less susceptible pathogens, such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, and should be preferred to optimize daily drug regimens in critically ill patients [5] (Fig. 1a). However, the evidence supporting that CI would also result in a better outcome when compared to standard regimens remains limited.

As such, in a recent article in *Intensive Care Medicine*, Abdul-Haziz et al. [6] evaluated the effects of CI of β-lactams on clinical cure at 14 days after antibiotic interruption, when compared to IA in patients with severe sepsis not requiring renal replacement therapy (RRT). A total of 140 patients were enrolled; CI was associated with a higher clinical cure rate (56 vs. 34 %, $p = 0.01$) and more ventilator-free days than IA. The target for optimal drug therapy (e.g., 100 % of T > MIC between two drug doses) was achieved more frequently in the CI than in the IA group on both day 1 (97 vs. 70 %, $p < 0.001$) and day 3 of treatment. No difference in 14-day or 30-day survival was observed between groups.

Should we then move to CI of β-lactams for all critically ill septic patients? Probably not! Previous studies have shown controversial results, although there may be sub-groups of patients in whom the CI of β-lactams could be of benefit. In one study from the Defining Antibiotic Levels in Intensive Care Unit database ($n = 182$), CI of piperacillin/tazobactam or meropenem resulted in a significantly higher survival rate at 30 days when compared to IA, but only in the subgroup of patients with respiratory infection (86 vs. 57 %, $p = 0.01$) [7]. Indeed, although penetration of β-lactams into the lungs is relatively limited, CI of ceftazidime was associated with a shorter time to adequate pulmonary concentrations and presented a more predictable PK profile than IA in patients with ventilator-associated pneumonia (VAP) [8]. The same study [7] also showed that CI of β-lactams was particularly effective in patients with high severity of disease when compared to IA (73 vs. 35 %, $p = 0.003$). Also, in another study on hospital-acquired pneumonia due to *Pseudomonas aeruginosa*, CI of piperacillin/tazobactam was associated with a lower 14-day mortality than IA only in those patients with an Acute Physiological and Chronic Health Evaluation (APACHE) II scores above 17 (12 vs. 32 %, $p = 0.04$) [9]. Another important confounder influencing the efficacy of CI in critically

*Correspondence: ftaccone@ulb.ac.be
[1] Department of Intensive Care, Hôpital Erasme, Route de Lennik, 808, 1070 Brussels, Belgium
Full list of author information is available at the end of the article

Springer

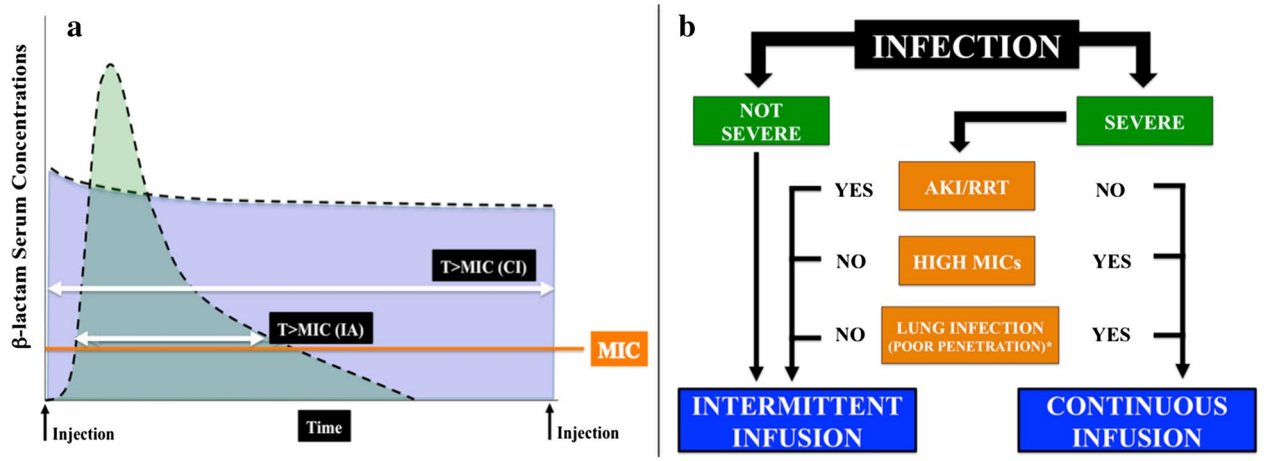

Fig. 1 **a** Differences in the time that β-lactam antibiotic concentrations exceed the minimal inhibitory concentration (T > MIC) of a pathogen between intermittent (*IA*, *light green*) and continuous infusion (*CI*, *light blue*). **b** A practical approach to identify those patients with the highest likehood to benefit from continuous infusion of β-lactam antibiotics during critical illness. *MIC* minimal inhibitory concentration. *Organs with poor antibiotic penetration

ill patients is the characteristics of the pathogen. While very susceptible bacteria can be adequately treated with standard IA, the risk of insufficient β-lactam antibiotic concentrations is high only for less susceptible strains, e.g., those with a higher MIC but still within the ranges that are associated with a positive response to antibiotic therapy according to international recommendations [4]. In one retrospective study, Lorente et al. showed that CI of piperacillin/tazobactam was associated with a higher probability of clinical cure than IA for the treatment of VAP in patients without renal failure, but only when the MIC of the isolated pathogen was ≥8 mg/L (15/17 vs. 7/21, $p = 0.002$) [10]. The final concern is about drug accumulation; no difference in 90-day survival (74 vs. 73 %, $p = 0.61$) or clinical cure (52 vs. 49 %, $p = 0.56$) was observed in a large cohort of septic patients ($n = 432$) when treated with CI or IA of β-lactams; however, drug concentrations were not measured and the inclusion of patients with renal failure or RRT, which are associated with significant drug accumulation and a lower risk for insufficient antibiotic concentrations even during IA, was a significant bias [11]. Also, very high levels of β-lactams may also be harmful in critically ill patients, with a potential risk of neurological complications that may overcome the beneficial effects on the control of the infection [12].

Importantly, although the Abdul-Haziz study [6] reported a dramatic benefit with CI of β-lactams in the management of severe sepsis, some important limitations also need to be clarified. First, this was an open-label clinical trial. Knowledge of treatment assignment may have led to differential management of patients but more importantly may have influenced the assessment of outcome. This study would have been greatly improved if a blinded adjudication committee to assess the final outcome was used. Secondly, the authors did not report real MIC values for their isolates but only susceptibility estimates from published guidelines. The fact that MIC values vary significantly internationally and even among hospitals within a region or over time periods raises serious questions about this practice. Moreover, more than one-third of patients achieving clinical cure had no pathogen identified, which would limit the calculation of drug concentrations required to improve drug effectiveness. Third, the authors found a high percentage of "difficult-to-treat" pathogens and this may not reflect the ecology of other countries with a different susceptibility patterns (e.g., limited external validity). Fourth, only serum drug concentrations were assessed, as this approach may be limited when dealing with infected sites with poor drug penetration, such as the brain, the peritoneum or the bones [13]. Also, respiratory infections represented the largest proportion of infected sites in this work and no conclusion on the potential benefits for CI could be drawn for other type of infections. Fifth, the proportion of patients with 100 % T > MIC was similar between patients with clinical response and failure. As such, although CI may provide some clinical benefits, this appeared not to be related to a longer and better exposure to therapeutic drug concentrations. Patients with clinical cure had a lower APACHE II score and received meropenem more frequently than those with clinical failure. Thus, an imbalance in the severity of disease and the spectrum or bactericidal activity may also account for the differences in outcome between groups. Finally, no

data on the emergence of resistant strains and/or superinfection were provided; although this issue is extremely difficult to address in clinical practice, these two complications may also be dependent on the achievement of adequate serum drug concentrations.

In conclusion, the concept of optimizing β-lactam antibiotic concentrations in severely ill patients using CI remains of great interest but is not convincingly proven. The body of evidence suggests that application of this strategy may be best in severe infections, in patients with normal renal function and lung infections, and when less susceptible pathogens are isolated or suspected (Fig. 1b). The impact of CI of β-lactams on patients' outcomes needs to be better characterized in future studies, especially when additional confounders, such as the use of RRT or renal failure, may further alter drug concentrations in this setting.

Author details
[1] Department of Intensive Care, Hôpital Erasme, Route de Lennik, 808, 1070 Brussels, Belgium. [2] Department of Medicine, Royal Inland Hospital, 311 Columbia Street, Kamloops, BC, Canada. [3] Department of Anesthesiology and Surgical Intensive Care, Bichat-Claude Bernard University Hospital Center, Paris Diderot University, Sorbonne Paris-Cité and AP-HP, 46 Rue Henri-Huchard, 75018 Paris, France.

Compliance with ethical standards

Conflicts of interest
No conflict of interest to declare.

Received: 5 January 2016 Accepted: 21 January 2016
Published online: 29 January 2016

References

1. Martin SJ, Yost RJ (2011) Infectious diseases in the critically ill patients. J Pharm Pract 24:35–43
2. Zhang D, Micek ST, Kollef MH (2015) Time to appropriate antibiotic therapy is an independent determinant of postinfection ICU and hospital lengths of stay in patients with sepsis. Crit Care Med 43:2133–2140
3. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
4. Taccone FS, Laterre PF, Dugernier T, Spapen H, Delattre I, Wittebole X, De Backer D, Layeux B, Wallemacq P, Vincent JL, Jacobs F (2010) Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care 14:R126
5. Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Lipman J (2013) Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis 56:236–244
6. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, Rai V, Wong KK, Hasan MS, Abd Rahman AN, Jamal JA, Wallis SC, Lipman J, Staatz CE, Roberts JA (2015) Beta-lactam infusion in severe sepsis (BLISS): a prospective, two-centre, open-labelled, randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. Intensive Care Med. doi:10.1007/s00134-015-4188-0
7. Abdul-Aziz MH, Lipman J, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Dulhunty J, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Roberts JA, DALI Study Group (2016) Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the defining antibiotic levels in intensive care unit patients (DALI) cohort. J Antimicrob Chemother 71:196–207
8. Cousson J, Floch T, Guillard T, Vernet V, Raclot P, Wolak-Thierry A, Jolly D (2015) Lung concentrations of ceftazidime administered by continuous versus intermittent infusion in patients with ventilator-associated pneumonia. Antimicrob Agents Chemother 59:1905–1909
9. Lodise TP Jr, Lomaestro B, Drusano GL (2007) Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 44:357–363
10. Lorente L, Jiménez A, Martín MM, Iribarren JL, Jiménez JJ, Mora ML (2009) Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. Int J Antimicrob Agents 33:464–468
11. Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Starr T, Paul SK, Lipman J (2015) A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis. Am J Respir Crit Care Med 192:1298–1305
12. Beumier M, Casu GS, Hites M, Wolff F, Cotton F, Vincent JL, Jacobs F, Taccone FS (2015) Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients. Minerva Anestesiol 81:497–506
13. Nalda-Molina R, Dokoumetzidis A, Charkoftaki G, Dimaraki E, Margetis K, Archontaki H, Markantonis S, Boutos N, Sakas D, Vryonis E, Skoutelis A, Valsami G (2012) Pharmacokinetics of doripenem in CSF of patients with non-inflamed meninges. J Antimicrob Chemother 67:1722–1729