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Title

A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

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J.M.D. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.L., J.M.D., J.A.R., J.S.D., S.A.R.W., R.B., C.G., C.S., G.M.E., J.M. and D.L.P. designed the study. J.L., S.A.R.W., J.A.R., J.M.D., J.S.D., R.B., D.L.P., J.M., C.S. and G.M.E. obtained funding. T.S. project managed the study. S.K.P. was the Principal Study Statistician. Statistical analysis was performed by S.K.P. and J.M.D. Microbiological review was performed by J.S.D. and S.A.R.W. J.M.D., J.A.R. and

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J.L. drafted the initial manuscript. All authors critically revised the manuscript for important intellectual content and read and approved the final version.

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Running title

Continuous versus Intermittent β-Lactam Infusion

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At a Glance Commentary

Scientific Knowledge on the Subject

β-lactam antibiotics are largely administered by intermittent dosing, despite time-dependent antibacterial activity and evidence from animal and *in vitro* studies that continuous infusion improves bacterial killing. Meta-analyses of the prospective randomized human trials conducted to date have not demonstrated that continuous infusion is superior to intermittent administration. These trials, however, have been underpowered and primarily conducted in non-critically ill patients with non-equivalent dosing between treatment arms.

What this Study Adds to the Field

Our results do not identify an outcome difference to favor one method of administration of β-lactam antibiotics over the other in a heterogeneous critical care patient population. Whether there is a mortality benefit in favour of continuous infusion requires evidence from a large Phase III multicentre randomised controlled trial.

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Abstract

Rationale: Continuous infusion of β-lactam antibiotics may improve outcomes due to time-dependent antibacterial activity compared to intermittent dosing.

Objectives: To evaluate the efficacy of continuous versus intermittent infusion in patients with severe sepsis.

Methods: We conducted a randomized controlled trial in 25 intensive care units (ICUs). Participants commenced on piperacillin-tazobactam, ticarcillin-clavulanate or meropenem were randomized to receive the prescribed antibiotic via continuous or 30-minute intermittent infusion for the remainder of the treatment course or until ICU discharge. The primary outcome was the number of alive ICU-free days at day 28. Secondary outcomes were 90-day survival, clinical cure 14 days post antibiotic cessation, alive organ failure-free days at day 14 and duration of bacteremia.

Measurements and Main Results: We enrolled 432 eligible participants with a median age of 64 years and an Acute Physiology and Chronic Health Evaluation II score of 20. There was no difference in ICU-free days: 18 days (IQR: 2–24) and 20 days (IQR 3–24) in the continuous and intermittent groups ($P = 0.38$). There was no difference in 90-day survival: 74.3% (156/210) and 72.5% (158/218); HR 0.91 (95% CI 0.63–1.31, $P = 0.61$). Clinical cure was 52.4% (111/212) and 49.5% (109/220); OR 1.12 (95% CI 0.77–1.63, $P = 0.56$). There was no difference in organ-failure free days (6 days, $P = 0.27$) and duration of bacteremia (0 days, $P = 0.24$).

Conclusions: In critically ill patients with severe sepsis, there was no difference in outcomes between β-lactam antibiotic administration by continuous and intermittent infusion.

Australian New Zealand Clinical Trials Registry number, ACTRN12612000138886.

Keywords: antibiotic, clinical outcome, intensive care, pharmacodynamics, pharmacokinetics

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Introduction

β-lactam antibiotics are used to treat life-threatening infections in critically ill patients with severe sepsis.[1,2] Bacterial killing by β-lactam antibiotics depends on the duration of time that bacteria are exposed to a concentration that exceeds the minimum inhibitory concentration (MIC) and is maximized at four times the MIC, particularly for Gram negative pathogens.[3-5] Standard practice in patients with life-threatening infections is intermittent dosing via administration as a bolus or short infusion,[1,6] although other methods of dosing delivery, such as continuous and extended infusions, are used in some regions.[7]

Continuous infusion is an alternative to intermittent dosing that may result in improved outcomes. Pharmacokinetic studies in both non-critically ill and critically ill patients have demonstrated that administration of β-lactam antibiotics by continuous infusion results in consistent attainment of drug exposures associated with maximal antibacterial effects.[6,8-12] Continuous infusion results in superior clinical outcomes compared with intermittent administration in *in vitro* and animal models and non-randomized studies.[3-5,13-16] Some prospective randomized human studies have also demonstrated clinical outcome advantages of continuous infusion,[17,18] although meta-analyses have not demonstrated significant associations between continuous and intermittent infusion on survival or rates of clinical cure.[19-21]

We hypothesized that the attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets by use of continuous infusion would result in improved clinical outcomes compared to intermittent infusion in patients with severe sepsis. The aim of the β-Lactam Infusion Group (BLING) II study, was to determine if there was a difference between continuous and intermittent β-lactam antibiotic infusion in patients with severe sepsis in alive ICU-free days.

Methods

Study design

The BLING II study was a prospective, multicenter, double-blind, double-dummy, randomized controlled trial that was conducted in 25 ICUs in Australia (17), New Zealand (7) and Hong Kong (1). The Royal Brisbane and Women's Hospital Human Research Ethics Committee provided lead site ethics approval for the trial (HREC/12/QRBW/26) with jurisdictional ethics committee and institutional approval obtained by other sites according to local requirements.

Participants

Adult patients meeting criteria for severe sepsis and commenced on piperacillin-tazobactam, ticarcillin-clavulanate or meropenem by the treating doctor were eligible for inclusion. Patients who had received the prescribed β-lactam antibiotic for more than 24 hours prior to randomization, were less than 18 years of age, were pregnant or had an allergy or potential allergy to study medications were excluded. A full list of entry and exclusion criteria is provided in the online data supplement (eTable 1 and eTable 2). Written consent prior to enrolment or, in permitted instances, delayed participant or legal surrogate written consent following enrolment was obtained. The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system was used to measure severity of illness and immunosuppression at ICU admission.[22]

Randomization and masking

Participants were randomized to receive the β-lactam antibiotic by either continuous infusion or intermittent infusion over 30-minutes, in addition to an infusion of 0.9% sodium chloride administered as a double-dummy placebo.[23] Permuted block randomization stratified by site

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allocated participants into treatment groups in a 1:1 ratio. The QIMR Berghofer Medical Research Institute generated the random allocation sequence, managed the trial database and conducted the data analysis according to a pre-specified statistical analysis plan with independent validation.[23] An unblinded staff member at each site used a consecutively labeled sealed opaque envelope to determine treatment allocation prior to study drug preparation. Concealment was achieved by opaque labeling and double-dummy administration with adequacy of blinding reported previously.[18] Participants, treating clinicians and study investigators undertaking study assessments or data collection were masked to treatment allocation.

Procedures

The Burns, Trauma and Critical Care Research Centre provided trial coordination. The George Institute for Global Health contributed to aspects of project development and management and conducted site monitoring. Study drugs were compounded on site, apart from 5 sites in New South Wales, Australia, for which study drug was prepared and delivered by Baxter Healthcare Pty Ltd following on-site compounding on day 1 (see eTable 3 for study drug concentrations). All participants received a loading dose prior to commencement of the blinded study drug infusion.[23] Study medications were administered via an infusion pump and a primed central venous line using a burette and infusion bag for intermittent and continuous infusions, respectively. Study drug administration was continued for the treatment course or until ICU discharge, whichever occurred first. A change between the three β-lactam study antibiotics and to blinded administration of flucloxacillin was permitted within 14 days of randomization. In participants where the study drug was changed, blinded administration was continued as per the allocated treatment arm following administration of one open-label

intermittent infusion as a loading dose. The total 24-hour dose was the same, regardless of group, and determined by the treating doctor.

The likely causative pathogen was identified by blood culture taken by venipuncture prior to commencement of the β-lactam antibiotic. Daily blood cultures were repeated until there was no growth of the initial pathogen 48 hours after collection. Reported microbiological details were independently reviewed by two investigators blinded to allocation status; organism susceptibility and clinical significance were clarified with site personnel where required. Organisms judged to be probable contaminants were excluded from the analysis.

Outcome

The primary outcome was alive ICU-free days determined at day 28 after randomization. Secondary outcome measures were day 90 mortality, clinical cure assessed at day 14 post antibiotic cessation (see eTable 4 in the online data supplement), alive organ failure-free days at day 14 and duration of bacteremia post randomisation.[23]

The investigators recorded all adverse events during the period of study treatment and assessed causality with study treatment using 1 of 4 categories: “almost certainly”, “probably”, “possibly” or “unlikely”. All deaths that occurred from the time of randomization to 48 hours post cessation of study treatment, or where causality with study treatment was suspected regardless of the timing of the event, were reported as serious adverse events.

Statistical analysis

Based on a previous trial conducted by our group,[18] we determined that a sample size of 210 in each group was required to achieve 90% power to detect a difference of 3 days in the

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primary outcome with an alpha of 0.05, i.e. 17 vs. 14 alive ICU-free days with a standard deviation of 9 days in both groups and non-parametric adjustment for a Mann-Whitney U test. The efficacy and safety analyses were based on the intention-to-treat principle. Participants who did not meet eligibility criteria or who did not provide consent for use of their data were excluded. A modified intention-to-treat analysis was conducted in all eligible participants who received study drug. An *a priori* per protocol analysis was conducted in eligible participants who received 3 or more days of blinded study drug.[23]

Basic characteristics of study participants were presented using number (%) and median (inter-quartile range [IQR]), as appropriate. The primary outcome measure of alive ICU-free days from the day of randomization to day 28 was compared between treatment groups using a Mann-Whitney U test. Survival at 90 days was compared between treatment groups using a log rank test with the hazard ratio (HR) and 95% confidence interval (CI) reported. Proportional differences in survival at ICU discharge, hospital discharge and day 90 were compared between treatment groups using a Pearson chi-square test. The likelihood of clinical cure in the continuous group compared to the intermittent group was evaluated using an odds ratio (OR) and 95% CI based on logistic regression. The median alive organ failure-free days to day 14 and duration of bacteremia in participants with a positive blood culture were compared by a Mann-Whitney U test. A two-sided p-value < 0.05 was considered evidence of a significant difference in the study outcomes. Statistical analysis was conducted using SAS software Version 9.3 (SAS Institute Inc., Cary, NC). PASS 2008 (NCSS, LLC, Kaysville, UT) was used for sample size calculations.

A data and safety monitoring committee undertook a mid-point safety analysis. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12612000138886.

Results

Screening and enrolment occurred from July 2, 2012, to April 10, 2014, with 90-day follow-up concluding on July 8, 2014. We randomized 432 eligible participants, of whom 422 received the study drug (Figure 1 and eTable 5 in the online data supplement). The baseline characteristics of the continuous and intermittent groups are reported in Table 1. A pathogen was isolated from blood in 83 participants (Table 2). There were 55 participants (25.9%) in the continuous group and 59 participants (26.8%) in the intermittent group who received continuous or intermittent renal replacement therapy during ICU admission.

Participants received a median of 13 hours (IQR: 4.3-22 hours) and 12 hours (IQR: 4.5-20 hours) open label treatment prior to commencement of blinded study in the continuous and intermittent groups, respectively. The median duration of blinded study drug treatment was 3.2 days (IQR 1.9–6.0) in the continuous group and 3.7 days (IQR 1.9–5.9) in the intermittent group. Total treatment course for the β-lactam antibiotic was 5.3 days (IQR: 2.9–7.7) in the continuous group and 5.0 days (IQR 3.1–8.0) in the intermittent group. There was a change in blinded study drug for 20 participants in the continuous group (9.4%) and 26 participants in the intermittent group (11.8%), primarily to meropenem (15 participants in the continuous group and 20 participants in the intervention group). The median 24-hour dose on day 1 was 13.5 g (IQR: 13.5–13.5 g) for piperacillin-tazobactam, 3.0 g (IQR 2.0–3.0 g) for meropenem and 12.4 g for ticarcillin-clavulanate (all 5 participants) in both groups. There was no difference in median dosing for participants who received renal replacement therapy.

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Concomitant antibiotic therapy for the continuous and intermittent groups was as follows: 77 (36.3%) and 69 (31.4%) for glycopeptide use, 42 (19.8%) and 51 (23.2%) for macrolide use, 27 (12.7%) and 32 (14.5%) for nitroimidazole use, 24 (11.3%) and 33 (15.0%) for aminoglycoside use and 20 (9.4%) and 30 (13.6%) for quinolone use, respectively.

Primary and secondary outcomes in the intention-to-treat population are reported in Table 3. At 28 days, there was no difference in the primary outcome measure of alive ICU-free days: 18 days (IQR 2–24) in the continuous group and 20 days (IQR 3–24) in the intermittent group ($P = 0.38$). At 90 days, there was no difference in survival between participants in the continuous and intermittent groups; HR 0.91 (95% CI 0.63–1.31, $P = 0.61$) (Figure 2). There was no difference in clinical cure assessed 14 days after antibiotic cessation in the continuous group compared with the intermittent group: OR 1.12 (95% CI 0.77–1.63, $P = 0.56$). Alive organ-failure free days at day 14 did not differ between treatment groups (Table 3). Only seven participants in the continuous group and 4 participants in the intermittent group had bacteremia that continued for more than 24 hours after randomization (see eTable 9 in the online data supplement). In participants with an identified pathogenic organism, there was no difference in the duration of bacteremia between groups (Table 3).

Primary and secondary outcomes in the modified intention-to-treat and per protocol populations are reported in the online data supplement (see eTable 10 and eTable 11). Survival in the continuous group compared to the intermittent group remained non-significantly different in the modified intention-to-treat population (Figure 3).

There were a total of 49 adverse events (11.3%) in 48 participants, 44 (10.2%) of which were deaths that occurred during receipt of the study drug or within 48 hours of cessation (Table 3).

All deaths were assessed as unlikely to be related to the study treatment. There were 3 non-serious adverse events attributed to the study drug (2 "possibly" and 1 "probably"): 3 adverse events occurred in the intermittent group, hypernatremia (2) and elevated bilirubin and alanine transaminase (1), and 1 adverse event, rash, in the continuous group. A second adverse event unlikely related to the study drug (pneumothorax) was reported in 1 participant in the intermittent group. There was no significant group difference in the number of participants with an adverse event (Table 3).

Discussion

In this multicenter, blinded, randomized trial with dosing independent of treatment arm, we found no difference between treatment groups in a range of outcomes including alive ICU-free days at day 28, 90-day survival, clinical cure, organ-failure free days at day 14 and duration of bacteremia. Although participants in the continuous group had a longer ICU stay of 1 day compared with the intermittent group, we found that this was not attributable to the duration of study treatment, which was equivalent in both groups. In addition, this difference could not be explained by pre-randomization factors with baseline balance for the type and severity of illness.

Compared to our earlier randomized trial,[18] we found a lower proportion of clinical cure (i.e. 52% vs. 77% in the continuous group), higher ICU and hospital mortality (i.e. a 8.4% and 10.8% absolute difference in the continuous group, respectively) and more conservative clinical outcome differences than previously observed. These differences may, in part, be attributable to the inclusion of patients on renal replacement therapy (i.e. 26% and 0) and shorter duration of blinded treatment (i.e. 3 days and 5 days in the continuous group) in the current trial compared with the earlier trial, respectively. The effect of including participants

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on renal replacement may reduce the between group difference because plasma antibiotic concentrations may be less likely to be sub-therapeutic with intermittent dosing than in patients not on renal replacement.[6,24] In addition, the lower rates of clinical cure in this study may have been impacted by use of pre-specified criteria for clinical resolution when clinician opinion was not available (see eTable 4 in the online data supplement).

Survival as measured at ICU discharge, hospital discharge and day 90 was not significantly different between groups. We observed hospital mortality to be 25.1% in the intermittent group, with an absolute difference of 4.3% in favor of the continuous group ($P = 0.28$). Our results are most comparable to those of Chytra et al. who, in a trial of 240 participants with 23.3% hospital mortality in the intermittent group, found a non-significant 5.8% mortality difference ($P = 0.34$) in critically ill participants randomized to receive meropenem by continuous infusion compared with intermittent infusion.[25] Previous meta-analyses by Roberts et al.[20] and Shui et al.[21], found no significant cumulative mortality difference between groups (i.e. 0.1%, $P = 1.0$, and 1.4%, $P = 0.42$), respectively, with mortality of 9.9–13.1% in the intermittent group. In contrast, Falagas et al. in their meta-analysis of observational and randomized controlled trials comparing continuous with intermittent infusion of carbapenems and piperacillin-tazobactam found a significant 4.9% absolute mortality difference with use continuous infusion ($P = 0.04$) and mortality of 8.8% in the continuous group.[16] The lower mortality rates observed in these meta-analyses are due to the fact that previous studies have largely been conducted in non-critically ill patient groups.

Critically ill patients with severe sepsis undergo pathophysiological changes,[26] that may result in markedly different antibiotic concentrations throughout the dosing interval than is commonly observed in non-critically ill patients.[9,26] In addition, the theoretical advantage of

continuous infusion is crucially dependent on the MIC of the antibiotic. When the MIC is elevated, as is commonly the case in ICUs,[27] then continuous infusion is more likely to achieve effective concentrations and potential clinical outcome advantages.[14,15,28] While MICs were not measured and only 19% of participants had an identified pathogen in our study, the most common organisms identified, *Escherichia coli* and *Klebsiella pneumoniae*, have a low prevalence of resistance (0–4.5%) to the study antibiotics in Australia.[29] Where the MIC is low, intermittent infusions will still achieve appropriate PK/PD targets, even in the presence of ICU-associated pathophysiological disturbances.[30]

There are a number of limitations of this study. This pragmatic trial commenced randomized treatment after a maximum period of 24 hours and this fact, combined with cessation of randomized treatment at ICU discharge, may have resulted in an underestimate of treatment effect. However, discharge from ICU would suggest clinical response and resolution of the acute phase of infection. The inclusion of participants with potential non-infectious diagnoses, non-susceptible infections and recipients of renal replacement therapy may disguise the potential advantages of continuous infusion for patients with normal renal function and susceptible infections. In addition, low and supra-normal renal clearance may have acted as confounders, although the use of renal replacement therapy was essentially the same in both treatment arms. Pathogenic organisms were identified in only 19% of participants, decreasing the ability to estimate susceptibility to study drug and suitability of dosing, e.g. higher piperacillin-tazobactam dosing in severe pseudomonal infection. We also did not report on post-ICU treatment, apart from the total duration of study drug treatment, subsequent hospital-acquired infections or the cause of death. Finally, this study was not powered to detect changes in mortality but provides useful information for power estimates for a definitive phase III trial.

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In summary, in a heterogeneous critical care patient population, there was no difference in alive ICU free days at day 28 with continuous compared to intermittent infusion of three common β-lactam antibiotics. Given our observations, definitive confirmation or rejection of a similar potential mortality effect would require a very large multicenter randomized controlled trial. We conclude that further research is required to identify specific ICU sub-populations that may have benefit from continuous infusion of β-lactam antibiotics, while in a heterogeneous population continuous and intermittent infusions appear to have equivalent outcomes.

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Figure legends

Figure 1. Trial profile

Figure 2. Kaplan-Meier plot for intention-to-treat population

Figure 3. Kaplan-Meier plot for modified intention-to-treat population

Table 1. Baseline characteristics of the intention-to-treat population

	Continuous (n = 212)	Intermittent (n = 220)
Age (years)	64 (54–72)	65 (53–72)
Sex (men)	130 (61.3)	135 (61.4)
APACHE II score	21 (17–26)	20 (16–25)
Immunocompromise	27 (12.7)	34 (15.5)
Study drug		
Piperacillin-tazobactam	147 (69.3)	157 (71.4)
Meropenem	63 (29.7)	60 (27.3)
Ticarcillin-clavulanate	2 (0.9)	3 (1.4)
Site of infection*		
Lung	115 (54.2)	120 (54.5)
Intra-abdominal	53 (25.0)	57 (25.9)
Primary blood stream infection	17 (8.0)	18 (8.2)
Urinary tract	16 (7.5)	18 (8.2)
Skin or skin structure	13 (6.1)	18 (8.2)
Other†	22 (10.4)	12 (5.5)
Unknown	14 (6.6)	14 (6.4)
Organ dysfunction		
Cardiovascular (shock)	154 (72.6)	163 (74.1)
Respiratory	135 (63.7)	139 (63.2)
Metabolic acidosis	68 (32.1)	70 (31.8)
Renal	49 (23.1)	53 (24.1)

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Hematologic	26 (12.3)	22 (10.0)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation.

Results are presented as median (interquartile range) or number (percentage).

*Multiple sites of infection in 30 participants in the continuous group (23 with 2 sites of infection, 6 with 3 sites of infection and 1 with 4 sites of infection [lung, blood, intra-abdominal and skin]) and 29 participants in the intermittent group (23 with 2 sites of infection and 6 with 3 sites of infection). The most common double sites of infection were lung and intra-abdominal (12), lung and blood (7) and lung and urinary tract (6). The most common triple sites of infection were lung, blood and intra-abdominal (4).

†See eTable 6 in the online data supplement.

Table 2. Microbiological characteristics

	Continuous (n = 40)	Intermittent (n = 43)
Gram positive	11 (27.5)	11 (25.6)
Gram negative	29 (72.5)	31 (72.1)
Susceptible to study drug*	39 (97.5)	37 (86.0)
Non-susceptible to study drug†	1 (2.5)	6 (14.0)

Results are presented as number (percentage) of participants with a pathogenic organism identified on blood culture. Multiple pathogens identified in 4 participants in the continuous group and 2 participants in the intermittent group.

*See eTable 7 in the online data supplement.

†See eTable 8 in the online data supplement.

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Table 3. Primary and secondary outcomes, clinical results and adverse events

	Continuous (n = 212)	Intermittent (n = 220)	*P* Value
Alive ICU-free days	18 (2–24)	20 (3–24)	0.38
ICU survivors	21 (12–24)	22 (14–25)	0.12
Day-90 survival*†	156 (74.3)	158 (72.5)	0.67
ICU survival†	180 (84.9)	182 (82.7)	0.54
Hospital survival†‡	168 (79.2)	164 (74.9)	0.28
Clinical cure	111 (52.4)	109 (49.5)	0.56
Organ failure-free days	6 (0–10)	6 (0–11)	0.27
Duration of bacteremia (days)§	0 (0–0)	0 (0–1)	0.24
ICU length of stay (days)‖	7 (3–13)	6 (3–11)	0.042
Hospital length of stay (days)‖	16 (8–32)	14 (8–27)	0.25
Adverse events	20 (9.4)	28 (12.7)	0.28
Serious adverse events	19 (9.0)	25 (11.4)	0.41

Definition of abbreviations: ICU = intensive care unit.

Results are presented as median (interquartile range) or number (percentage).

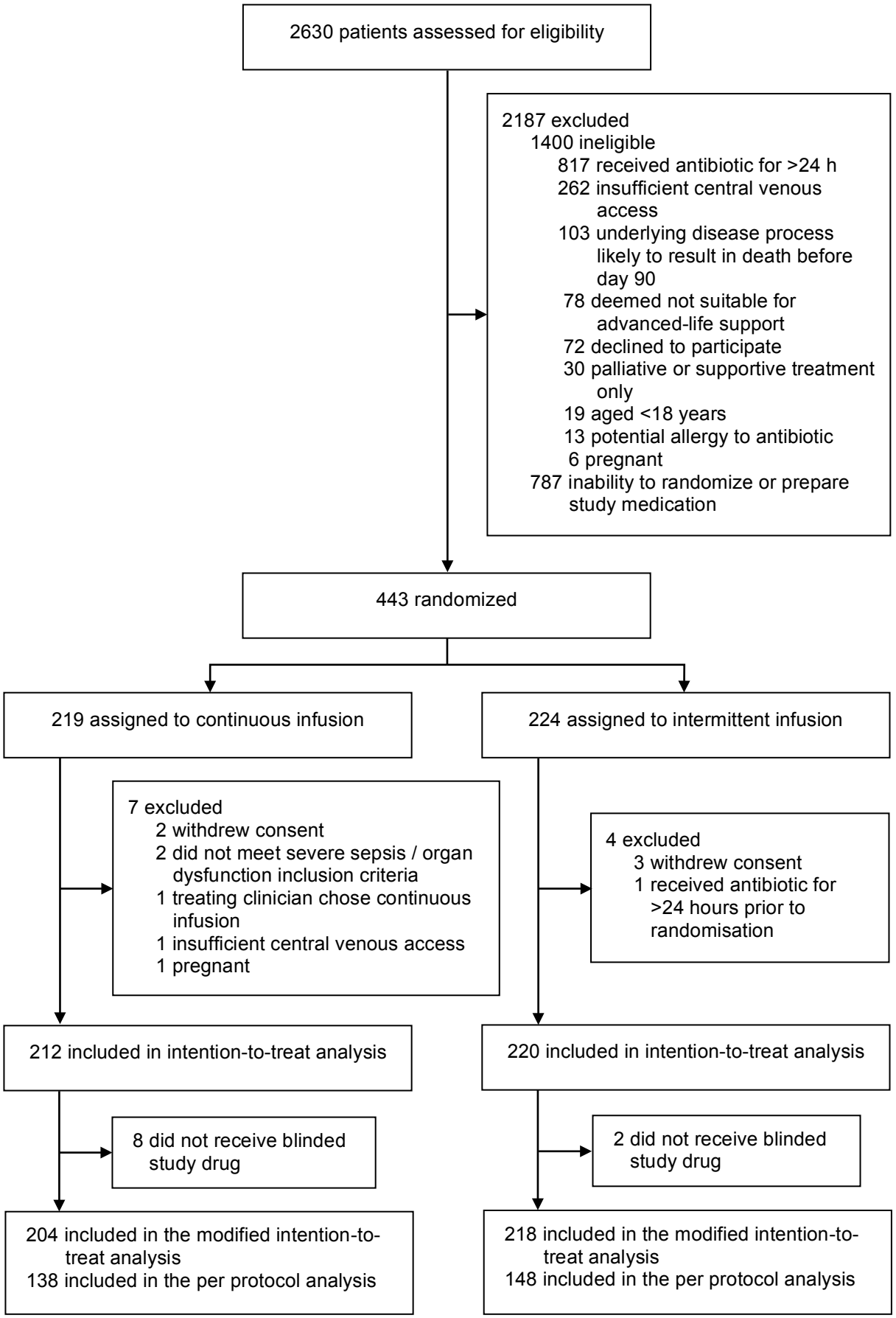
*Missing data for 2 participants in continuous group (lost to follow-up) and 2 participants in intermittent group (withdrawal [1] and lost to follow-up [1]).

†*P* value refers to Pearson chi-square test.

‡One participant in the continuous group was censored as alive in hospital at day 90 due to database lock; missing data for 1 participant in the intermittent group (lost to follow-up post inter-hospital transfer).

§Assessed in 40 participants in the continuous group and 43 participants in the intermittent group with a pathogenic organism identified on blood culture.

‖Post-randomization.



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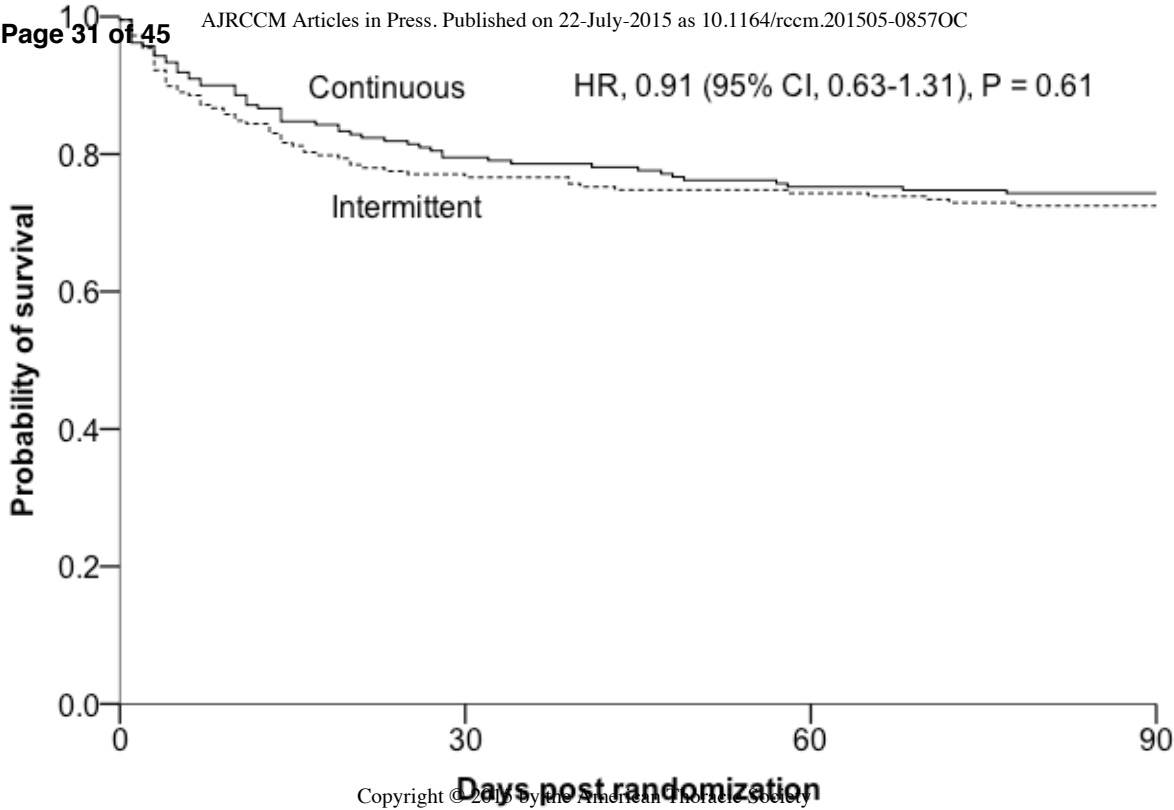

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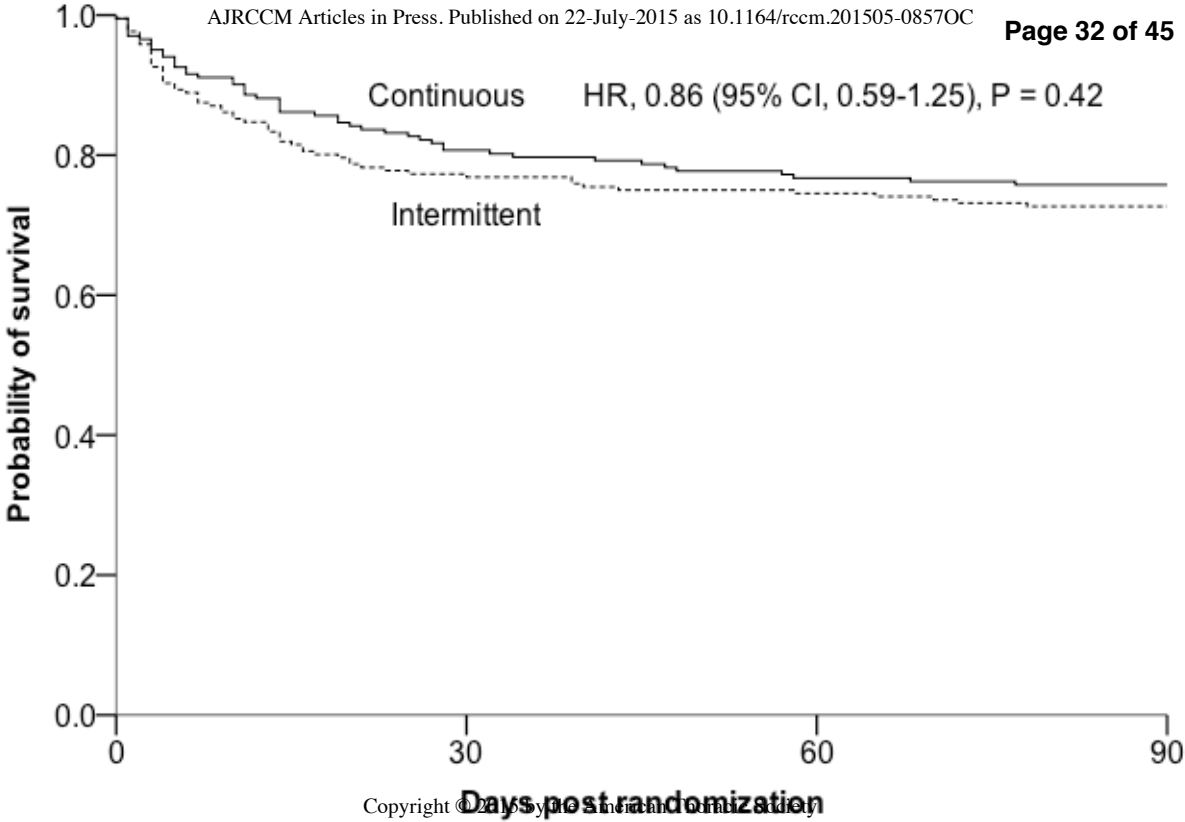

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Online Data Supplement

Title: A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

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eTable 1. Inclusion criteria

Inclusion criteria
1. Severe sepsis: confirmed or suspected infection meeting one or more of the following organ dysfunction entry criteria in the previous 24 hours: • Cardiovascular (shock): arterial SBP ≤ 90 mmHg or MAP ≤ 70 mmHg for ≥ 1 hour, despite adequate fluid resuscitation or adequate intravascular volume status and/or need for vasopressors,[1] to achieve a SBP or MAP target (specified by the treating doctor) for > 1 hour. • Renal: acute kidney injury with serum creatinine > 1.5 times the hospital admission creatinine, or urine output < 0.5 ml/kg/hour for 6 hours (excluding loss of kidney function or end-stage kidney disease).[2] • Respiratory: PaO_2/FiO_2 ≤ 200. • Hematologic: platelet count < 80 x 10^9/L or > 50% decrease in platelet count from highest recorded value within preceding 3 days. • Metabolic acidosis: pH < 7.30, base deficit > 5.0 mmol/L or a venous or arterial plasma lactate level > 1.5 times the upper limit of normal for the reporting laboratory.
2. Piperacillin-tazobactam, ticarcillin-clavulanate or meropenem used to treat the infectious episode.
3. Treating doctor is uncertain if administration of chosen antibiotic by intermittent or continuous infusion is superior.
4. At assessment of eligibility, treating doctor expects patient to need treatment in ICU beyond the next calendar day.

Definition of abbreviations: ICU=intensive care unit; MAP=mean arterial pressure; SBP=systolic blood pressure.

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eTable 2. Exclusion criteria

Exclusion criteria
1. Receipt of potential study medication for > 24 hours before randomization.
2. Age < 18 years.
3. Allergy or potential allergy to the study medications.
4. Pregnancy.
5. No central venous catheter access with three or more lumens.
6. Receiving palliative or supportive treatment only at the time of assessment for eligibility.
7. Treating doctor not committed to provision of advanced life-support, including any of mechanical ventilation, dialysis and vasopressor administration for at least the next 48 hours.
8. Death is deemed imminent and inevitable.
9. Patient has an underlying process that is likely to result in death before 90 days of follow-up.
10. Consent not gained for study participation and entry under a waiver-of-consent not approved by the jurisdictional human research ethics committee.

eTable 3. Concentration of compounded study drugs

Study drug	Continuous (Infusion bag)	Intermittent (Syringe)*
Meropenem	1 g / 100 ml = 0.01 g/ml	1 g / 20 ml = 0.05 g/ml
Piperacillin-tazobactam	13.5 g / 250 ml = 0.05 g/ml	4.5 g / 20 ml = 0.23 g/ml
Ticarcillin-clavulanate	12.4 g / 250 ml = 0.05 g/ml	3.1 g / 20 ml = 0.16 g/ml

Reported concentrations are based on median doses administered. *Concentrations for study drugs prepared by Baxter Healthcare Pty Ltd were lower due to use of 50 ml syringes.

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eTable 4. Definition of clinical cure at test of cure date

Scoring criteria

Clinical response was assessed by a clinician 14 days post cessation of the β-lactam antibiotic as follows:

- Resolution: disappearance of all signs and symptoms related to the infection.
- Improvement: marked or moderate reduction in the severity and/or number of signs and symptoms of infection.
- Failure: insufficient reduction of the signs and symptoms of infection to qualify as improvement, including death or indeterminate (no evaluation possible, for any reason).

Participants discharged from hospital within 14 days following cessation of the β-lactam antibiotic were assessed for clinical response on the day of discharge.

For participants who continued on the β-lactam antibiotic after 14 days of blinded treatment, test of cure was assessed 14 days from the last day of blinded treatment.

For participants where the clinician was unable to assess clinical response on the test of cure date, clinical response was evaluated by review of the patient record on the test of cure date (midnight to midnight) as follows:

- Resolution: absence of any SIRS criteria attributable to infection.
- Improvement: only 1 SIRS criterion, at any time point, that was attributable to infection.
- Failure: 2 or more SIRS criteria met concurrently and attributable to infection.

SIRS criteria are as follows:

- Temperature > 38°C or < 36°C.
- Heart rate > 90 beats per minute.
- Respiratory rate > 20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) < 32 mm Hg.
- White blood cell count < 4 x 10^9 cells/L or > 12 x 10^9 cells/L; or the presence of > 10% immature neutrophils (band forms).[3]

For participants with a separate episode of infection (e.g. an alternate organism or site of infection) on the test of cure date, clinical response was rated for any day (midnight to midnight) in the preceding 7 days (i.e. 7-14 days following β-lactam antibiotic cessation). The best clinical response during this period was recorded.

Clinical cure was defined as:

- Resolution: disappearance of all signs and symptoms related to the infection, or
- Resolution: absence of any SIRS criteria attributable to infection.

Definition of abbreviations: SIRS = Systemic Inflammatory Response Syndrome.

eTable 5. Study numbers by site

Site	Eligible participants (%)
Austin Hospital	49 (11.3)
Royal Brisbane and Women's Hospital	45 (10.4)
Wellington Hospital	39 (9.0)
Auckland City Hospital (Cardiothoracic and Vascular ICU)	34 (7.9)
Blacktown Hospital	28 (6.5)
Westmead Hospital	26 (6.0)
Christchurch Hospital	25 (5.8)
Flinders Medical Centre	20 (4.6)
Royal Hobart Hospital	20 (4.6)
Geelong Hospital	18 (4.2)
Lyell McEwin Hospital	18 (4.2)
St George Hospital	18 (4.2)
Bendigo Hospital	14 (3.2)
Hawkes Bay Hospital	13 (3.0)
Toowoomba Hospital	11 (2.5)
Middlemore Hospital	10 (2.3)
Redcliffe Hospital	9 (2.1)
Auckland City Hospital (Department of Intensive Care Medicine)	8 (1.9)
Canberra Hospital	8 (1.9)
Gosford Hospital	8 (1.9)
St Vincent's Hospital	5 (1.2)
QEII Jubilee Hospital	2 (0.5)
Sir Charles Gairdner Hospital	2 (0.5)
Prince of Wales Hospital	1 (0.2)
Waikato Hospital	1 (0.2)

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eTable 6. Other sites of infection

Site	Continuous (n = 212)	Intermittent (n = 220)
Head/ears/eyes/nose/throat	2 (0.9)	4 (1.8)
Central nervous system	4 (1.9)	1 (0.5)
Indwelling vascular catheter	4 (1.9)	1 (0.5)
Pleural	2 (0.9)	3 (1.4)
Bone/joint	4 (1.9)	0
Cardiac	3 (1.4)	1 (0.5)
Gynecologic	1 (0.5)	0
Various*	2 (9.4)	2 (0.9)

*Continuous group: anastomotic leak from esophagectomy (1) and gastroenteritis (1). Intermittent group: non-specified colorectal infection (1) and infected abdominal aortic aneurysm graft (1).

eTable 7. Susceptible organisms

Organism	Continuous (n = 39)*	Intermittent (n = 37)*
Escherichia coli†	15	11
Klebsiella pneumoniae	8	3
Staphylococcus aureus (methicillin-sensitive)	5	3
Enterococcus faecalis	2	2
Enterobacter cloacae†	2	2
Streptococcus pneumoniae	2	1
Streptococcus pyogenes	1	2
Enterobacter aerogenes	0	2
Klebsiella oxytoca	0	2
Klebsiella unspecified sp.	1	1
Pseudomonas aeroginosa	0	2
Pseudomonas putida	0	2
Serratia marcescens	1	1
Streptococcus anginosus	0	2
Acinetobacter baumannii	0	1
Acinetobacter unspecified sp.	1	0
Citrobacter koseri	1	0
Dialister pneumosintes	1	0
Granulicatella adiacens	0	1
Haemophilus influenzae	1	0
Streptococcus constellatus	1	0
Streptococcus dysgalactiae	1	0
Streptococcus mitis/oralis	1	0
Raoultella planticola	0	1

*Continuous group: multiple pathogenic organisms identified in 4 participants. Presumed contaminants (excluded): *Staphylococcus capitis* (1), *Staphylococcus epidermidis* (1), *Staphylococcus haemolyticus* (1). Intermittent group: multiple pathogenic organisms identified in 2 participants. Presumed contaminants (excluded): *Staphylococcus capitis* (1).

†Continuous group: extended-spectrum β-lactamase-producing *E. coli* (1). Intermittent group: extended-spectrum β-lactamase-producing *E. cloacae* (1).

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eTable 8. Non-susceptible organisms

Organism	Continuous (n = 1)	Intermittent (n = 6)
Enterobacter cloacae	0	2
Acinetobacter baumannii	1	0
Candida glabrata	0	1
Morganella morganii	0	1
Serratia marcescens	0	1
Staphylococcus aureus (methicillin-resistant)	0	1

eTable 9. Duration of bacteremia from time of randomization

Days	Continuous (n = 40)	Intermittent (n = 43)
0	33 (82.5)	39 (90.7)
1	3 (7.5)	3 (7.0)
2	1 (2.5)	1 (2.3)*
3	2 (5.0)	0
4	1 (2.5)	0

*Organism non-susceptible to study drug.

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eTable 10. Outcomes in the modified intention-to-treat population

Outcome	Continuous (n = 204)	Intermittent (n = 218)	*P* Value
Alive ICU-free days	19 (3–24)	20 (4–24)	0.47
Day-90 survival*†	153 (75.7)	157 (72.7)	0.48
Clinical cure‡	110 (53.9)	108 (49.5)	0.37
Organ failure-free days	6 (0–10)	6 (0–11)	0.44
Duration of bacteremia	0 (0–0)	0 (0–0)	0.19

Definition of abbreviations: ICU = intensive care unit.

Results are presented as median (interquartile range) or number (percentage).

*Missing data for 2 participants in the continuous group (lost to follow-up) and 2 participants in the intermittent group (withdrawal [1] and lost to follow-up [1]). *P* value refers to Pearson chi-square test.

†Hazard Ratio 0.86 (95% Confidence Interval 0.59–1.25, *P* = 0.42) using a log rank test.

‡Odds Ratio 1.19 (95% Confidence Interval 0.81–1.75) using logistic regression.

eTable 11. Outcomes in the per protocol population

Outcome	Continuous (n = 138)	Intermittent (n = 148)	*P* Value
Alive ICU-free days	18 (3–23)	18 (4–23)	0.84
Day-90 survival*†	109 (79.6)	106 (72.6)	0.17
Clinical cure‡	76 (55.1)	76 (51.4)	0.53
Organ failure-free days	5 (0–9)	5 (0–10)	0.57
Duration of bacteremia	0 (0–1)	0 (0–0)	0.14

Definition of abbreviations: ICU = intensive care unit.

Results are presented as median (interquartile range) or number (percentage).

*Missing data for 1 participant in the continuous group (lost to follow-up) and 2 participants in the intermittent group (withdrawal [1] and lost to follow-up [1]). *P* value refers to Pearson chi-square test.

†Hazard Ratio 0.71 (95% Confidence Interval 0.44–1.15, *P* = 0.16) using a log rank test.

‡Odds Ratio 1.16 (95% Confidence Interval 0.73–1.85) using logistic regression.

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