ORIGINAL ARTICLE

Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

A Meta-analysis of Individual Patient Data from Randomized Trials

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Abstract

Rationale: Optimization of β-lactam antibiotic dosing for critically ill patients is an intervention that may improve outcomes in severe sepsis.

Objectives: In this individual patient data meta-analysis of critically ill patients with severe sepsis, we aimed to compare clinical outcomes of those treated with continuous versus intermittent infusion of β-lactam antibiotics.

Methods: We identified relevant randomized controlled trials comparing continuous versus intermittent infusion of β-lactam antibiotics in critically ill patients with severe sepsis. We assessed the quality of the studies according to four criteria. We combined individual patient data from studies and assessed data integrity for common baseline demographics and study endpoints, including hospital mortality censored at 30 days and clinical cure. We then determined the pooled estimates of effect and investigated factors associated with hospital mortality in multivariable analysis.

Measurements and Main Results: We identified three randomized controlled trials in which researchers recruited a total of 632 patients with severe sepsis. The two groups were well balanced in terms of age, sex, and illness severity. The rates of hospital mortality and clinical cure for the continuous versus intermittent infusion groups were 19.6% versus 26.3% (relative risk, 0.74; 95% confidence interval, 0.56–1.00; $P = 0.045$) and 55.4% versus 46.3% (relative risk, 1.20; 95% confidence interval, 1.03–1.40; $P = 0.021$), respectively. In a multivariable model, intermittent β-lactam administration, higher Acute Physiology and Chronic Health Evaluation II score, use of renal replacement therapy, and infection by nonfermenting gram-negative bacilli were significantly associated with hospital mortality. Continuous β-lactam administration was not independently associated with clinical cure.

Conclusions: Compared with intermittent dosing, administration of β-lactam antibiotics by continuous infusion in critically ill patients with severe sepsis is associated with decreased hospital mortality.

Keywords: antibiotic; meropenem; pharmacodynamics; pharmacokinetics; piperacillin-tazobactam

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At a Glance Commentary

Scientific Knowledge on the Subject: There is a mechanistic rationale for continuous infusion of β-lactam antibiotics to provide improved patient outcomes compared with intermittent dosing. However, all available studies have been statistically underpowered to test mortality benefits.

What This Study Adds to the Field: In this individual patient data meta-analysis of a large critical care patient population with severe sepsis, we found that administration of β-lactam antibiotics by continuous infusion was associated with decreased hospital mortality compared with intermittent dosing.

Table 1. Definitions of Common Clinical Endpoints

Endpoint	Definition and Description
Hospital mortality censored at Day 30	Proportion of patients who died before hospital discharge censored at 30 d postrandomization.
ICU mortality	Proportion of patients who died before discharge from the ICU.
Clinical cure	Clinical cure was evaluated 7–14 d after cessation of study antibiotic and was defined as disappearance of all signs and symptoms, including SIRS criteria*, related to infection. Clinical cure was evaluated by a blinded clinician if the participant was still in the ICU or by blinded review of the patient record if the participant was discharged from the ICU.
ICU-free days at Day 28	The number of days the participant was ICU free after successful transfer to a general ward in the first 28 d postrandomization. ICU-free days were assigned as 0 if a patient died or stayed in the ICU for ⩾28 d.

Definitions of abbreviations: ICU = intensive care unit; SIRS = systemic inflammatory response syndrome.
*SIRS criteria are temperature greater than 38°C or less than 36°C, heart rate more than 90 beats per minute, respiratory rate more than 20 breaths per minute or Pa_{CO_2} less than 32 mm Hg, white blood cell count fewer than 4×10^9 cells per liter or more than 12×10^9 cells per liter, or the presence of more than 10% immature neutrophils (band forms) (18).

Serious infections in critically ill patients are associated with high morbidity and mortality (1, 2). Early recognition and prompt administration of appropriate antibiotic therapy is a standard of care in such patients (3–5). Choice of antibiotic is important to ensure that the antibiotic spectrum includes known or potential pathogens. However, there is uncertainty about the most effective method of drug dosing and administration, despite recognized associations between the achievement of target antibiotic concentrations and improved patient-centered outcomes (5–8).

β-Lactam antibiotics are widely used to treat patients in critical care units (9, 10). They are time-dependent antibiotics with which maintenance of concentrations above the minimum inhibitory concentration (MIC) of the pathogen is associated with maximal bacterial killing (11, 12). Pathophysiological perturbations in critically ill patients may reduce the time that β-lactam antibiotic concentrations are maintained above the MIC when these drugs are administered by intermittent dosing (5, 13). Administering β-lactam antibiotics by continuous infusion results in sustained concentrations throughout the dosing interval, increased time above the MIC, and enhanced bacterial killing (14, 15). Despite some clinical uptake, the efficacy of continuous infusion of β-lactam antibiotics on patient-centered outcomes, such as interval mortality, has not been demonstrated in high-quality randomized controlled trials (RCTs) to date. In a recent aggregated data meta-analysis of RCTs comparing continuous and intermittent infusions of β-lactam antibiotics in hospitalized patients, researchers reported no significant differences in mortality (16). However, that meta-analysis included patients with nonsevere sepsis and had significant heterogeneity.

We aimed to combine patient-level data from RCTs to compare interval mortality and clinical cure rates of continuous versus intermittent infusion of β-lactam antibiotics in critically ill patients with severe sepsis. In addition, we sought to identify patient subgroups that may benefit from administration by continuous infusion.

Methods

Identification and Selection of Studies

This meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (17). We

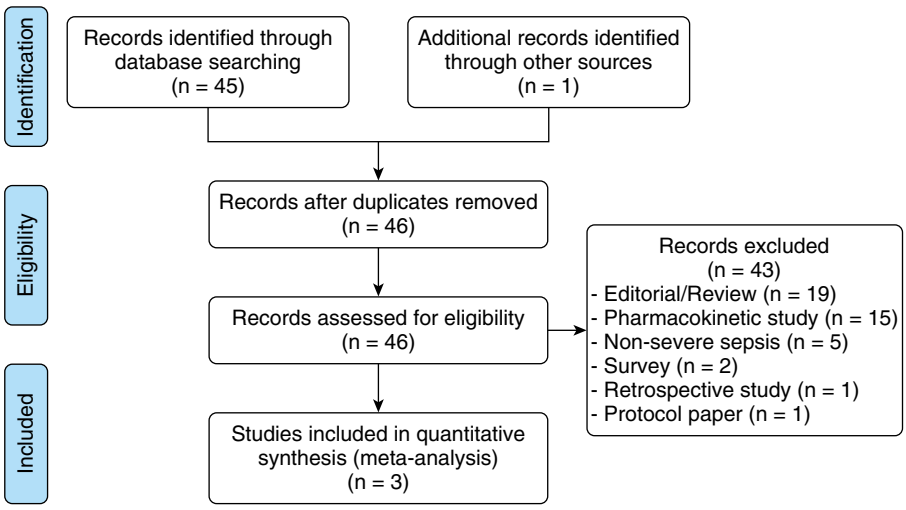

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart for identification of included studies.

conducted a literature review in PubMed in November 2015 to identify all completed prospective RCTs in which investigators reported patient outcomes with continuous and intermittent infusion of β-lactam antibiotics in critically ill patients with severe sepsis. Studies were identified using keywords including "β-lactam," "penicillin," "cephalosporin," "carbapenem," or "monobactam"; "severe sepsis," "septic shock," "ICU," or "critically ill"; and "continuous infusion," "prolonged infusion," or "extended infusion." We hand searched reference lists of the identified papers for additional studies. There were no exclusions made for language of publication. We manually checked all reference sources containing any mention of continuous infusion of β-lactam antibiotics to determine if they reported prospective RCTs. Retrospective studies, pharmacokinetic studies, studies of patients not meeting criteria for severe sepsis, studies with nonequivalent dosing between treatment groups, review articles, editorials, surveys, and protocol papers were excluded. We then undertook full-text reviews of the remaining studies, and study methodology details were documented. Studies were included in this meta-analysis if they (*1*) were prospective, (*2*) enrolled patients with severe sepsis or septic shock (18), (*3*) randomized patients to receive intermittent or continuous administration of one or more β-lactam antibiotics with equivalent (or blinded clinician) dosing in each treatment arm, and (*4*) reported assessment of outcomes by a clinician blinded to treatment allocation. We invited authors of identified studies to participate in this analysis and provide original, deidentified individual patient data from their trials.

Quality Assessment and Data Extraction

We used the Cochrane Collaboration tool for evaluation of the risk of bias to assess study quality (19). Specifically, the tool was used to assess whether there was adequate generation of randomization sequences, concealment of treatment allocation, masking of assessors, and appropriate methods for addressing missing data. Two researchers (J.A.R. and M.-H.A.-A.) independently conducted quality assessments and agreed on the final categorization. We tested for publication bias by examining a funnel plot produced by using the trim-and-fill procedure with the Review Manager version 5.3 program (The Nordic Cochrane Centre, Copenhagen, Denmark).

Ethical Approval

All included studies received ethical approval from their local ethical review boards. The Royal Brisbane and Women's Hospital Human Research Ethics Committee waived the requirement for a full ethical review for this meta-analysis.

Definitions

Table 1 defines the common clinical endpoints available for testing in this analysis. Hospital or intensive care unit (ICU) mortality was defined as the proportion of patients who died before discharge from the hospital or from the ICU, respectively. Hospital mortality was pragmatically censored at 30 days. "Clinical cure" was defined as the disappearance of all infection-related symptoms and signs, as assessed by a blinded clinician 7–14 days after the cessation of study antibiotics (20).

We defined "continuous infusion" as constant intravenous administration throughout a 24-hour period and "intermittent dosing" as administration of an intravenous infusion for less than or equal to 30 minutes. We defined nonfermenting gram-negative bacilli to be

Table 2. Baseline Demographic and Clinical Characteristics of the Combined Study Population

Characteristic	Continuous Infusion (*n* = *312*)	Intermittent Dosing (*n* = *320*)
Age, yr	61 (49–70)	63 (49–72)
Male sex	198 (63.5)	204 (63.8)
APACHE II score	21 (16–26)	20 (16–25)
Organism identified	97 (31.1)	114 (35.6)
Study antibiotic		
Piperacillin-tazobactam	203 (65.1)	221 (69.1)
Meropenem	94 (30.1)	93 (29.1)
Cefepime	11 (3.5)	2 (0.6)
Ticarcillin-clavulanate	4 (1.3)	4 (1.2)
Antibiotic 24-h dose, g		
Piperacillin-tazobactam	13.5 (13.5–18.0)	13.5 (13.5–18.0)
Meropenem	3.0 (2.0–3.0)	3.0 (1.7–3.0)
Cefepime	6.0 (6.0–6.0)	6.0
Ticarcillin-clavulanate	12.4 (12.4–13.2)	12.4
Duration from ICU admission to randomization, d	1 (0–4)	1 (1–4)
Duration of randomized treatment, d	5 (2–7)	4 (2–7)
Postrandomization length of ICU stay, d	7 (4–12)	6 (3–12)
Organ dysfunction		
Cardiovascular	214 (68.6)	217 (67.8)
Respiratory	207 (66.3)	208 (65.0)
Renal	74 (23.7)	82 (25.6)
Metabolic acidosis	71 (25.2)	73 (25.2)
Hematological	45 (14.4)	32 (10.0)
Primary infection site		
Lung	175 (56.1)	172 (53.8)
Intraabdominal	70 (22.4)	79 (24.7)
Blood	28 (9.0)	31 (9.7)
Skin or skin structure	22 (7.1)	28 (8.8)
Urinary tract	21 (6.7)	23 (7.2)
Central nervous system	4 (1.3)	7 (2.2)
Ear, nose, and throat	4 (1.3)	2 (0.6)
Indwelling vascular catheter	4 (1.3)	1 (0.3)
Pleural	2 (0.6)	3 (0.9)
Bone and joint	4 (1.3)	0 (0.0)
Cardiac	3 (1.0)	1 (0.3)
Gynecological	1 (0.3)	0 (0.0)
Others	10 (3.2)	4 (1.3)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit.
Data are presented as median (interquartile range) or number (percentage).

Table 3. Microbiological Characteristics of the Combined Study Population

Characteristic	Continuous Infusion (*n* = 312)	Intermittent Dosing (*n* = 320)
Organism identified	96 (30.8)	112 (35.0)
Gram-positive	25 (26.0)	32 (28.6)
Methicillin-susceptible *Staphylococcus aureus*	9 (36.0)	5 (15.6)
Methicillin-resistant *Staphylococcus aureus*	2 (8.0)	9 (28.1)
Streptococcus pneumoniae	4 (16.0)	3 (9.4)
Streptococcus milleri group	2 (8.0)	5 (15.6)
Enterococcus faecalis	3 (12.0)	2 (6.3)
Staphylococcus epidermidis	2 (8.0)	2 (6.3)
Streptococcus pyogenes	1 (4.0)	3 (9.4)
Enterococcus faecium	0 (0.0)	1 (3.1)
Granulicatella adiacens	0 (0.0)	1 (3.1)
Mycoplasma pneumoniae	0 (0.0)	1 (3.1)
Streptococcus mitis	1 (4.0)	0 (0.0)
Streptococcus dysgalactiae	1 (4.0)	0 (0.0)
Gram-negative	71 (74.0)	80 (71.4)
Escherichia coli	19 (26.8)*	15 (18.8)
Acinetobacter baumannii	16 (22.5)†	16 (20.0)‡
Klebsiella pneumoniae	14 (19.7)§	14 (17.5)
Pseudomonas aeruginosa	14 (19.7)	12 (15.0)
Enterobacter cloacae	1 (1.4)	5 (6.3)‖
Serratia marcescens	1 (1.4)	5 (6.3)¶
Haemophilus influenzae	1 (1.4)	1 (1.3)
Klebsiella oxytoca	0 (0.0)	2 (2.5)
Morganella morganii	0 (0.0)	2 (2.5)¶
Proteus mirabilis	2 (2.8)	0 (0.0)
Stenotrophomonas maltophilia	0 (0.0)	2 (2.5)
Bulkholderia cepacia	0 (0.0)	1 (1.3)
Bulkholderia pseudomallei	1 (1.4)	0 (0.0)
Chlamydophila pneumoniae	0 (0.0)	1 (1.3)
Citrobacter koseri	1 (1.4)	0 (0.0)
Coxiella burnetii	0 (0.0)	1 (1.3)
Enterobacter aerogenes	0 (0.0)	1 (1.3)
Raoultella planticola	0 (0.0)	1 (1.3)
Salmonella typhimurium	1 (1.4)	0 (0.0)
Vibrio vulnificus	0 (0.0)	1 (1.3)
Polymicrobial infection, n (%)	25 (25.8)	29 (25.4)

Data are presented as number (percentage).
*Three isolates were extended-spectrum β-lactamase *Escherichia coli*.
†Five isolates were multidrug-resistant *Acinetobacter baumannii*.
‡Three isolates were resistant *Acinetobacter baumannii*.
§One isolate was extended-spectrum β-lactamase *Klebsiella pneumoniae*.
‖Three isolates were extended-spectrum β-lactamase *Enterobacter cloacae*.
¶One isolate was a nonsusceptible organism.

the following organisms: *Acinetobacter baumannii*, *Bulkholderia cepacia*, *Bulkholderia pseudomallei*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. "Multidrug-resistant" gram-negative organisms were defined as those nonsusceptible to at least one agent in three or more antimicrobial categories (21). "Nonsusceptible organisms" were defined in relationship to the randomized β-lactam antibiotic. Illness severity was estimated using Acute Physiology and Chronic Health Evaluation (APACHE) II scores (ranging from 0 to 71, with higher scores indicating an increased risk of death) (22), and they were calculated using the most abnormal data for the first 24 hours after ICU admission.

Individual Patient Data Meta-analysis

Researchers with access to the primary data (J.A.R., M.-H.A.-A., and J.M.D.) reviewed individual study variables and extracted relevant common variables into a single dataset. Data on hospital mortality and 90-day mortality were recoded into a single variable ("hospital mortality censored at 30 days"). There were no duplicate participants in the included studies, and missing data and logic testing were performed on the combined dataset.

We used intention-to-treat principles to conduct the efficacy analysis. Basic characteristics of study participants were presented using number (percentage) and median (interquartile range [IQR]), as appropriate. Heterogeneity between studies was assessed using a χ^2 test and was considered significant if the P value was less than 0.10 or the I^2 statistic was greater than 50%. Depending on the observed heterogeneity, pooled estimates of effect and the 95% confidence interval (CI) were reported for the combined population using a fixed or random effects model; the random effects model was selected when the I^2 statistic was greater than or equal to 50%. Relative risk (RR) was used for dichotomous outcomes (mortality and clinical cure), and median difference was used for continuous outcomes (ICU-free days at Day 28). We constructed a Kaplan–Meier survival curve to compare survival trends censored at hospital discharge or Day 30, whichever was sooner, and comparison between the two treatment groups was performed using a log-rank test with the hazard ratio and 95% CI reported.

We constructed a multivariable logistic regression model and a Cox proportional hazards model to identify significant predictors associated with hospital survival censored at Day 30 and clinical cure, respectively, with the odds ratio and 95% CI reported. In both models, baseline variables considered to be biologically plausible and with a P value less than or equal to 0.15 in univariate analysis were entered into the model. In all models, a study variable was entered as a fixed covariate and interactions between covariates and treatment effect were explored. Goodness of fit for the multivariable logistic regression model was assessed using the Hosmer–Lemeshow test. We also explored the association of three *a priori* variables—culture-positive infection, infection by a gram-negative pathogen, and requirement for acute renal replacement therapy during ICU admission—with the outcomes of interest. A Classification and Regression

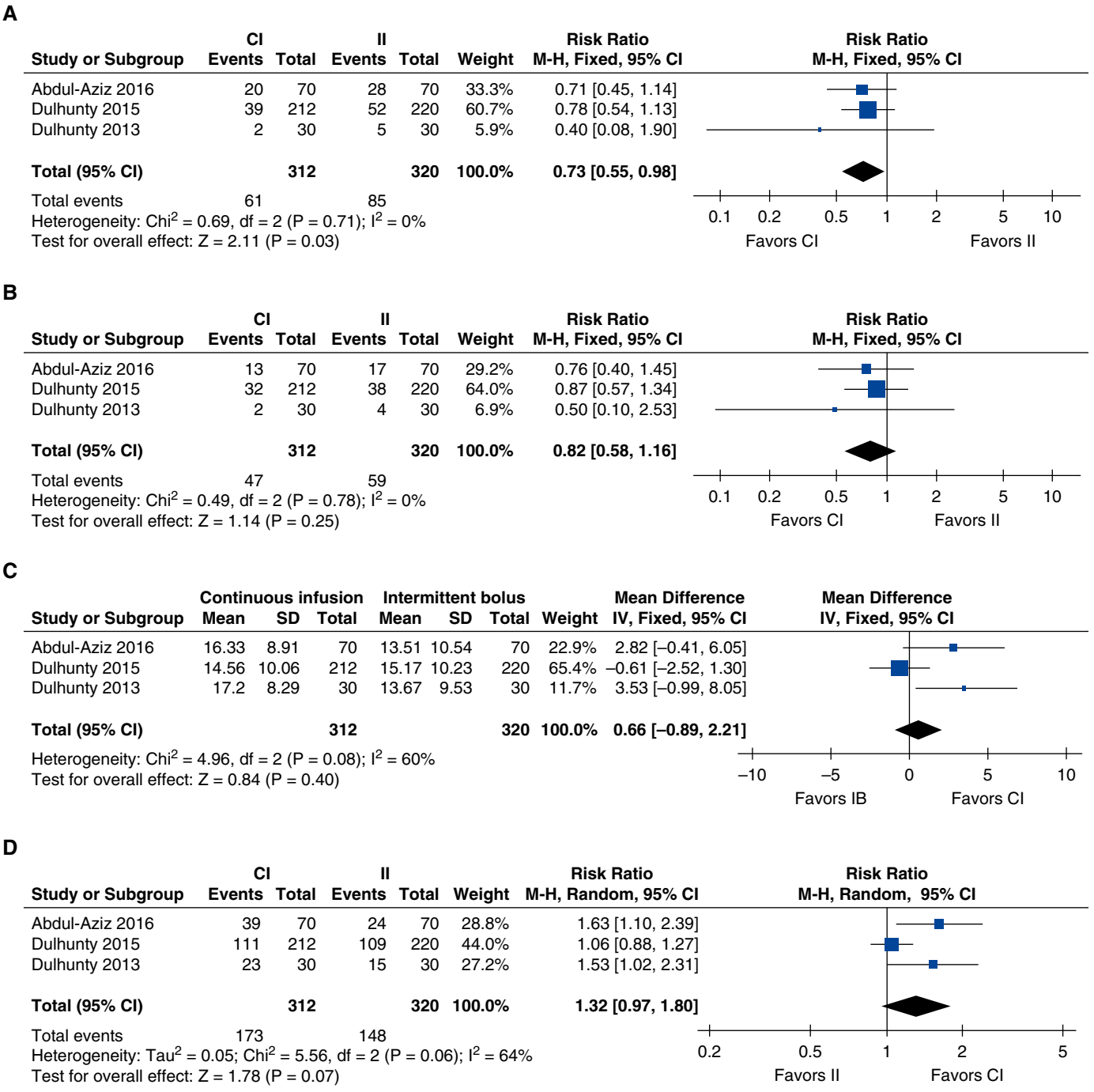

Figure 2. Differences in mortality and clinical cure, along with 95% confidence intervals (95% CIs), for continuous infusion (CI) versus intermittent infusion (II). (*A*) Hospital mortality censored at Day 30. (*B*) Intensive care unit mortality. (*C*) Intensive care unit–free days at Day 28. (*D*) Clinical cure. df = degrees of freedom; IB = intermittent bolus; IV = inverse variance; M-H = Mantel–Haenszel test.

Tree analysis was used to delineate patient subgroups associated with greatest separation in the outcome of interest for each treatment group (23).

Statistical analysis was performed using IBM SPSS Statistics version 22 software (IBM Corp., Armonk, NY). A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Study Selection and Characteristics

A Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart for

identification of included studies is presented in Figure 1. We identified three RCTs of critically ill patients with severe sepsis. These RCTs recruited a total of 632 patients, for all of whom the trial authors provided the requested data (20, 24, 25). Of these, 312 patients were assigned to receive β-lactam antibiotic therapy by continuous infusion and 320 patients were assigned to receive β-lactam antibiotic intermittent dosing. The three studies contributed 432 (20), 140 (24), and 60 (25) patients from 26, 2, and 5 centers, respectively, and were conducted across Australia, New Zealand, Hong Kong, and Malaysia. All studies met the four quality assessment criteria (*see* Table E1 in the online supplement). There were no missing data in any of the trials for hospital mortality, clinical cure, ICU-free days at Day 28, or ICU mortality. We could find no significant evidence of heterogeneity between the included studies (*see* Figure E1).

Individual Patient Data Meta-analysis

Patient characteristics. The baseline characteristics of the continuous and intermittent dosing groups for the population as a whole and by study are reported in Table 2 and Table E2, respectively. There were no significant baseline differences between the treatment groups. A pathogen was isolated from blood in 31 participants (9.7%) in the intermittent dosing group and 28 participants (9.0%) in the continuous dosing group (Table 2). The median durations of study drug administration were 4 days (IQR, 2–7) in the intermittent dosing group and 5 days (IQR, 2–7) in the continuous dosing group ($P = 0.57$). Randomization occurred within 1 day (IQR, 0–4) of ICU admission in the continuous dosing group and also within 1 day (IQR, 1–4) in the intermittent dosing group. The three most commonly identified causative organisms were *Escherichia coli*, *A. baumannii*, and *Staphylococcus aureus* (Table 3).

Patient outcomes. In the combined study population, hospital mortality was significantly lower (RR, 0.74; 95% CI, 0.56–1.00; $P = 0.045$) and clinical cure was significantly higher (RR, 1.20; 95% CI, 1.03–1.40; $P = 0.021$) in the continuous dosing group than in the intermittent dosing group (Figure 2). The numbers needed to treat with continuous infusion to improve patient survival and clinical cure were 15 and 11 patients, respectively. The Kaplan–Meier 30-day survival curve for the combined study population is shown in Figure 3. There was no difference between the groups in terms of ICU-free days at Day 28 (RR, 0; 95% CI, −3 to 3; $P = 0.90$) or ICU mortality (RR, 0.82; 95% CI, 0.58–1.16; $P = 0.26$).

The factors predicting hospital mortality and clinical cure are summarized in Table 4. Higher APACHE II score, receipt of acute renal replacement therapy, respiratory and cardiovascular dysfunction on admission, β-lactam antibiotic administration by intermittent dosing, infection by nonfermenting gram-negative bacilli, and older age were all statistically significant predictors of hospital mortality. The absence of acute renal replacement therapy during ICU admission, lower APACHE II score, younger age, and nonbloodstream infection were all statistically significant for clinical cure. β-Lactam antibiotic administration by continuous infusion was not independently associated with clinical cure.

Subgroup analyses. Using a Classification and Regression Tree analysis, APACHE II scores less than 22 were associated with improved hospital survival ($P = 0.024$) and clinical cure ($P = 0.019$). The patient outcome data for APACHE II and renal replacement therapy subgroups are presented in Table 5. In these groups, statistically significant advantages were observed for clinical cure only. The Cox regression 30-day hospital survival curve for the combined study population is shown in Figure 4.

We also examined the effect of infection caused by a gram-negative pathogen and the presence of acute renal replacement therapy on outcomes. We found no differences between the continuous infusion and intermittent dosing groups for hospital mortality (RR, 1.17; 95% CI, 0.74–1.86; $P = 0.50$), clinical cure (RR, 1.04; 95% CI, 0.74–1.45; $P = 0.84$), or ICU mortality (RR, 1.47; 95% CI, 0.77–2.82; $P = 0.24$) in patients in whom the infection was caused by a gram-negative pathogen.

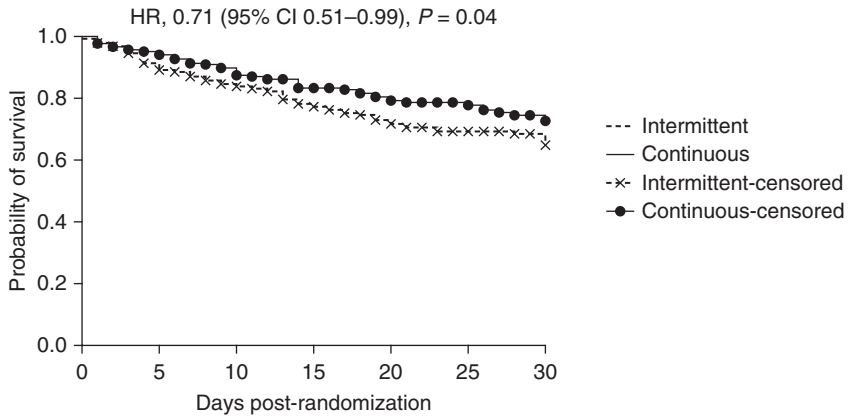

Figure 3. Kaplan–Meier 30-day survival curves for combined study population. CI = confidence interval; HR = hazard ratio.

Discussion

Key Findings

In this individual patient data meta-analysis including data from 632 randomized patients, we found that, compared with intermittent infusion, continuous infusion of β-lactam antibiotics was associated with lower hospital mortality censored at 30 days. Clinical cure was higher in the continuous dosing group, although this was not statistically significant after adjusting for between-study heterogeneity and in multivariable analysis. We also identified patient subgroups in whom further prospective RCTs should be considered, namely patients with higher APACHE II scores and those not

Table 4. Factors Associated with Hospital Mortality Censored at 30 Days and Clinical Cure for the Combined Study Population

Variable	All Factors Included in the Model		Final Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Factors predicting hospital mortality censored at 30 d				
APACHE II score, per 1-point increase	1.08 (1.05–1.11)	<0.001	1.08 (1.05–1.11)	<0.001
Renal replacement therapy	2.48 (1.40–4.39)	0.002	3.02 (1.76–5.18)	<0.001
Study		0.01		0.003
Dulhunty and colleagues (25)	0.70 (0.23–2.15)	0.54	0.66 (0.26–1.67)	0.38
Abdul-Aziz and colleagues (24)	2.89 (1.33–6.24)	0.01	2.55 (1.35–4.79)	0.01
Dulhunty and colleagues (20) (reference group)	1.00		1.00	
Respiratory dysfunction on admission	1.86 (1.15–3.00)	0.01	1.71 (1.07–2.75)	0.03
Infection by NFGNB*	2.85 (1.35–6.04)	0.01	2.72 (1.32–5.62)	0.01
Age, per 1-yr increase	1.02 (1.00–1.03)	0.02	1.02 (1.00–1.03)	0.03
Cardiovascular dysfunction on admission	1.68 (1.03–2.75)	0.03	1.72 (1.06–2.80)	0.02
Hematological dysfunction on admission	1.78 (0.97–3.25)	0.06	—	—
Renal dysfunction on admission	1.41 (0.87–2.28)	0.17	—	—
Continuous infusion	0.52 (0.08–3.21)	0.48	0.62 (0.41–0.94)	0.03
Continuous infusion × study interaction		0.69	—	—
Dulhunty and colleagues (25) compared with Dulhunty and colleagues (20) × continuous infusion	0.77 (0.12–5.10)	0.79	—	—
Abdul-Aziz and colleagues (24) compared with Dulhunty and colleagues (20) × continuous infusion	0.67 (0.26–1.71)	0.89	—	—
Causative organism identified	0.76 (0.18–3.17)	0.70	—	—
Goodness of fit				
Hosmer–Lemeshow test	$\chi^2 = 3.26$, $df = 8$	0.917	$\chi^2 = 3.21$, $df = 8$	0.921
Factors predicting clinical cure				
Renal replacement therapy	0.41 (0.25–0.69)	0.001	0.38 (0.24–0.62)	<0.001
APACHE II score, per 1-point increase	0.97 (0.94–0.99)	0.01	0.97 (0.94–0.99)	0.003
Age, per 1-yr increase	0.99 (0.98–0.99)	0.03	0.98 (0.97–0.99)	0.03
Bacteremia	0.54 (0.29–1.00)	0.05	0.51 (0.28–0.92)	0.03
Study		0.05		0.01
Dulhunty and colleagues (25)	1.02 (0.45–2.30)	0.97	0.87 (0.40–1.89)	0.73
Abdul-Aziz and colleagues (24)	0.45 (0.23–0.87)	0.02	0.36 (0.20–0.62)	0.001
Dulhunty and colleagues (20) (reference group)	1.00		1.00	
Continuous infusion	1.17 (0.78–1.74)	0.45	—	—
Continuous infusion × study interaction		0.08		0.01
Dulhunty and colleagues (25) compared with Dulhunty and colleagues (20) × continuous infusion	2.50 (0.75–8.37)	0.14	2.45 (1.22–4.92)	0.06
Abdul-Aziz and colleagues (24) compared with Dulhunty and colleagues (20) × continuous infusion	2.20 (0.97–4.97)	0.06	3.02 (0.97–9.37)	0.01
Urinary tract infections	1.82 (0.92–3.63)	0.09	—	—
Skin or skin structure infections	0.64 (0.34–1.21)	0.17	—	—
Hematological dysfunction on admission	0.77 (0.45–1.34)	0.36	—	—
Causative organism identified	1.85 (0.47–7.38)	0.38	—	—
Infection by NFGNB*	0.77 (0.45–1.34)	0.46	—	—
Renal dysfunction on admission	1.11 (0.72–1.71)	0.63	—	—
Goodness-of-fit				
Hosmer–Lemeshow test	$\chi^2 = 8.01$, $df = 8$	0.433	$\chi^2 = 10.2$, $df = 8$	0.252

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; *df* = degrees of freedom; NFGNB = nonfermenting gram-negative bacilli; OR = odds ratio.
*Nonfermenting gram-negative bacilli in this study included *Acinetobacter baumannii*, *Bulkholderia cepacia*, *Bulkholderia pseudomallei*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*.

requiring renal replacement therapy (26, 27).

Relationship to Previous Papers

We focused on patients with severe sepsis rather than sepsis overall, as these patients are more likely to have pathophysiological changes leading to subtherapeutic drug concentrations (5, 13, 28). Researchers in pharmacokinetic studies of critically ill patients with sepsis have concluded that administration by continuous infusion increases the achievement of target concentrations, both in plasma and in tissues, compared with intermittent dosing (5, 14, 15, 25, 27, 29).

Table 5. Treatment Group Comparisons by Acute Physiology and Chronic Health Evaluation II Score and Renal Replacement Therapy Subgroups

	Continuous Infusion	Intermittent Dosing	RR (95% CI)	*P* Value
		Hospital mortality censored at 30 d		
APACHE II score ⩾22*	44 (29.7)	57 (40.4)	0.74 (0.53–1.01)	0.06
APACHE II score <22†	17 (10.4)	27 (15.1)	0.69 (0.39–1.21)	0.19
RRT‡	21 (38.2)	27 (45.8)	0.83 (0.54–1.29)	0.41
Without RRT§	40 (15.6)	57 (21.8)	0.71 (0.49–1.03)	0.07
Culture-positive infection‖	32 (33.3)	30 (26.8)	1.24 (0.82–1.88)	0.30
Gram-positive organism¶	7 (28.0)	6 (18.8)	1.49 (0.57–3.89)	0.41
Gram-negative organism**	25 (35.2)	24 (30.0)	1.17 (0.74–1.86)	0.50
Culture-negative infection††	29 (13.4)	54 (26.0)	0.52 (0.34–0.78)	0.001
Susceptible microorganism‡‡	34 (29.8)	32 (28.1)	1.06 (0.71–1.60)	0.77
Piperacillin-tazobactam§§	33 (16.3)	57 (25.8)	0.63 (0.43–0.93)	0.02
Meropenem‖‖	20 (21.3)	27 (29.0)	0.73 (0.44–1.21)	0.22
Lung infection¶¶	40 (22.9)	43 (25.0)	0.91 (0.63–1.33)	0.64
Intraabdominal infection***	19 (27.1)	21 (26.6)	1.02 (0.60–1.74)	0.94
		ICU mortality		
APACHE II score ⩾22*	34 (23.0)	41 (29.1)	0.79 (0.53–1.17)	0.24
APACHE II score <22†	13 (7.9)	18 (10.1)	0.79 (0.40–1.56)	0.49
RRT‡	18 (32.7)	23 (39.0)	0.84 (0.51–1.38)	0.49
Without RRT§	29 (11.3)	36 (13.8)	0.82 (0.52–1.29)	0.39
Culture-positive infection‖	22 (22.9)	18 (16.1)	1.43 (0.81–2.50)	0.21
Gram-positive organism¶	5 (20.0)	5 (15.6)	1.28 (0.42–3.94)	0.67
Gram-negative organism**	17 (23.9)	13 (16.3)	1.47 (0.77–2.82)	0.24
Culture-negative infection††	25 (11.6)	41 (19.7)	0.59 (0.37–0.93)	0.02
Susceptible microorganism‡‡	23 (20.2)	22 (19.3)	1.05 (0.62–1.77)	0.87
Piperacillin-tazobactam§§	28 (13.8)	39 (17.6)	0.78 (0.50–1.22)	0.28
Meropenem‖‖	13 (13.8)	20 (21.5)	0.64 (0.34–1.22)	0.17
Lung infection¶¶	32 (18.3)	30 (17.4)	1.04 (0.67–1.65)	0.84
Intraabdominal infection***	13 (18.6)	13 (16.5)	1.13 (0.56–2.27)	0.73
		Clinical cure		
APACHE II score ⩾22*	69 (46.6)	47 (33.3)	1.40 (1.05–1.87)	0.02
APACHE II score <22†	104 (63.4)	101 (56.4)	1.12 (0.94–1.34)	0.19
RRT‡	15 (27.3)	19 (32.2)	0.85 (0.48–1.50)	0.57
Without RRT§	158 (61.5)	129 (49.4)	1.24 (1.06–1.45)	0.01
Culture-positive infection‖	44 (45.8)	49 (43.8)	1.05 (0.77–1.42)	0.76
Gram-positive organism¶	10 (40.0)	12 (37.5)	1.07 (0.55–2.06)	0.85
Gram-negative organism**	34 (47.9)	37 (46.3)	1.04 (0.74–1.45)	0.84
Culture-negative infection††	129 (59.7)	99 (47.6)	1.25 (1.05–1.50)	0.01
Susceptible microorganism‡‡	60 (52.6)	49 (43.0)	1.22 (0.93–1.61)	0.15
Piperacillin-tazobactam§§	113 (55.7)	93 (42.1)	1.32 (1.09–1.61)	0.01
Meropenem‖‖	53 (56.4)	50 (53.8)	1.05 (0.81–1.36)	0.72
Lung infection¶¶	91 (52.0)	81 (47.1)	1.10 (0.89–1.37)	0.36
Intraabdominal infection***	35 (50.0)	39 (49.4)	1.01 (0.73–1.40)	0.94
		ICU-free days censored at Day 28		
APACHE II score ⩾22*	15 (0–22)	12 (0–22)	3 (−4 to 10)	0.47
APACHE II score <22†	21 (15–24)	22 (11–25)	−1 (−3 to 1)	0.78
RRT‡	2 (0–18)	3 (0–20)	−1 (−9.76 to 7.76)	0.98
Without RRT§	20 (12–24)	21 (6–24)	−1 (−2.77 to 0.77)	0.92
Culture-positive infection‖	18 (0–22)	19 (4–24)	−1 (−6 to 3)	0.22
Gram-positive organism¶	17 (1–21)	19 (12–24)	−2 (−13 to 10)	0.10
Gram-negative organism**	18 (0–23)	19 (1–23)	−1 (−6 to 4)	0.69
Culture-negative infection††	20 (6–24)	19 (0–24)	1 (−2 to 4)	0.36
Susceptible microorganism‡‡	19 (2–23)	19 (0–23)	0 (−3 to 4)	0.94
Piperacillin-tazobactam§§	19 (6–24)	20 (3–24)	−1 (−4 to 2)	0.96
Meropenem‖‖	18 (4–23)	17 (0–23)	1 (−6 to 7)	0.25
Lung infection¶¶	18 (2–22)	17 (0–23)	1 (−2 to 4)	0.69
Intraabdominal infection***	17 (0–24)	21 (4–24)	−4 (−11 to 2)	0.46

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; ICU = intensive care unit; RR = relative risk; RRT = renal replacement therapy.

Intermittent dosing is the reference group for the treatment group comparisons.

*n = 289; continuous infusion = 148, intermittent dosing = 141.

†n = 343; continuous infusion = 164, intermittent dosing = 179.

‡n = 114; continuous infusion = 55, intermittent dosing = 59.

§n = 518; continuous infusion = 257, intermittent dosing = 261.

‖n = 208; continuous infusion = 96, intermittent dosing = 112.

¶n = 57; continuous infusion = 25, intermittent dosing = 32.

**n = 151; continuous infusion = 71, intermittent dosing = 80.

††n = 424; continuous infusion = 216, intermittent dosing = 208.

‡‡n = 228; continuous infusion = 114, intermittent dosing = 114.

§§n = 424; continuous infusion = 203, intermittent dosing = 221.

‖‖n = 187; continuous infusion = 94, intermittent dosing = 93.

¶¶n = 347; continuous infusion = 175, intermittent dosing = 172.

***n = 149; continuous infusion = 70, intermittent dosing = 79.

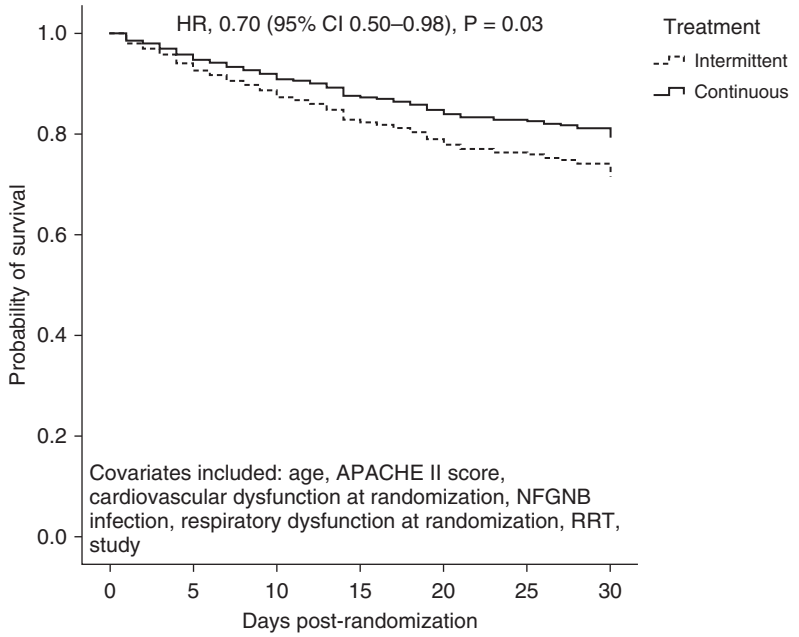

Figure 4. Cox regression 30-day survival curves for combined study population. APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; HR = hazard ratio; NFGNB = nonfermenting gram-negative bacilli (*Acinetobacter baumannii*, *Bulkholderia cepacia*, *Bulkholderia pseudomallei*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*); RRT = renal replacement therapy.

Several RCTs comparing continuous infusion and intermittent dosing of β-lactam antibiotics have been conducted in critically ill patients, although none have had adequate statistical power to detect a difference in mortality (20, 24, 25, 30–35). In contrast to the present study, authors of previous aggregated data metaanalyses of this question found no significant difference in mortality between the continuous and intermittent dosing groups (16, 36–40). These metaanalyses were less selective than the present analysis in their inclusion criteria, included data from both critically ill and non–critically ill patients, and allowed differing antibiotic doses in the two treatment groups, all of which may have diluted any advantage of continuous infusion.

Implications of Study Findings

The results of our meta-analysis imply that administration of β-lactam antibiotics by continuous infusion compared with intermittent infusion in critically ill patients with severe sepsis may decrease hospital mortality, although the relationship with clinical cure was more complex and may have been influenced by the subjective limitations of this endpoint. Moreover, our findings imply that patients receiving renal replacement therapy may not derive a significant benefit from continuous infusion. In addition, they imply that the beneficial impact of continuous infusion is likely greatest in infections with nonfermenting gram-negative bacilli (e.g., *A. baumannii* and *P. aeruginosa*).

These implications are biologically plausible because patients receiving renal replacement therapy are likely to have reduced drug clearance and hence higher serum antibiotic concentrations, regardless of which antibiotic administration method is used (41). Similarly, nonfermenting gram-negative bacilli tend to have higher MICs than β-lactam antibiotics (42), supporting data from pharmacokinetic and dosing simulation studies indicating that continuous infusion of β-lactam antibiotics is more likely than intermittent dosing to achieve therapeutic targets for less-susceptible pathogens (14, 15).

Strengths and Limitations

Owing to the stringency of our inclusion criteria, only three studies were included in this analysis. However, these inclusion criteria were all selected *a priori*, had mechanistic precedents, and were applied equally to all studies identified in our systematic literature search. The fact that the included patients were enrolled across only four countries means that the results may not be generalizable to all treatment settings. We did observe that study was independently associated with mortality and clinical cure, suggesting some degree of between-study heterogeneity. This was particularly true for one study (24) when compared with the other two (20, 25), highlighting potential differences in baseline factors by geographical region. However, despite this, a statistically significant interaction effect between study and treatment was observed only for clinical cure and not for mortality. This leads us to conclude that the treatment effect observed was consistent across studies for mortality, while study variability in a (nonsignificant) treatment effect on clinical cure may have been influenced by subjective differences between studies in how this endpoint was assessed. The relatively low proportion of patients with identified pathogens and the lack of MIC data across each of the studies prevented us from testing the importance of pathogen MIC on patient outcomes. Although such an analysis would provide useful mechanistic data, it would be of secondary importance to the patient-centered outcomes reported in the present study.

Conclusions

In this individual patient data meta-analysis of a large critical care patient population with severe sepsis, we found that administration of β-lactam antibiotics by continuous infusion is associated with decreased hospital mortality and a higher rate of clinical cure compared with intermittent dosing. Given these findings, we recommend that a definitive RCT be conducted in patients with a higher level of sickness severity who are not receiving renal replacement therapy and are at risk of infection by less-susceptible pathogens such as nonfermenting gram-negative bacilli.

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

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