

Detailed regimens for the prolonged β -lactam infusion therapy

Hideharu Hagiya ^{a*}

^aDepartment of Infectious Diseases, Okayama University Hospital, Okayama, 700-8558, Japan

***Corresponding Author:**

Hideharu Hagiya, MD, PhD

Department of Infectious Diseases, Okayama University Hospital

2-5-1 Shikata-cho, Kitaku, Okayama, 700-8558, Japan

TEL: +81-86-235-7342; FAX: +81-86-235-7345

E-mail: hagiya@okayama-u.ac.jp

Keywords: sepsis, continuous infusion, prolonged infusion, pharmacokinetics

ICMJE Statement: H. Hagiya was responsible for the study design, data collection, and writing of the manuscript.

Abstract

A recent systematic review and meta-analysis of randomized controlled trials (RCTs) evaluated the efficacy and safety of prolonged versus intermittent β -lactam infusion in adult sepsis patients. The findings revealed a significant decrease in all-cause mortality and marked clinical success in the prolonged infusion group. Unfortunately, however, the manuscript lacked data and discussion for the specific regimens of prolonged β -lactam infusion defined in the included 15 RCT studies, which are herein additionally provided. Excluding one RCT, all protocols adopted a continuous infusion for the prolonged treatment. Except for three RCTs, dosages and timings of bolus injection were clearly defined. The total daily antibiotic dose for the continuous therapy was equivalent to those recommended for intermittent therapy. We believe this supplementary data aids clinicians in providing prolonged β -lactam infusions, contributing to enhanced treatment outcomes for patients suffering from severe sepsis or septic shock.

TEXT

With great interest, we read the article recently published by Zhao et al. in another journal [1].

Their systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to

evaluate the efficacy and safety of prolonged versus intermittent β -lactam infusion in adult sepsis

patients. The findings revealed a significant decrease in all-cause mortality and marked clinical

success in the prolonged infusion group. Additionally, subgroup analyses highlighted the

superiority of prolonged infusion over conventional intermittent therapy, especially in studies

with adequate sample sizes (≥ 20 individuals per group), conducted post-2010, predominantly

involving patients with Gram-negative bacterial infections, incorporating a loading dose, and the

treatment with penicillin. These insights have the potential to significantly influence clinical

practice and may resolve the long-lasting debates in this field. ~~However, the analysis insufficiently~~

~~addresses the specific regimens of prolonged β -lactam infusion, leaving a gap in~~

~~recommendations for clinical application.~~

A sufficient loading dose plays a crucial role in improving the prognosis of patients in

critical condition~~The importance of the loading dose in enhancing outcomes for critically ill~~

~~patients has been well established [2–4].~~ This attribute is attributed to the altered

pharmacokinetics of β -lactam antibiotics in severe sepsis and septic shock, such as increased

distribution volume and accelerated drug clearance [5]. To counteract reduced initial drug

書式変更: フォントの色 : 赤

書式変更: フォントの色 : 赤

51 concentrations, the author asserts the necessity^{ies} of bolus administration prior to continuous
52 therapy ~~and, the initiation (The timing of the of post-loading prolonged infusion initiation post-~~
53 ~~loading is crucial due to the short half lives of β lactam antibiotics, typically ranging from 30~~
54 ~~minutes to 1-2 hours. This important information was omitted in the review article [1], prompting~~
55 ~~an in-depth examination of the eligible RCTs for clarification. However, there is no detailed note~~
56 ~~on the specific regimens of prolonged β -lactam infusion in the article [1], leaving a practical gap~~
57 ~~in recommendations for clinical application.~~

書式変更: フォントの色 : 赤

58 The regimens for prolonged β -lactam antibiotics infusions are summarized in **Table 1**.
59 Excluding one RCT by Mirjalili *et al.*, all protocols implemented a continuous approach for the
60 prolonged infusion. Among 15 RCTs, three studies did not explicitly describe the loading protocol,
61 but the remainder included a bolus injection before initiating continuous therapy. Although
62 loading doses varied across RCTs, a half or single dose of each antibiotic was mostly adopted;
63 *i.e.*, 0.5 g or 1 g of meropenem, 2.25 g or 4.5 g of piperacillin/tazobactam, 0.5 g of ceftriaxone.
64 In 11 RCTs that detailed the initiation timing for continuous infusions, 10 commenced the
65 continuous infusions immediately after the loading dose. The total daily antibiotic dose for the
66 continuous therapy was equivalent to those recommended for intermittent therapy.

67 ~~I hope ^Tthis supplementary data supports clinicians in implementing the promising~~
68 therapeutic strategy of prolonged infusions of β -lactam antibiotics, ~~To avoid the potential~~

書式変更: フォントの色 : 赤

書式変更: フォントの色 : 赤

書式変更: フォントの色 : 赤

69 underdosing in critically ill patients with augmented renal clearance, the bolus administration of
70 antibiotics is highly essential. ~~The author anticipates that the information~~ provided herein will
71 contribute to enhanced treatment outcomes for patients suffering from severe sepsis or septic
72 shock.

73

74

75

76 **Acknowledgment**

77 None to report.

78 **Funding**

79 None to report.

80 **Conflict of disclosure**

81 None to declare.

82 **Ethical statement**

83 N/A

84 **Data Availability declaration**

85 Not applicable

86

書式変更: フォントの色 : 赤

References

- [1] Zhao Y, Zang B, Wang Q. Prolonged versus intermittent β -lactam infusion in sepsis: a systematic review and meta-analysis of randomized controlled trials. *Ann Intensive Care* 2024;14:30.
- [2] Hong LT, Downes KJ, FakhriRavari A, Abdul-Mutakabbir JC, Kuti JL, Jorgensen S, et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: Endorsed by the American College of Clinical Pharmacy, British Society for Antimicrobial Chemotherapy, Cystic Fibrosis Foundation, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America, Society of Critical Care Medicine, and Society of Infectious Diseases Pharmacists: An executive summary. *Pharmacotherapy* 2023;43:736–9.
- [3] Abdul-Aziz MH, Sulaiman H, Mat-Nor M-B, Rai V, Wong KK, Hasan MS, et al. 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* 2016;42:1535–45.
- [4] Venuti F, Trunfio M, Martson A-G, Lipani F, Audagnotto S, Di Perri G, et al. Extended and Continuous Infusion of Novel Protected β -Lactam Antibiotics: A Narrative Review. *Drugs* 2023;83:967–83.

105 [5] Gatti M, Pea F. Jumping into the future: overcoming pharmacokinetic/ pharmacodynamic
106 hurdles to optimize the treatment of severe difficult to treat-Gram-negative infections with
107 novel beta-lactams. Expert Rev Anti Infect Ther 2023;21:149–66.