Acta Anaesthesiologica Scandinavica

RESEARCH ARTICLE OPEN ACCESS

Plasma Trough Concentrations of Beta-Lactam Antibiotics in the Early Phase of Septic Shock

Malin Hägglund[1,2] | Magnus Brink[1,2] | Ulrika Snygg Martin[1,2] | Daniel Bremell[1,2] | Carl Johan Svensson[3,4]

[1]Department of Infectious Diseases, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden | [2]Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden | [3]Department of Anaesthesiology and Intensive Care, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden | [4]Department of Anaesthesiology and Intensive Care Medicine, Institute of Clinical Sciences at the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Correspondence: Malin Hägglund (malin.hagglund@vgregion.se)

Received: 20 January 2025 | **Revised:** 30 March 2025 | **Accepted:** 19 April 2025

Funding: This project was funded by Göteborgs Läkarsällskap (GS-879901).

Keywords: beta-lactam antibiotics | early-phase pharmacokinetics | plasma drug concentrations | septic shock | therapeutic drug monitoring (TDM)

ABSTRACT

Introduction: Septic shock necessitates timely antibiotic therapy, often with broad-spectrum beta-lactam antibiotics (ß-LA). To our knowledge, no previous study has examined antibiotic concentrations repeatedly during the initial phase of treatment. This observational study aimed to assess early-phase plasma concentrations of ß-LA in patients with septic shock.

Method: Prospective observational study of patients with septic shock, according to the SEPSIS-3 criteria, who received cefotaxime, piperacillin/tazobactam, or meropenem in accordance with Swedish practice. Demographic and clinical data were recorded for each patient. Consecutive blood samples were obtained during the first 24 h of treatment, and total antibiotic concentrations were measured using liquid chromatography mass spectrometry. Target concentrations were defined as 100% of the time that free (unbound) antibiotic concentrations remained above the minimal inhibitory concentration ($fT > MIC$).

Results: Twenty-two patients were included, 15 (68%) were male and the median age was 65.5 years (IQR 46.3–65.5). In-hospital mortality was 7/22 (32%). Antibiotic exposure exceeding 100% $fT > MIC$ was achieved in 16 (73%) of the patients. Four patients did not receive the recommended additional dose between the first and second doses of antibiotics; two of them still achieved 100% $fT > MIC$, whereas the other two attained 66% and 33% $fT > MIC$, respectively. Among the patients who received the additional dose, four did not achieve 100% $fT > MIC$. No relationship between mortality and $fT > MIC$ was observed. Significant associations with achieving 100% $fT > MIC$ were observed for older age ($p = 0.045$) and illness severity (SAPS3, $p = 0.025$).

Conclusion: Our findings demonstrate considerable variability in antibiotic exposure during the initial 24 h of septic shock treatment, highlighting a critical gap in understanding the clinical relevance of sub-optimal serum antibiotic concentrations and their potential impact on patient outcomes.

Editorial Comment: Therapeutic drug monitoring of antimicrobials is increasingly being used in research and clinical practice.

1 | Introduction

Septic shock is a medical emergency where adequate and timely empirical antibiotic treatment is of paramount importance. Since the specific etiological agent is initially unknown, empirical antibiotic regimens usually include a broad-spectrum agent [1].

Beta-lactam antibiotics (ß-LA) (penicillins, cephalosporins, carbapenems, and monobactams) are the most used group of

antibiotics in bacterial infections, including sepsis, due to their broad spectrum of activity and wide therapeutic index [2]. The bactericidal pharmacodynamic effect of ß-LA is time-dependent, directly related to the time that the free (unbound) antibiotic concentration exceeds the minimum inhibitory concentration ($fT > MIC$) of the targeted bacteria [3]. For non-critical infections, there is evidence that the free antibiotic concentration needs to exceed the MIC for the targeted bacteria for up to 50%, 70%, and 40% of the dosing interval for penicillins, cephalosporins, and carbapenems, respectively. Increasing concentrations beyond 4 times MIC does not yield any additional bactericidal effect [4]. There is little data regarding optimal plasma concentrations of ß-LA in patients with septic shock; however, based on theoretical reasoning and previous research, $fT > MIC$ 100% or even $fT > 4 \times MIC$ 100% has been suggested as target plasma concentrations [5–7].

The pathophysiology in septic shock, such as capillary leak with large fluid shifts to the extravascular compartments, and for some patients augmented renal clearance, tends to lower plasma concentrations of highly water-soluble substances, including ß-LA [8–10]. Hence, higher than normal doses of antibiotics are usually recommended to patients with septic shock, but the clinical evidence is still sparse and there is no international consensus regarding dosage regimens. In Sweden, treatment for septic shock has traditionally included high-dose ß-LA administered at frequent intervals, with an added dose between the initial two doses [11]. This regimen, with the added extra dose, intends to rapidly reach and sustain plasma antibiotic concentrations above the minimum inhibitory concentration for the yet unknown pathogens throughout the dosing interval ([AB] 100% $fT > MIC$).

Adequate plasma antibiotic concentration is vital during the early phase of infection when a high pathogen burden in the circulation plays a central role as a driving force for the systemic inflammatory response and secondary organ failure. The aim of this study was to measure ß-LA concentrations in plasma at the very early phase of treatment in patients with septic shock treated with ß-LA in intermittent dosing in accordance with Swedish practice.

2 | Method

An observational study was conducted at the Central Intensive Care Unit (ICU) at Sahlgrenska University Hospital/East between November 2018 and February 2020. Approval according to the Declaration of Helsinki was obtained from the Regional Ethical Committee (No. 758–18). The study included adult patients with community-acquired septic shock according to SEPSIS-3 criteria [12] who were admitted to the ICU directly from the emergency department (ED) and who received empiric antibiotic therapy with cefotaxime, piperacillin/tazobactam, or meropenem. It was required that the patients had received no more than one dose of antibiotics in the ED or that the treatment was started in the ICU. All patients received the same antibiotic doses per administration: piperacillin 4 g, cefotaxime 2 g, or meropenem 1 g. Piperacillin was administered as an infusion over 30 min, while the other antibiotics were given as intravenous bolus injections. The choice of antibiotics and dosing regimen was made by the attending intensive care physician. Preliminary informed consent was obtained verbally from patients meeting the inclusion criteria, with written consent subsequently obtained whenever feasible. In cases where the patient was unable to provide consent at inclusion, next of kin were consulted regarding the presumed wish of the patient. If the next of kin believed that the patient would consent to participation, the study proceeded in accordance with their input, and written informed consent was obtained from the patient when possible.

Blood samples for determination of antibiotic concentration in plasma were collected just before the second (i.e., the extra dose in 18 of 22 patients), third, and fourth given dose (trough concentrations) of the respective ß-LA. Following collection, samples were immediately stored away from light at +8°C to ensure minimal degradation [13] related to storage. The samples were subsequently centrifuged and frozen at −70°C as soon as possible after the last sample was collected, with a maximum refrigeration period of 24 h, as specified in the study protocol. The median storage duration for each sample at +8°C was 13 h. Samples remained frozen at −70°C until analysis. Sample analyses were performed at the Department of Clinical Biochemistry, Sahlgrenska University Hospital, Gothenburg, using liquid chromatography coupled to tandem mass spectrometry, providing total antibiotic concentrations in plasma. Demographic and clinical data including sex, age, height, weight, Simplified Acute Physiology Score (SAPS3) as well as laboratory and culture results were retrieved from patient records. The Charlson Comorbidity Index (CCI) [14] was used to assess the overall burden of comorbidities in the study population.

Based on published data, the approximate protein binding rates of the antibiotics were estimated; 30% for piperacillin, 2% for meropenem, and 40% for cefotaxime [15, 16]. The empirical treatment target was set at 100% $fT > ECOFF$, considering the 'worst-case scenario' of potential causative organisms, based on epidemiological cut-off values (ECOFF). Specifically, the ECOFF values used were 16 mg/L for *Pseudomonas aeruginosa* with piperacillin/tazobactam, 2 mg/L for *Pseudomonas aeruginosa* with meropenem, and 4 mg/L for *Staphylococcus aureus* with cefotaxime [17]. Data on toxic plasma concentrations are scarce; previously published thresholds were used as a reference for potentially toxic levels [7, 18].

2.1 | Statistical Analysis

Fisher's Exact Test, Kruskal-Wallis H test, Chi-square test, and Mann–Whitney U-test were performed where appropriate using Prism v.10.4.0 (527).

3 | Results

A total of 22 patients meeting the SEPSIS-3 criteria for septic shock were included in the study. Administered ß-LA were piperacillin/tazobactam ($n = 11$), meropenem ($n = 7$), and cefotaxime ($n = 4$). Most patients were male, 68% (15/22), with a median age of 65.5 years (IQR 46.3–65.5) (Table 1). The in-hospital mortality was 32% (7/22). The most common diagnosis was pneumonia (7 patients), followed by urogenital infection and

TABLE 1 | Baseline patient characteristics, test results, and selected outcomes.

	All ($N=22$)	Piperacillin ($N=11$)	Meropenem ($N=7$)	Cefotaxime ($N=4$)
Age	65.5 (46.3–65.5)	69 (60–80)	68 (53–79)	41 (18.75–64)
Male (%)	15 (68)	8 (73)	6 (86)	1 (25)
BMI (kg/m^2)	25.4 (23.1–28.1)	24.4 (21.9–27.1)	27.7 (24.4–29.4)	25.2 (21.8–28.5)
CCI[a]	4 (0.8–5)	4 (2–5)	4 (1–5)	2 (0–4)
Pl-Creatinine (μmol/L)[g]	134 (109–213)	180 (110–334)	115 (97–142)	119 (94.8–186.8)
SAPS3[b]	70.5 (56.5–76)	73 (66–76)	71 (50–79)	56.5 (48.5–75)
aB-Lactate (mmol/L)[h]	4.1 (2.8–6.3)	3.7 (2.5–6.7)	3.8 (2.7–7.1)	4.6 (4.4–5.8)
fT > MIC100%[c] (%)	16 (73)	9 (82)	5 (71)	2 (50)
In-hospital mortality (%)	7 (32)	3 (27)	3 (43)	1 (14)
Blood culture positive (%)	13 (59)	6 (55)	5 (71)	0
Total dose[d] (gram)	—	16 (16–20)	4 (4–5)	8 (6.5–8)
Extra dose of antibiotics[e] (%)	18/22 (82)	9/11 (82)	6/7 (86)	3/4 (75)
Concomitant antibiotics[f] (%)	13/22 (59)	6/11 (55)	5/7 (71)	2/4 (50)

Note: Median (IQR) unless other is written.
[a]Charslon comorbidity index.
[b]Initial creatinine.
[c]Simplified acute physiology score.
[d]Peak lactate the first 24 h of treatment.
[e]Empirical treatment target 100%-ime above MIC (Minimal Inhibitory Concentration).
[f]Total dose of antibiotics the first 24 h.
[g]Extra dose of antibiotics between first and second dose.
[h]Aminoglycosides and/or clindamycin or erythromycin.

sepsis of unknown focus (5 patients each). Necrotizing soft tissue infection was diagnosed in four patients, and two had an abdominal source of infection. Blood cultures were positive in 11 patients (50%). Concomitant antibiotics were given in 59% (13/22) of the cases. All patients received the same standard dose of ß-LA per administration; however, the dosing intervals varied (Figure 1A–C). In accordance with Swedish guidelines for septic shock, the majority, 82% (18/22), received an additional dose between the first and second regular doses (Table 1).

In 73% (16/22) of the patients, all three antibiotic trough concentrations measured during the first 24 h resulted in calculated free drug concentrations exceeding the MIC (ECOFF), corresponding to 100% fT > MIC. Six patients 27%, (6/22), two in each group of antibiotics, did not reach the empirical treatment target of fT > MIC 100% of the dosing interval (Figure 1A–C). Among these six patients, four had received the recommended additional dose between the first and second regular doses. One patient treated with meropenem had concentrations associated with toxicity (Figure 1B).

Mortality was not significantly associated with plasma antibiotic concentrations below fT > MIC 100%. Significant associations with achieving 100% fT > MIC were found for older age ($p=0.045$) and higher SAPS3 scores ($p=0.025$). Borderline significance was noted for the association between elevated creatinine ($p=0.051$) and CCI ($p=0.062$) with100% fT > MIC, while no associations were found for sex or lactate. No BMI-based comparisons were made due to missing data in two patients.

In 50% (11/22) of the patients, bacteria were detected in blood cultures, and based on species-specific EUCAST breakpoints, 100% fT > MIC target fulfillment was achieved in all of these cases. Details on patient characteristics, culture results, total measured antibiotic concentrations, and concomitant antibiotics are provided in the Table S1.

4 | Discussion

To our knowledge, this is the first study that has measured antibiotic concentrations repeatedly in the early treatment phase of septic shock. In our observational study of 22 patients, one-quarter exhibited antibiotic concentrations below the target at the third sampling. The majority showed a trend toward decreasing concentrations despite an extra dose, suggesting increased volume of distribution and possibly, in some cases, increased renal elimination. Additionally, one patient exhibited concentrations associated with toxic levels, highlighting the potential risks of excessive β-lactam exposure.

Clinical TDM studies on β-lactam toxicity remain limited, with proposed thresholds largely based on expert opinion rather than robust trials. While continuous infusion maintains prolonged fT > MIC, sustained high concentrations, particularly in patients with impaired renal function, may increase neurotoxicity risk [19]. However, evidence on toxicity thresholds is scarce, underscoring the need for further research to define safe and effective concentration targets.

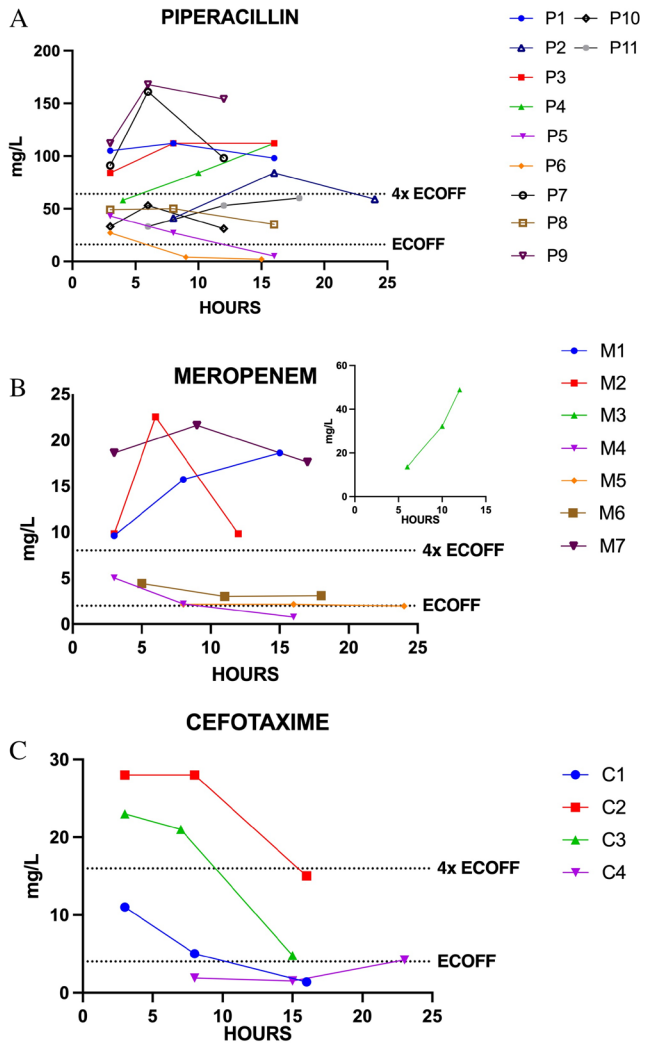

FIGURE 1 | (A) Piperacillin level, free unbound fraction calculated as 70% of total plasma concentration 15. Empirical treatment target; epidemiological cut-off value/ECOFF Pseudomonas: 16 mg/L. First dose of antibiotics given at $T=0$. Sampling of trough values just before the next dose. Two patients did not receive an extra dose (P2, P11). Two patients did not reach the goal of 100%-time above MIC (P5, P6). (B) Meropenem, free unbound fraction calculated as 98% of total plasmaconcentration 15. Empirical treatment target; epidemiological cut-off value/ECOFF P. aerguinosa: 2 mg/L. First dose of antibiotics given at $T=0$. Sampling of trough value just before the next dose. One patient did not receive an extra dose (M5). Two patients did not reach the goal of 100%-time above MIC (M4, M5). One patient with possible toxic concentrations (M3). (C) Cefotaxime, free unbound fraction calculated as 60% of total plasma concentration 15. Empirical treatment target; epidemiological cut-off value/ECOFF: S. aureus: 4 mg/L. First dose of antibiotics given at $T=0$. Sampling of trough value just before the next dose. One patient did not receive an extra dose (C4). Two patients did not reach the goal of 100%-time above MIC (C1, C4).

While pharmacodynamic targets for ß-LA typically range between 40% and 70% $fT>MIC$, based largely on in vitro studies, critically ill patients often exhibit altered drug distribution, elimination, and immune dysregulation, implying the need for higher exposure. Clinical trial data remain sparse, though a few multicenter studies suggest that 100% $fT>MIC$ may improve outcomes over 50% $fT>MIC$ in septic ICU patients [5–7]. Despite these uncertainties, our findings still support optimizing β-lactam dosing strategies in patients with septic shock.

Our findings align with those of other studies on antibiotic concentrations in patients with sepsis and septic shock [5, 20–23]. However, these studies typically measured antibiotic concentrations later in the treatment course, usually from the second day onward. It can be assumed that maintaining high antibiotic concentrations in plasma during the initial phase of septic shock is crucial for rapidly eradicating circulating bacteria and interrupting the inflammatory cascade that drives progressive organ dysfunction. Subsequently, antibacterial activity primarily occurs in the parenchyma and supporting tissues of affected organs. These deeper compartments exhibit different pharmacokinetic properties compared to the bloodstream, which is why plasma trough concentrations may provide an incomplete and potentially misleading picture of the conditions at the infection site outside the bloodstream.

The additional antibiotic dose administered between the first and second regular doses, as recommended in Sweden and received by the majority of our study patients, aims to quickly achieve and maintain sufficiently high plasma concentrations during the critical first day of treatment in sepsis and septic shock.

These findings together highlight the pharmacokinetic variability in critically ill patients and suggest the potential benefit of individualized dosing, including therapeutic drug monitoring. The largest controlled clinical trial to date comparing intermittent versus continuous antibiotic infusion in intensive care patients with sepsis and septic shock did not demonstrate a significant difference in survival between the two groups [24]. That said, a recent meta-analysis that included this study found higher survival rates with longer infusion times compared to intermittent administration. Although the difference in survival was of limited magnitude, it should still be considered clinically meaningful and a step towards improving survival in critical infections [25]. Given the large inter-individual variation in plasma concentrations with intermittent dosing, as demonstrated by our and previous studies, continuous antibiotic infusion should potentially be supported with therapeutic drug monitoring (TDM). Patients with pharmacokinetics resulting in deviant trough concentrations with intermittent administration may, with standard dosing of continuously administered antibiotics, experience constant suboptimal or, in some cases, toxic plasma concentrations, necessitating adjustment of the infusion rate. The clinical significance of this issue remains uncertain, and investigations that evaluate current dosing regimens, as well as prolonged and continuous infusion with regards to antibiotic concentrations in different patient categories, are needed to establish pharmacokinetic targets and to address the practical challenges associated with TDM in clinical settings.

4.1 | Limitations

This was a single-centre observational study with a limited sample size, and inherent variability in adherence to recommended dosing regimens. The limited sample size increases the risk of statistical error and represents a methodological limitation that should be considered when interpreting the findings. Measurement of total concentration and not microbiologically

active free unbound fraction is not optimal but monitoring of free antibiotic fraction is not readily available in most clinical settings. Given the short half-life of ß-LA, even minor deviations in sampling time could have influenced measured concentrations, introducing variability. Although strict adherence to the study protocol minimized this risk, it cannot be entirely eliminated.

5 | Conclusion

In summary, the observed variability in antibiotic concentrations during the very early phase of septic shock underscores the potential risk of inadequate plasma levels with intermittent dosing. While the threshold for underexposure remains uncertain, these findings highlight the need for further research to identify key factors, ranging from pharmacological variability to logistical challenges, that influence antibiotic efficacy and to develop strategies that ensure sufficient antibiotic exposure in this critically ill population.

Author contributions

MB and **CJS** were responsible for the study protocol and study set-up, **CJS** oversaw data collection. **MH**, **MB**, and **CJS** were all involved in data analysis and interpretation, with expert input from **USM** and **DB**. **MH** drafted the manuscript. **MB** and **CJS** were main contributors to the manuscript revision, with substantial input from **USM** and **DB**.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The majority of the data supporting the findings of this study are available in the Supporting Information. Additional data are available from the corresponding author upon reasonable request, in accordance with ethical and privacy regulations.

References

1. A. Rhodes, L. E. Evans, W. Alhazzani, et al., "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016," *Intensive Care Medicine* 43 (2017): 304–377.

2. E. J. Septimus, C. M. Coopersmith, J. Whittle, C. P. Hale, N. O. Fishman, and T. J. Kim, "Sepsis National Hospital Inpatient Quality Measure (SEP-1): Multistakeholder Work Group Recommendations for Appropriate Antibiotics for the Treatment of Sepsis," *Clinical Infectious Diseases* 65 (2017): 1565–1569.

3. W. A. Craig, "Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men," *Clinical Infectious Diseases* 26 (1998): 1–10.

4. R. Williamson and A. Tomasz, "Inhibition of Cell Wall Synthesis and Acylation of the Penicillin Binding Proteins During Prolonged Exposure of Growing *Streptococcus pneumoniae* to Benzylpenicillin," *European Journal of Biochemistry* 151 (1985): 475–483.

5. J. A. Roberts, S. K. Paul, M. Akova, et al., "DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?," *Clinical Infectious Diseases* 58 (2014): 1072–1083.

6. R. Guilhaumou, S. Benaboud, Y. Bennis, et al., "Optimization of the Treatment With Beta-Lactam Antibiotics in Critically Ill Patients-Guidelines From the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique-SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française D'anesthésie et Réanimation-SFAR)," *Critical Care* 23 (2019): 104.

7. M. H. Abdul-Aziz, J. C. Alffenaar, M. Bassetti, et al., "Antimicrobial Therapeutic Drug Monitoring in Critically Ill Adult Patients: A Position Paper," *Intensive Care Medicine* 46, no. 6 (2020): 1127–1153, https://doi.org/10.1007/s00134-020-06050-1.

8. R. P. Veiga and J. A. Paiva, "Pharmacokinetics-Pharmacodynamics Issues Relevant for the Clinical Use of Beta-Lactam Antibiotics in Critically Ill Patients," *Critical Care* 22 (2018): 233.

9. J. A. Roberts and J. Lipman, "Pharmacokinetic Issues for Antibiotics in the Critically Ill Patient," *Critical Care Medicine* 37 (2009): 840–851.

10. M. G. Sinnollareddy, M. S. Roberts, J. Lipman, and J. A. Roberts, "β-Lactam Pharmacokinetics and Pharmacodynamics in Critically Ill Patients and Strategies for Dose Optimization: A Structured Review," *Clinical and Experimental Pharmacology & Physiology* 39 (2012): 489–496.

11. Infektionsläkarförieningen S, "Vårdprogram Sepsis och Septisk Chock," 2022, https://infektion.net/wp-content/uploads/2022/07/vardprogram_sepsis_maj-2023.pdf.

12. C. W. Seymour, V. X. Liu, T. J. Iwashyna, et al., "Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)," *JAMA* 315 (2016): 762–774.

13. I. H. Chen, E. K. Martin, D. P. Nicolau, and J. L. Kuti, "Assessment of Meropenem and Vaborbactam Room Temperature and Refrigerated Stability in Polyvinyl Chloride Bags and Elastomeric Devices," *Clinical Therapeutics* 42 (2020): 606–613.

14. H. Quan, B. Li, C. M. Couris, et al., "Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries," *American Journal of Epidemiology* 173 (2011): 676–682.

15. M. Ulldemolins, J. A. Roberts, J. Rello, D. L. Paterson, and J. Lipman, "The Effects of Hypoalbuminaemia on Optimizing Antibacterial Dosing in Critically Ill Patients," *Clinical Pharmacokinetics* 50 (2011): 99–110.

16. G. Wong, S. Briscoe, S. Adnan, et al., "Protein Binding of Beta-Lactam Antibiotics in Critically Ill Patients: Can We Successfully Predict Unbound Concentrations?," *Antimicrobial Agents and Chemotherapy* 57 (2013): 6165–6170.

17. European Committee on Antimicrobial Susceptibility Testing E, "Clinical Breakpoints—Breakpoints and Guidance," 2021.

18. S. Imani, H. Buscher, D. Marriott, S. Gentili, and I. Sandaradura, "Too Much of a Good Thing: A Retrospective Study of β-Lactam Concentration-Toxicity Relationships," *Journal of Antimicrobial Chemotherapy* 72 (2017): 2891–2897.

19. Y. Zerbib, C. Gaulin, S. Bodeau, et al., "Neurological Burden and Outcomes of Excessive β-Lactam Serum Concentrations of Critically Ill Septic Patients: A Prospective Cohort Study," *Journal of Antimicrobial Chemotherapy* 78 (2023): 2691–2695.

20. R. Pai Mangalore, A. Ashok, S. J. Lee, et al., "Beta-Lactam Antibiotic Therapeutic Drug Monitoring in Critically Ill Patients: A Systematic Review and Meta-Analysis," *Clinical Infectious Diseases* 75 (2022): 1848–1860.

21. A. K. Smekal, M. Furebring, E. Eliasson, and M. Lipcsey, "Low Attainment to PK/PD-Targets for β-Lactams in a Multi-Center Study on the First 72 h of Treatment in ICU Patients," *Scientific Reports* 12 (2022): 21891.

22. N. G. Chua, L. Loo, D. K. H. Hee, et al., "Therapeutic Drug Monitoring of Meropenem and Piperacillin-Tazobactam in the Singapore Critically Ill Population—A Prospective, Multi-Center, Observational Study (BLAST 1)," *Journal of Critical Care* 68 (2022): 107–113, https://doi.org/10.1016/j.jcrc.2021.12.013.

23. F. S. Taccone, P. F. Laterre, T. Dugernier, et al., "Insufficient β-Lactam Concentrations in the Early Phase of Severe Sepsis and Septic Shock," *Critical Care* 14 (2010): R126.

24. J. M. Dulhunty, S. J. Brett, J. J. De Waele, et al., "Continuous vs. Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis: The BLING III Randomized Clinical Trial," *JAMA* 332 (2024): 629–637.

25. M. H. Abdul-Aziz, N. E. Hammond, S. J. Brett, et al., "Prolonged vs. Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock: A Systematic Review and Meta-Analysis," *JAMA* 332 (2024): 638–648.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.