

# Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

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(See the Editorial Commentary by Drusano and Lodise, on pages 245–7, and the Invited Article by Falagas et al, on pages 272–82.)

**Background.** Beta-lactam antibiotics are a commonly used treatment for severe sepsis, with intermittent bolus dosing standard therapy, despite a strong theoretical rationale for continuous administration. The aim of this trial was to determine the clinical and pharmacokinetic differences between continuous and intermittent dosing in patients with severe sepsis.

**Methods.** This was a prospective, double-blind, randomized controlled trial of continuous infusion versus intermittent bolus dosing of piperacillin-tazobactam, meropenem, and ticarcillin-clavulanate conducted in 5 intensive care units across Australia and Hong Kong. The primary pharmacokinetic outcome on treatment analysis was plasma antibiotic concentration above the minimum inhibitory concentration (MIC) on days 3 and 4. The assessed clinical outcomes were clinical response 7–14 days after study drug cessation, ICU-free days at day 28 and hospital survival.

**Results.** Sixty patients were enrolled with 30 patients each allocated to the intervention and control groups. Plasma antibiotic concentrations exceeded the MIC in 82% of patients (18 of 22) in the continuous arm versus 29% (6 of 21) in the intermittent arm ( $P = .001$ ). Clinical cure was higher in the continuous group (70% vs 43%;  $P = .037$ ), but ICU-free days (19.5 vs 17 days;  $P = .14$ ) did not significantly differ between groups. Survival to hospital discharge was 90% in the continuous group versus 80% in the intermittent group ( $P = .47$ ).

**Conclusions.** Continuous administration of beta-lactam antibiotics achieved higher plasma antibiotic concentrations than intermittent administration with improvement in clinical cure. This study provides a strong rationale for further multicenter trials with sufficient power to identify differences in patient-centered endpoints.

**Keywords.** pharmacokinetics; clinical outcome; meropenem; piperacillin-tazobactam; ticarcillin-clavulanate.

Severe sepsis is a major cause of mortality worldwide. In Australia and New Zealand, 11.8% of intensive care unit

(ICU) admissions are associated with severe sepsis (over 17 000 episodes per annum) with in-hospital mortality of 37.5% and a mortality burden 4 times the Australian annual road toll [1, 2]. This burden is evident globally [3–5]. Early administration of antibiotics active against the infecting organism is a cornerstone of effective management [6]. In a recent point prevalence study of ICU antibiotic usage in Australia and New Zealand, 3 of the 4 most commonly used antibiotics in treatment were beta-lactams, with ticarcillin-clavulanate, meropenem, and piperacillin-tazobactam accounting for 56% of all

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antibiotics used [7]. Given that subtherapeutic dosing is associated with poorer clinical outcomes and increased incidence of drug resistance [8–10], optimal dosing of beta-lactam antibiotics has the potential to improve the outcome for critically ill patients with severe sepsis.

Beta-lactam antibiotics are administered almost exclusively by intermittent bolus dosing [7]. However, there are strong pharmacodynamic data suggesting that this mode of administration may be less effective than administration by continuous infusion. Bacterial killing for beta-lactam antibiotics is related to the duration of time that bacteria are exposed to a concentration of antibiotic that exceeds the minimum inhibitory concentration (MIC), that is,  $T_{>MIC}$  [11]. Administration of beta-lactam antibiotics by infusion produces higher blood and interstitial fluid concentrations with greater time above the MIC compared with intermittent dosing, particularly for bacteria with high MIC values, which are common in the ICU [12–14].

Although continuous infusion has been shown to be superior to intermittent administration in animal and *ex vivo* models, 2 meta-analyses of the human trials to date have not demonstrated differences in clinical cure or survival [11, 15]. These human trials, however, have been primarily conducted in noncritically ill patients and were underpowered, even when pooled, limiting their applicability to patients with severe sepsis. In addition, 13 of the 14 studies included in a recent meta-analysis used non-equivalent dosing in the treatment arms limiting direct comparisons between the 2 delivery methods [11]. The aim of this trial was to determine the clinical and pharmacokinetic differences between continuous and intermittent dosing in critically ill patients with severe sepsis to establish feasibility to proceed with a larger multicenter trial.

## METHODS

### Study Design and Setting

This prospective, multicenter, double-blind, concealed, randomized controlled trial was conducted at Royal Brisbane and Women's Hospital, Austin Hospital, Blacktown Hospital, and Royal Darwin Hospital, Australia, and Prince of Wales Hospital, Hong Kong. Recruitment occurred between April 2010 and November 2011. Institutional ethics approval for the study was obtained at each site. Consent was obtained from the patient or from a substitute decision maker prior to study enrollment. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000238077).

### Selection Criteria

Patients were eligible if they met all of the following inclusion criteria: (1) severe sepsis in the previous 48 hours, defined as confirmed or suspected infection with new organ dysfunction based on diagnostic criteria published elsewhere [1, 16]; (2)

planned commencement or commencement within the previous 24 hours of ticarcillin-clavulanate, piperacillin-tazobactam or meropenem; and (3) an expected or actual ICU stay greater than 48 hours. Patients were excluded if they were <18 years of age, had an allergy to one or more of the study medications, were receiving palliative or supportive treatment only, were receiving continuous renal replacement therapy, did not have central venous catheter access with at least 3 lumens (a dedicated lumen was required for study drug administration), or had received the study drug for >24 hours.

### Intervention

Patients were randomized to receive either (1) active infusion and placebo boluses (intervention arm) or (2) placebo infusion and active boluses (control arm). The 24-hour dose was clinician-chosen and unaffected by randomization. Ticarcillin-clavulanate and piperacillin-tazobactam (or placebo) infusions were changed every 24 hours, while meropenem (or placebo) infusions were changed 8 hourly, as determined by antibiotic stability at room temperature [17–21]. Labeling was used to conceal the syringe contents for bolus administration. Infusion contents were concealed by dilution of medication in 100–250 mL infusion bags. Both methods of administration were used with the active treatment contained in only one administration route. Clinical staff, data collectors, and patients were blinded to allocation status.

### Antibiotic Plasma Levels

A maximum of 3 blood samples per patient were taken immediately prior to the active (or placebo) bolus dose during a 48-hour window period on days 3 and 4 to determine plasma trough levels. Blood samples were centrifuged at 3000 rpm for 10 minutes and the plasma stored at  $-80^{\circ}\text{C}$  until batched analysis at a central laboratory; samples were stored at  $-20^{\circ}\text{C}$  for <30 hours at one site until storage at  $-80^{\circ}\text{C}$ . Antibiotic concentration was determined by validated high performance liquid chromatography [22], which included within-batch calibrators and quality controls [23]. Samples were prepared by protein precipitation with a dichloromethane wash, and the extracts separated on a C18 stationary phase and monitored by ultraviolet. Accuracy and precision of the assays were validated at high, medium, and low concentrations of the calibration range. All results met the bioanalysis acceptance criteria of the US Food and Drug Administration [23]. Free (unbound) drug concentrations were determined using published protein binding values (2% for meropenem, 21% for piperacillin, and 45% for ticarcillin) [24–26].

### Outcomes and Measurements

The primary pharmacokinetic endpoint was plasma antibiotic concentration above MIC, scored as a dichotomous variable.

MIC breakpoints for *Pseudomonas aeruginosa* (16 mg/L for piperacillin and ticarcillin, and 2 mg/L for meropenem) were used and scored as positive if all measured free plasma antibiotic concentrations exceeded the breakpoint [27].

Secondary endpoints included clinical response rated by blinded clinicians at a test of cure date 7–14 days after study drug cessation (Table 1) [28]. Time to clinical resolution was defined as the number of days from randomization to the first identified date of clinical resolution; this was set at 28 days for patients who did not achieve clinical cure within a 28-day period. Vital status at ICU and hospital discharge and ICU-free days at day 28 were also evaluated. “ICU-free days” was defined as the number of days alive and free of ICU admission in the first 28 days postrandomization. Daily sequential organ failure assessment (SOFA) scores were recorded [29]. The focus of infection, concomitant antibiotic use, and duration of therapy were recorded. Adverse events during treatment were evaluated as, almost certainly, probably, possibly, or unlikely caused by study medications.

### Sample Size

A sample of 60 patients was calculated to achieve a power of 80% to detect a 15% absolute difference in the primary outcome at a significance level of 5%, with a target of 8–16 participants per site.

### Randomization and Masking

Randomization was stratified by institution with 1:1 allocation to treatment arm. Following study enrollment, an unblinded research nurse or pharmacist responsible for preparation of the blinded medications determined allocation status by opening a sequentially numbered sealed envelope.

**Table 1. Clinician-Rated Outcome Definitions**

Clinical response
<ol style="list-style-type: none"> <li>1. Resolution—disappearance of all signs and symptoms related to the infection</li> <li>2. Improvement—a marked or moderate reduction in the severity and/or number of signs and symptoms of infection</li> <li>3. Failure—insufficient lessening of the signs and symptoms of infection to qualify as improvement, including death or indeterminate (no evaluation possible, for any reason)</li> </ol>
Clinical cure
<ol style="list-style-type: none"> <li>1. Resolution—as above</li> <li>2. All other findings (ie, sum of 2 and 3 above)</li> </ol>
Clinical cure (treatment exclusions)
Participants where the study drug, excluding beta-lactam antibiotic de-escalation, was changed due to nonresolution of infection are defined as nonresolution (regardless of clinical response at test of cure date)—otherwise as above

Adequacy of blinding was assessed by clinician survey. A nurse on day 1 or 2 and a medical officer at a later date during study enrollment were asked whether they thought the patient was receiving continuous or intermittent treatment and the degree of certainty in this decision using a 5-point scale [30].

### Statistical Analysis

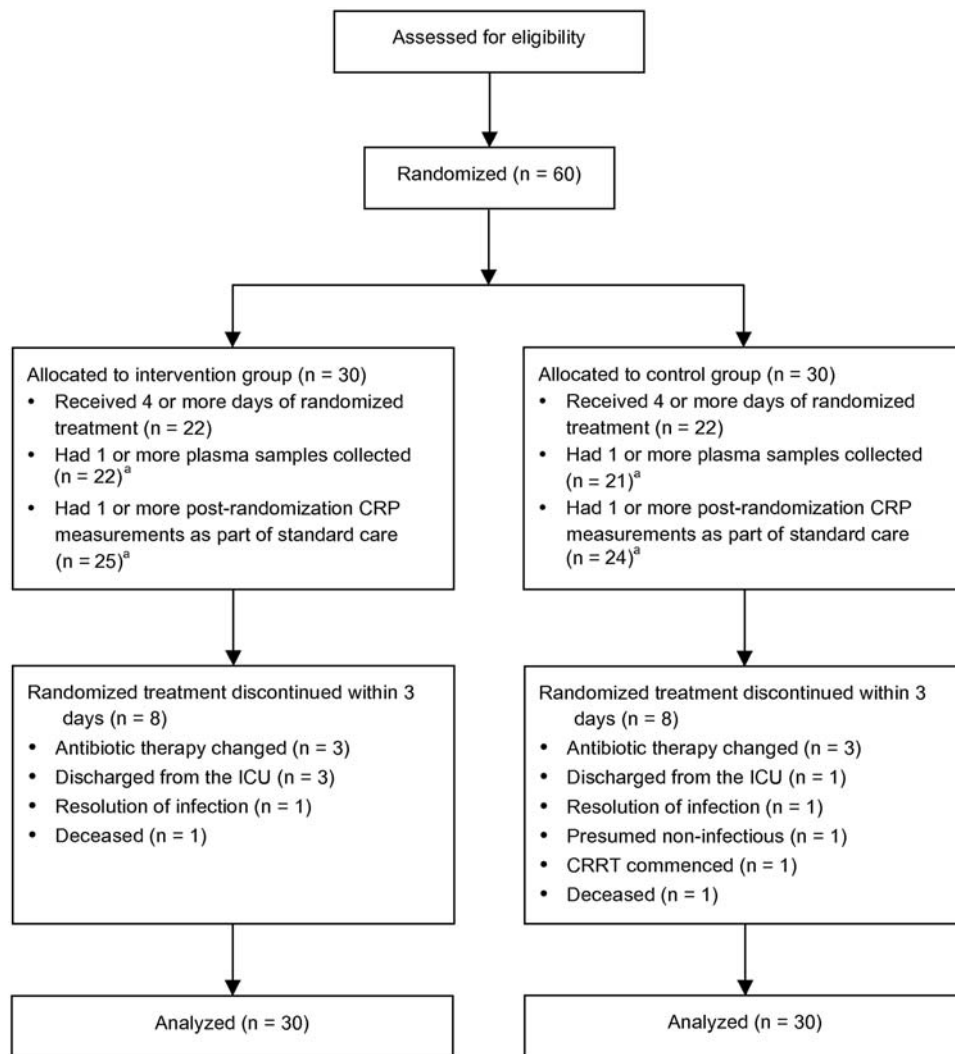
An on-treatment analysis of all patients with plasma antibiotic samples taken on days 3 and 4 was performed for the primary pharmacokinetic endpoint ( $n = 22$  and  $21$  for the intervention and control group, respectively). Free plasma antibiotic concentration differences were analyzed by Mann-Whitney U test and expressed as box (median and interquartile range [IQR]) and whiskers (10–90 percentile). An intention-to-treat analysis of all randomized patients was performed for clinical endpoints ( $n = 30$  in each group). The primary outcome was evaluated by Fisher exact test. Secondary outcomes were analyzed by Student  $t$  test or Mann-Whitney U test depending on whether inspection of a normal Q-Q plot confirmed or rejected the normality assumption, respectively. A Kaplan-Meier curve, with follow-up until hospital discharge, was plotted to show survival trend; a log-rank test was used to compare treatment groups. Mean  $\pm$  standard deviation are reported for normally distributed variables and median [IQR] for nonnormal variables. A 2-sided  $P$  value  $<.05$  was considered statistically significant. Statistical analysis was conducted using IBM SPSS Statistics 19 (IBM Corporation, Armonk, New York). James and Bang blinding indices [31] were computed using Stata software (StataCorp LP, College Station, Texas). Box and whisker plots were generated in GraphPad Prism 5 (GraphPad Software, Inc, La Jolla, California).

## RESULTS

### Recruitment and Baseline Characteristics

Sixty patients were enrolled; 16 at Royal Brisbane and Women’s Hospital, 14 at Austin Hospital, 12 at Blacktown Hospital, 10 at Royal Darwin Hospital, and 8 at Prince of Wales Hospital. Forty-four patients (73%) completed 4 or more days of randomized treatment, with equal distribution between treatment arms (Figure 1). Four patients were discharged from the ICU within 48 hours of randomization, and 2 patients died during this period. The 24-hour antibiotic dose for the intervention and control groups was comparable: 13.5 [13.5–13.5] g versus 13.5 [11.3–13.5] g for piperacillin-tazobactam, 3.0 [3.0–3.8] g versus 3.0 [3.0–3.0] g for meropenem, and 12.4–13.5 g (2 participants) versus 12.4 g (1 participant) for ticarcillin-clavulanate.

Fourteen patients in each group had a beta-lactam susceptible organism identified as the primary causative organism (Table 2). Four patients in the intervention group had a non-susceptible organism identified (*Enterococcus* species in 3



**Figure 1.** CONSORT flow diagram. Abbreviations: CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVC, central venous catheter; ICU, intensive care unit. <sup>a</sup>Sub-group analysis.

patients and human metapneumovirus in a fourth). Four patients in the control group had a nonsusceptible organism identified: methicillin-resistant *Staphylococcus aureus* in 2 patients, *Coxiella burnetii* (Q fever) in one, and *Stenotrophomonas maltophilia* in a fourth. Baseline characteristics of the 2 groups are reported in Table 3.

### Study Endpoints

Plasma antibiotic concentration measured in the first sample was significantly higher in the intervention group compared with the control group for meropenem (9.2 [7.9–12.9] µg/mL vs 3.3 [0.8–4.2] µg/mL), but not for piperacillin (35.6 [21.4–52.0] µg/mL vs 36.4 [6.2–142.2] µg/mL) or ticarcillin (9.1 µg/mL and 130.9 µg/mL vs 14.1 µg/mL, respectively; Figure 2).

The ratio of plasma antibiotic concentration to MIC for the intervention and control group is displayed in Figure 3 for all 3 samples: 3.3 [1.9–4.8] µg/mL vs 1.7 [0.4–3.8] µg/mL for sample 1, 3.0 [1.6–4.1] µg/mL vs 1.1 [0.5–6.8] µg/mL for sample 2, and 2.8 [1.5–4.8] µg/mL vs 1.0 [0.3–2.2] µg/mL for sample 3, respectively.

Study endpoints are displayed in Table 4, and survival analysis is shown in Figure 4. For patients receiving meropenem, plasma antibiotic concentration was greater than MIC for all samples in 8 of 8 patients (100%) in the intervention group, compared with 2 of 9 (22%) in the control group; for patients receiving piperacillin-tazobactam, group differences in plasma antibiotic concentration above MIC were 9 of 12 (75%) vs 4 of 11 (36%), and for ticarcillin-clavulanate 1 of 2 (50%) vs 0 of 1, respectively.

**Table 2. Organisms Identified on Blood Culture**

Organism	Intervention Group	Control Group
MSSA	3 <sup>b</sup>	2
MRSA	0	2 <sup>c</sup>
<i>Enterococcus</i> spp <sup>a</sup>	3 <sup>d,e</sup>	0
<i>Escherichia coli</i>	1	2
ESBL <i>E. coli</i>	1	0
<i>Pseudomonas aeruginosa</i>	2 <sup>b</sup>	1
<i>Serratia marcescens</i>	0	2 <sup>c</sup>
<i>Proteus mirabilis</i>	2 <sup>e</sup>	0
ABC	1	0
<i>Aeromonas hydrophila</i>	1 <sup>d</sup>	0
<i>Burkholderia cepacia</i>	0	1
<i>Enterobacter cloacae</i>	0	1
<i>Haemophilus influenzae</i>	0	1
<i>Klebsiella oxytoca</i>	1 <sup>b</sup>	0
<i>Morganella morganii</i>	0	1
<i>Salmonella typhimurium</i>	1	0
<i>Stenotrophomonas maltophilia</i>	0	1
<i>Streptococcus milleri</i>	1 <sup>e</sup>	0
<i>Streptococcus pneumoniae</i>	0	1
<i>Streptococcus pyogenes</i>	0	1
<i>Vibrio vulnificus</i>	0	1

Abbreviations: ABC, *Acinetobacter baumannii-calcoaceticus* complex; ESBL, extended-spectrum beta-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

<sup>a</sup> *Enterococcus faecalis* in 2 cases and *Enterococcus* spp (unidentified) in 1 case.

<sup>b-e</sup> Indicate multiple organisms identified in 4 cases.

### Adequacy of Blinding

Nursing and medical staff completed a blinding questionnaire for 56 (93.3%) and 51 study participants (85.0%), respectively. Perceptions of randomization status are displayed in Table 5. Of the 33 respondents (30.8%) who believed they knew which treatment arm the participant was in, 13 made a judgment based on physical characteristics of the infusion bag or syringe, and 9 made the judgment with reference to improvement or nonimprovement in the patients' condition, with various reasons provided for the remaining judgments. Blinding indices are reported in Table 6.

### Adverse Events

No adverse events occurred as a result of study participation. Two patients died during study enrolment: one patient deteriorated following consent but prior to commencement of the blinded medication with the cause of death septic shock due to aspiration pneumonitis, and one patient with deteriorating respiratory failure and septic shock died 3 days after ICU admission due to pneumonia. Both events were assessed as unlikely to be related to the study drug or intervention.

**Table 3. Baseline and Study Characteristics**

Characteristic	Intervention Group	Control Group
Sex (male)	23 (76.7%)	19 (63.3%)
Age	54 ± 19	60 ± 19
APACHE II score	21 ± 8.6	23 ± 7.6
Chronic health evaluation		
Respiratory	7 (23.3%)	2 (6.7%)
Cardiovascular	1 (3.3%)	2 (6.7%)
Liver	1 (3.3%)	1 (3.3%)
Renal	0	0
Immunodeficiency	3 (10.0%)	1 (3.3%)
Nil	20 (66.7%)	24 (80.0%)
Pre-ICU-acquired infection	25 (83.3%)	21 (70.0%)
Study drug		
Piperacillin-tazobactam	18 (60.0%)	17 (56.7%)
Meropenem	10 (33.3%)	12 (40.0%)
Ticarcillin-clavulanate	2 (6.7%)	1 (3.3%)
Duration of study treatment (days)	5 (2–6.25)	4.5 (2–7)
Organism identified	13 (43.3%)	17 (56.7%)
Site of infection		
Lung	14 (36.8%)	16 (43.2%)
Blood	7 (18.4%) <sup>a</sup>	7 (18.9%) <sup>a</sup>
Intra-abdominal	6 (15.8%)	7 (18.9%)
Skin or skin structure	3 (7.9%)	3 (8.1%)
Urinary tract	3 (7.9%)	2 (5.4%)
Central nervous system	2 (5.3%) <sup>b</sup>	0
Unknown	1 (2.6%)	0
Postrandomization CRP	25 (83.3%)	24 (80.0%)
Plasma samples		
Piperacillin-tazobactam	12 (40.0%)	11 (36.7%)
Meropenem	8 (26.7%)	9 (30.0%)
Ticarcillin-clavulanate	2 (6.7%)	1 (3.3%)
Nil	8 (26.7%)	9 (30.0%)
ICU length of stay (prerandomization)	1 (0–3)	1 (0–4.25)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; ICU, intensive care unit.

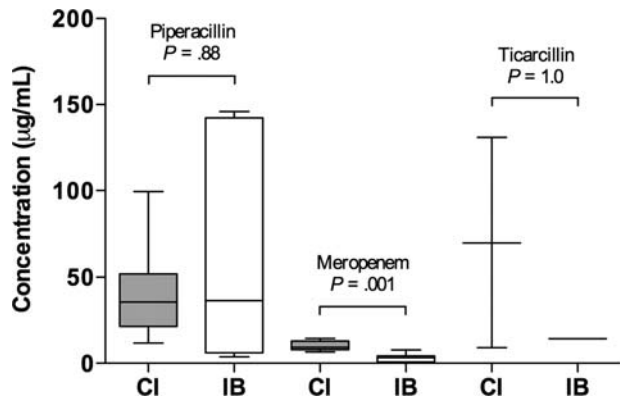
<sup>a</sup> Five participants in each group had an additional site of identified infection (lung, urinary tract, and intra-abdominal).

<sup>b</sup> One participant had an additional site of infection (lung).

## DISCUSSION

This is the first multicenter ICU trial to our knowledge comparing the effects of continuous and intermittent administration of beta-lactam antibiotics. Our results showed that continuous infusion of beta-lactam antibiotics achieved significant pharmacokinetic separation in  $T_{> MIC}$  and higher rates of clinical cure compared with intermittent administration in critically ill patients with severe sepsis. Our study is the only

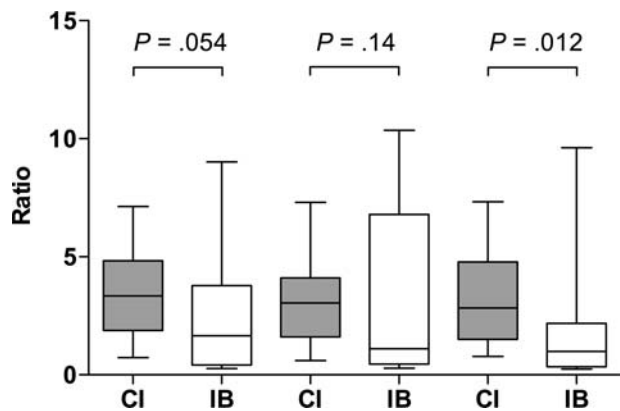




**Figure 2.** Free plasma antibiotic concentration between treatment groups on the first sample. Abbreviations: CI, continuous infusion; IB, intermittent bolus.

continuous vs intermittent beta-lactam dosing trial that has been conducted in a blinded fashion with allocation concealment [11], and the largest of a limited number of studies conducted exclusively in an ICU setting [28, 32–35]. This multicenter study demonstrated the feasibility of randomizing patients following commencement of 3 commonly prescribed beta-lactam antibiotics for severe sepsis and the ability to administer concealed medications in the ICU in a safe manner.

Continuous infusion has shown to produce higher blood and interstitial fluid concentrations and more rapid bacterial killing, particularly for bacteria with high MIC values in immunodeficient ex vivo and animal models [12–14, 36]. A retrospective study by Lodise and colleagues in critically ill patients with *P. aeruginosa* found that using extended infusions of piperacillin-tazobactam to increase  $T_{>MIC}$  resulted in



**Figure 3.** Free plasma antibiotic concentration to minimum inhibitory concentration ratio for 3 samples. Abbreviations: CI, continuous infusion; IB, intermittent bolus.

**Table 4. Study Endpoints by Treatment Group**

Endpoint	Intervention Group	Control Group	P
Plasma antibiotic concentration >MIC	18 (81.8%) <sup>a</sup>	6 (28.6%) <sup>a</sup>	.001
Clinical cure (test of cure date)	23 (76.7%)	15 (50.0%)	.032
Clinical cure (test of cure date with treatment exclusions)	21 (70.0%)	13 (43.3%)	.037
Clinical cure (last day of blinding)	9 (30.0%)	6 (20.0%)	.37
Time to clinical resolution (days)	11 (6.75–24.25) <sup>b</sup>	16.5 (7–28) <sup>b</sup>	.14
Time to resolution of CRP (days)	6 (2.5–22.5) <sup>c</sup>	5 (3–27) <sup>c</sup>	.79
ICU length of stay (postrandomization)	7.5 (4–12)	9 (5–14.25)	.50
ICU-free days			
All	19.5 (12.75–24)	17 (.75–22)	.14
ICU survivors	20.5 (16–24) <sup>d</sup>	18 (12.75–22) <sup>d</sup>	.22
ICU survival	28 (93.3%)	26 (86.7%)	.67
Hospital survival	27 (90.0%)	24 (80.0%)	.47

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; MIC, minimum inhibitory concentration.

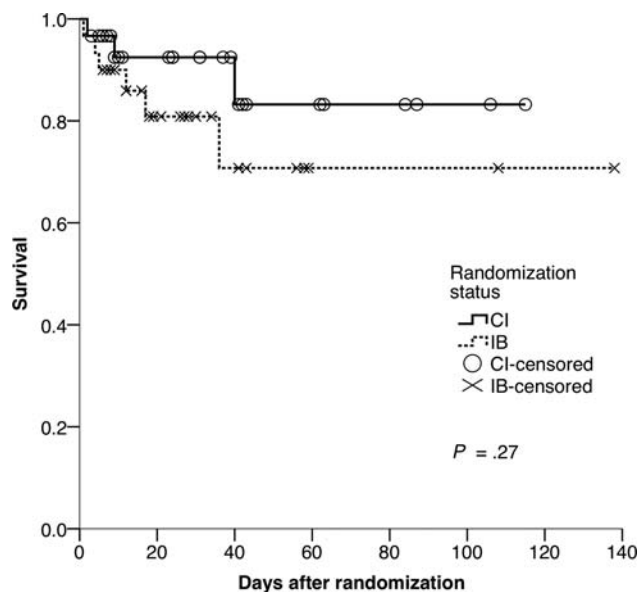
<sup>a</sup> Plasma samples were available for 22 and 21 patients in the intervention and control groups, respectively (subgroup analysis).

<sup>b</sup> Time to clinical resolution was set at 28 d for 7 and 13 patients in the intervention and control groups, respectively, as clinical resolution did not occur during this period.

<sup>c</sup> Postrandomization CRP levels were available for 25 and 24 patients in the intervention and control groups, respectively (subgroup analysis); time to resolution of CRP was set at 28 d for 6 patients in each group as CRP was not measured below 100 mg/L during this period.

<sup>d</sup> Subgroup analysis (28 and 26 patients in intervention and control groups, respectively).

improved 14-day survival (12.2% vs 31.6%,  $P = .04$ ) in a subpopulation of patients with high levels of sickness severity (APACHE II score >17) compared with a historical cohort [8]. Another retrospective review of 359 patients treated for gram-negative infections across 14 hospitals in the United States found that extended infusion of piperacillin-tazobactam prolonged survival by 2.8 days ( $P < .01$ ) compared with nonextended infusion of beta-lactam antibiotics [37]. However, apart from a single center ICU study by Roberts and colleagues, which observed a 27% higher cure rate with continuous infusion of ceftriaxone ( $P = .06$ ) [28], our study is the only trial to our knowledge to report a significant difference in clinical cure rates for continuous versus intermittent administration of beta-lactam antibiotics. This may in part be explained by a focus on patients with a higher acuity of illness and dosing that was independent of treatment arm. Given previous data showing that, in critically ill patients in the ICU,



**Figure 4.** Survival curve for patients in both treatment groups (data have been censored for patients discharged from hospital). Abbreviations: CI, continuous infusion; IB, intermittent bolus.

maintaining 100%  $T_{>MIC}$  for beta-lactam antibiotics is associated with greater clinical cure than dosing that results in anything <100% (82% vs 33%,  $P = .002$ ) [9], the nonequivalent dosing between treatment arms (lower in the continuous arm) in 13 of the 14 previous trials may be a significant confounding factor [11]. Our study demonstrated that clinician-determined dosing by continuous infusion might alone be sufficient to improve clinical cure. Although differences in plasma antibiotic concentration between groups were most prominent in patients receiving meropenem, higher rates of 100%  $T_{>MIC}$  in measured samples were also present for patients on piperacillin-tazobactam. This was evidenced by the

**Table 5. Perception of Blinding Status**

Response Category	Nursing Staff		Medical Staff	
	Intervention	Control	Intervention	Control
Strongly believe — continuous	5 (16.7%)	3 (11.5%)	0	0
Somewhat believe — continuous	3 (10.0%)	6 (23.1%)	1 (3.6%)	0
Somewhat believe — intermittent	3 (10.0%)	3 (11.5%)	1 (3.6%)	2 (8.7%)
Strongly believe — intermittent	1 (3.3%)	2 (7.7%)	1 (3.6%)	2 (8.7%)
Don't know	18 (60%)	12 (46.2%)	25 (89.3%)	19 (82.6%)

**Table 6. Blinding Indices**

Measure of Blinding	Nursing Staff Index (95% CI)	Medical Staff Index (95% CI)
James' BI	.76 (.67, .85) <sup>a</sup>	.91 (.84, .97) <sup>a</sup>
Bang's BI — intervention arm	.13 (−.011, .27) <sup>b</sup>	−.036 (−.11, .035) <sup>b</sup>
Bang's BI — control arm	−.096 (−.026, .071) <sup>b</sup>	.13 (.027, .23)

Abbreviations: BI, blinding index; CI, confidence interval.

James' BI reference range (0 to 1): 0 = complete unblinding, .5 = random guessing, 1 = complete blinding. Bang's BI reference range (−1 to 1): −1 = complete blinding, 0 = random guessing, 1 = complete unblinding.

<sup>a</sup> 95% CIs that are >.5 indicate adequate blinding.

<sup>b</sup> 95% CIs that include 0 indicate adequate blinding.

greater concentration range in the piperacillin-tazobactam bolus group, including a greater number of patients with low concentrations.

The study was not powered to evaluate any effect on survival and suggests a clinical signal for the surrogate endpoint of clinical cure at 7–14 days after study drug cessation (27% higher in the intervention group), even after adjusting for treatment changes. Additionally, a number of other surrogate clinical endpoints, including ICU-free days at day 28 moved in a favorable direction but did not achieve statistical significance. The progression to achieving a definitive clinical answer via a stepwise research program is well described in the literature [38]. Our study provides an important step in establishing suitable endpoints for a large well-designed prospective phase II multicenter study of continuous administration of beta-lactam antibiotics in critically ill patients with severe sepsis.

The potential benefits to patients and the health system by improved methods of antibiotic delivery of beta-lactam antibiotics are considerable. If a 4% absolute reduction in hospital mortality is achievable (with point estimates of 6.6%–10.0% observed in this study), then this intervention has the potential to save over 800 lives each year in Australia and New Zealand [1], and over 37 000 lives in the United States [3]. In addition, in an era of increasingly expensive therapies, administration of beta-lactam antibiotics via continuous infusion compared with intermittent dosing represents greater cost-efficiency in terms of workload and labor costs, while remaining cost neutral in terms of drug costs [14, 36].

This study has a number of limitations. Despite treatment groups being largely well balanced, differences existed for some baseline characteristics, such as 6 years younger mean age, 13% more males, 13% higher comorbidity, and a 13% higher proportion of pre-ICU infections in the intervention group. A modest sample size in each group may have similarly

resulted in potential confounding by unmeasured variables. In terms of plasma antibiotic concentrations, only trough concentrations were measured. Therefore, concentrations at 40%–70%  $T_{>MIC}$  could only be inferred to be greater than the MIC. A limited number of extreme concentration values in the intermittent group suggested the presence of some sample timing error.

Clinician blinding is important for surrogate outcomes, such as ICU-free days, which can be influenced by discharge decisions and clinician ratings of clinical cure. Although a minority of staff was able to determine treatment arm by subtle physical indicators, we demonstrated that concealed administration achieved satisfactory levels of blinding in a multicenter context. In particular, compounding of antibiotic medications in infusion bags and labeling of syringes to obscure content for intermittent dosing was sufficient to achieve blinding without the need for more costly and labor-intensive measures, such as colored tubing and covered infusion bags. The finding that medical staff identified the intermittent arm at a significantly higher rate than chance may relate to a smaller sample size, given that a similar identification rate for nursing staff in the intermittent group was nonsignificant.

## CONCLUSION

This is the first multicenter ICU trial that we are aware of that compares continuous and intermittent administration of beta-lactam antibiotics. The results provide evidence of the pharmacokinetic separation of continuous infusions against bolus dosing, higher rates of clinical cure associated with continuous infusion, and the feasibility of blinding study medications in a multicenter study. We believe evaluating continuous infusion in a severe sepsis cohort via a phase II randomized controlled trial is both justified and feasible.

## Notes

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**Potential conflicts of interest.** J. A. R. has served as a consultant for AstraZeneca, Pfizer, Gilead and Janssen-Cilag. S. A. R. W. has attended Advisory Boards and acted as a consultant to Janssen-Cilag and AstraZeneca. C. G. has served as a consultant for Janssen-Cilag and Pfizer. J. M. has received travel and speaker fees in relation to investigator-initiated research projects from Fresenius Kabi. D. L. P. has received research grants from AstraZeneca and has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from Three Rivers Pharmaceuticals, Merck, AstraZeneca, SanofiAventis, Pfizer, Johnson & Johnson, and Leo Pharmaceuticals. J. L. has received research grants from AstraZeneca and has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from AstraZeneca, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, and Wyeth Australia. All other authors report no potential conflicts.

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