

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

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Abstract

Rationale: Continuous infusion of β -lactam antibiotics may improve outcomes because of time-dependent antibacterial activity compared with 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 (interquartile range, 2–24) and 20 days (interquartile range, 3–24) in the continuous and intermittent groups ($P = 0.38$). There was no difference in 90-day survival: 74.3% (156 of 210) and 72.5% (158 of 218); hazard ratio, 0.91 (95% confidence interval, 0.63–1.31; $P = 0.61$). Clinical cure was 52.4% (111 of 212) and 49.5% (109 of 220); odds ratio, 1.12 (95% confidence interval, 0.77–1.63; $P = 0.56$). There was no difference in organ failure-free days (6 d; $P = 0.27$) and duration of bacteremia (0 d; $P = 0.24$).

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

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

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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. Metaanalyses 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 noncritically ill patients with nonequivalent 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 favor of continuous infusion requires evidence from a large phase III multicenter randomized controlled trial.

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 noncritically 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 nonrandomized studies (3–5, 13–16). Some prospective randomized human studies have also demonstrated clinical outcome advantages of continuous infusion (17, 18), although metaanalyses 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 targets by use of continuous infusion would result in improved clinical outcomes compared with 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 intensive care unit (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 before 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 supplement (*see* Tables E1 and E2). Written consent before enrollment or, in permitted instances, delayed participant or legal surrogate written consent following

enrollment was obtained. The Acute Physiology and Chronic Health Evaluation 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 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 prespecified 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 before 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 five 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* Table E3 for study drug concentrations). All participants received a loading dose before 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

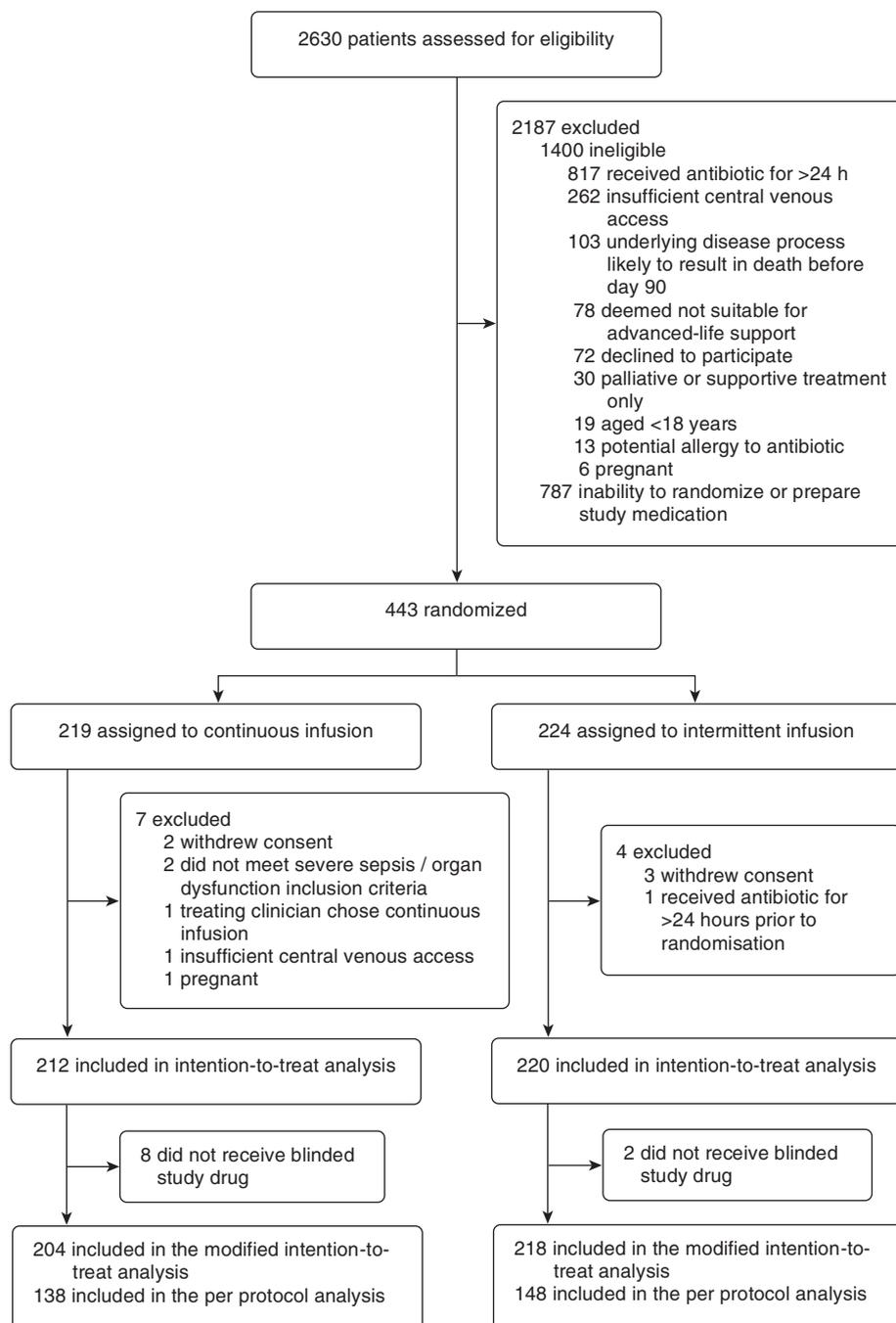


Figure 1. Trial profile.

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 before 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 microbiologic 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 Table E4), alive organ failure-free days at Day 14, and duration of bacteremia postrandomization (23).

The investigators recorded all adverse events during the period of study treatment and assessed causality with study treatment using one of four categories: (1) “almost certainly,” (2) “probably,” (3) “possibly,” or (4) “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 primary outcome with an alpha of 0.05 (i.e., 17 vs. 14 alive ICU-free d with a standard deviation of 9 d in both groups and nonparametric 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 (interquartile 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 and 95% confidence interval

Table 1. Baseline Characteristics of the Intention-to-Treat Population

	Continuous (n = 212)	Intermittent (n = 220)
Age, yr	64 (54–72)	65 (53–72)
Sex, male	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)
Intraabdominal	53 (25.0)	57 (25.9)
Primary bloodstream 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)
Hematologic	26 (12.3)	22 (10.0)

Definition of abbreviation: 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 two sites of infection, six with three sites of infection, and one with four sites of infection [lung, blood, intraabdominal, and skin]) and 29 participants in the intermittent group (23 with two sites of infection and six with three sites of infection). The most common double sites of infection were lung and intraabdominal (12), lung and blood (seven), and lung and urinary tract (six). The most common triple sites of infection were lung, blood, and intraabdominal (four).

[†]See Table E6.

(CI) reported. Proportional differences in survival at ICU discharge, hospital discharge, and Day 90 were compared between treatment groups using a Pearson chi-squared test. The likelihood of clinical cure in the continuous group compared with the intermittent group was evaluated using an odds ratio 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

less than 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 midpoint safety analysis. The trial is registered with the Australian New Zealand Clinical Trials Registry (number ACTRN12612000138886).

Table 2. Microbiologic 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)
Nonsusceptible 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 four participants in the continuous group and two participants in the intermittent group.

*See Table E7.

[†]See Table E8.

Results

Screening and enrollment 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; see Table E5). 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) and 12 hours (IQR, 4.5–20) open-label treatment before commencement of the blinded study drug 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 intermittent group). The median 24-hour dose on Day 1 was 13.5 g (IQR, 13.5–13.5) for piperacillin–tazobactam, 3.0 g (IQR, 2.0–3.0) for meropenem, and 12.4 g for ticarcillin–clavulanate (all five participants) in both groups. There was no difference in median dosing for participants who received renal-replacement therapy. 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)

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, d [§]	0 (0–0)	0 (0–1)	0.24
ICU length of stay, d	7 (3–13)	6 (3–11)	0.042
Hospital length of stay, d	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 abbreviation: ICU = intensive care unit.

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

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

†P value refers to Pearson chi-squared test.

‡One participant in the continuous group was censored as alive in hospital at Day 90 because of database lock; missing data for one participant in the intermittent group (lost to follow-up post interhospital transfer).

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

||Postrandomization.

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; hazard ratio, 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: odds ratio, 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 four participants in the intermittent group had bacteremia that continued for more than 24 hours after randomization (see Table E9). 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

supplement (see Tables E10 and E11). Survival in the continuous group compared with the intermittent group remained nonsignificantly 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 three nonserious adverse events attributed to the study drug (two “possibly” and one “probably”): three adverse events occurred in the intermittent group (hypernatremia [2], and elevated bilirubin and alanine transaminase [1]), and one adverse event (rash) in the continuous group. A second adverse event unlikely related to the study drug (pneumothorax) was reported in one 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 prerandomization factors with baseline balance for the type and severity of illness.

Compared with 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., 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 and 5 d in the continuous group) in the current trial compared with

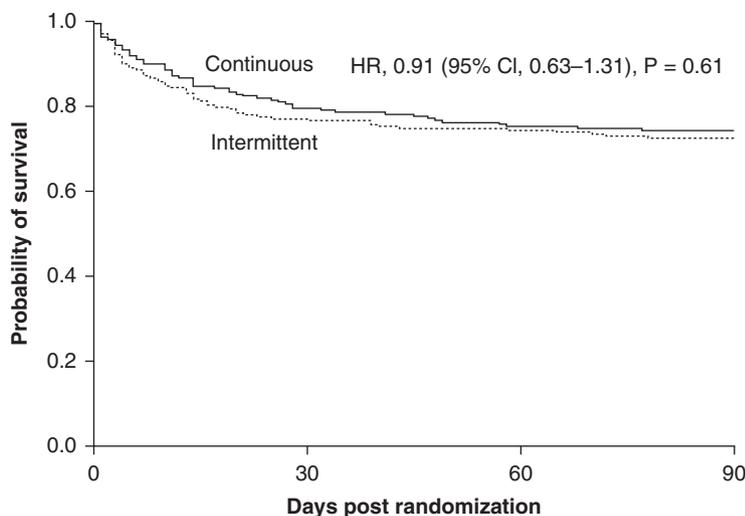


Figure 2. Kaplan-Meier plot for intention-to-treat population. CI = confidence interval; HR = hazard ratio.

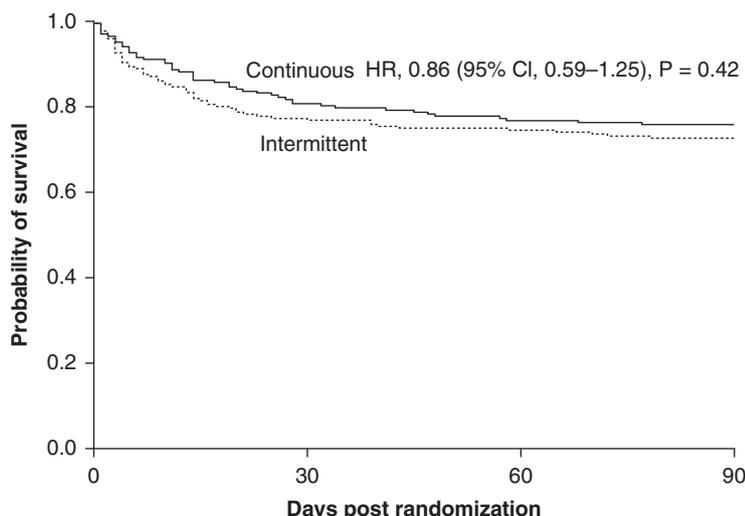


Figure 3. Kaplan-Meier plot for modified intention-to-treat population. CI = confidence interval; HR = hazard ratio.

the earlier trial, respectively. The effect of including participants on renal replacement may reduce the between-group difference because plasma antibiotic concentrations may be less likely to be subtherapeutic 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 prespecified criteria for clinical resolution when clinician opinion was not available (see Table E4).

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 with those of Chytra and colleagues (25) who, in a trial of 240 participants with 23.3% hospital mortality in the intermittent group, found a nonsignificant 5.8% mortality difference ($P = 0.34$) in critically ill participants randomized to receive meropenem by continuous infusion compared with intermittent infusion. Previous metaanalyses by Roberts and colleagues (20) and Shui and colleagues (21) found no significant cumulative mortality difference between groups (i.e., 0.1%, $P = 1.0$; 1.4%, $P = 0.42$), respectively, with mortality of 9.9–13.1% in the intermittent group. In contrast, Falagas and colleagues (16) in their metaanalysis 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 of continuous infusion ($P = 0.04$) and mortality of 8.8% in the continuous group. The lower mortality rates observed in these metaanalyses are caused by the fact that previous studies have largely been conducted in noncritically ill patient groups.

Critically ill patients with severe sepsis undergo pathophysiologic changes (26) that may result in markedly different antibiotic concentrations throughout the dosing interval than is commonly observed in noncritically 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). Although 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 still achieve appropriate pharmacokinetic/pharmacodynamic targets, even in the presence of ICU-associated pathophysiologic disturbances (30).

There are several 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 suggests clinical response and resolution of the acute phase of infection. The inclusion of participants with potential noninfectious diagnoses, nonsusceptible 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.

In summary, in a heterogeneous critical care patient population, there was no difference in alive ICU-free days at Day 28 with continuous compared with 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 subpopulations that may have benefit from continuous infusion of β -lactam antibiotics, whereas in a heterogeneous population continuous and intermittent infusions seem to have equivalent outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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