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## Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis

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**Abstract Purpose:** This study  
aims to determine if continuous  
infusion (CI) is associated with better  
clinical and pharmacokinetic/phar-  
macodynamic (PK/PD) outcomes  
compared to intermittent bolus (IB)  
dosing in critically ill patients with

severe sepsis. **Methods:** This was a  
two-centre randomised controlled  
trial of CI versus IB dosing of beta-  
lactam antibiotics, which enrolled  
critically ill participants with severe  
sepsis who were not on renal  
replacement therapy (RRT). The pri-  
mary outcome was clinical cure at  
14 days after antibiotic cessation.  
Secondary outcomes were PK/PD  
target attainment, ICU-free days and  
ventilator-free days at day 28 post-  
randomisation, 14- and 30-day sur-  
vival, and time to white cell count  
normalisation. **Results:** A total of  
140 participants were enrolled with  
70 participants each allocated to CI  
and IB dosing. CI participants had  
higher clinical cure rates (56 versus  
34 %,  $p = 0.011$ ) and higher median  
ventilator-free days (22 versus  
14 days,  $p < 0.043$ ) than IB partici-  
pants. PK/PD target attainment rates  
were higher in the CI arm at 100 %  
 $fT_{>MIC}$  than the IB arm on day 1 (97  
versus 70 %,  $p < 0.001$ ) and day 3  
(97 versus 68 %,  $p < 0.001$ ) post-  
randomisation. There was no differ-  
ence in 14-day or 30-day survival  
between the treatment arms. **Conclu-  
sions:** In critically ill patients with  
severe sepsis not receiving RRT, CI  
demonstrated higher clinical cure

rates and had better PK/PD target attainment compared to IB dosing of beta-lactam antibiotics. Continuous beta-lactam infusion may be mostly advantageous for critically ill patients with high levels of illness severity

and not receiving RRT. Malaysian National Medical Research Register ID: NMRR-12-1013-14017.

**Keywords** Antibiotics · Critically ill · Intermittent bolus · Pharmacokinetics · Pharmacodynamics · Prolonged infusion

## Introduction

Mortality due to severe infections remains persistently high worldwide, ranging from 30 to 50 % in patients with severe sepsis and 40 to 80 % in those with septic shock [1]. Optimised antibiotic therapy is an intervention likely to improve treatment outcomes in severe sepsis [2].

Beta-lactam antibiotics display time-dependent activity where bacterial killing and treatment efficacy correlate with the duration of time ( $T$ ) that free (unbound) plasma drug concentrations remain above the minimum inhibitory concentration (MIC) of the offending pathogen ( $fT_{>MIC}$ ) [3]. Based on this characteristic, maximal beta-lactam effects are considered more likely with continuous infusion (CI) rather than traditional intermittent bolus (IB) dosing. IB dosing may produce beta-lactam concentrations below the MIC for much of the dosing interval [4], particularly in the ICU where pathogens with higher MIC values are relatively common [5].

Although CI has been shown to be superior to IB dosing in numerous preclinical and pharmacokinetic/pharmacodynamic (PK/PD) simulation studies [4], most clinical comparative trials have failed to demonstrate a clinical advantage of CI dosing in terms of clinical cure and/or patient survival [6–13]. Meta-analyses of prospective studies have also not found any significant clinical benefits favouring CI over IB dosing [14–16]. However, most of the studies recruited heterogeneous patient groups and have important methodological flaws, potentially masking any possible benefits of CI dosing in critically ill patients [14, 15]. Three recent randomized clinical trials (RCT) have demonstrated some clinical outcome advantages favouring CI administration of beta-lactam antibiotics when only critically ill patients were recruited [17–19]. As most of the current evidence was derived from Western countries, the wider applicability of CI dosing remains largely unexplored in some regions which are plagued by more resistant pathogens and patients with higher levels of sickness severity [20]. Data from such areas, particularly from the South East Asian countries, are vital in order to support a global practice change if subsequent studies identify CI benefits in critically ill patients. The primary aim of the Beta-Lactam Infusion in Severe Sepsis (BLISS) study was to determine if CI of beta-lactam antibiotics is associated with improved clinical outcomes compared to IB dosing in a

large cohort of critically ill patients with severe sepsis in a Malaysian ICU setting.

Findings of the BLISS study were presented, in part, at the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, CA, 18–21 September 2015 [21].

## Methods

### Study design

The BLISS study was a prospective, two-centre, open-labelled RCT of CI versus IB dosing of beta-lactam antibiotics in critically ill patients with severe sepsis from the two following Malaysian ICUs: (1) Tengku Ampuan Afzan Hospital (HTAA), Kuantan; and (2) University Malaya Medical Centre (UMMC), Kuala Lumpur. Institutional ethics approval was obtained at each participating site. Written informed consent to participate in the study was obtained from each participant prior to study enrolment. The study was registered with the Malaysian National Medical Research Register (ID: NMRR-12-1013-14017).

### Participants and randomisation

ICU patients were eligible for inclusion if they met all of the following criteria: (1) adult ( $\geq 18$  years); (2) developed severe sepsis (defined as presumed or confirmed infection with new organ dysfunction) [24] in the previous 48 h; (3) indication for cefepime, meropenem or piperacillin/tazobactam with  $< 24$  h therapy at time of assessment; and (4) expected ICU stay greater than 48 h. Patients were excluded if they (1) were receiving renal replacement therapy (RRT); (2) had impaired hepatic function (defined as total bilirubin  $> 100$   $\mu\text{mol/mL}$ ); (3) were receiving palliative treatment; (4) had inadequate central venous catheter access; or (5) death was deemed imminent.

Participants currently receiving, or about to receive, cefepime, meropenem or piperacillin/tazobactam were randomly allocated to either a CI (intervention arm) or IB (control arm) treatment arm. Randomisation was performed using a computer program (<http://www.>

randomization.com) based on blocks of four with an allocation ratio of 1:1 stratified by participating sites. Following study enrolment, an on-duty, unblinded pharmacist who was responsible for preparing medications determined treatment allocation by opening sequentially numbered opaque, sealed and stapled envelopes. The tamper-evident envelopes were prepared by an unblinded investigator and were provided to each participating site.

### Intervention

Each antibiotic dose was prepared by an on-duty, unblinded ICU pharmacist in accordance with standard pharmacy practice. The dosing regimen was determined by the treating intensivist, with guidance from a local dosing protocol (Supplementary Table 1). To ensure early achievement of therapeutic beta-lactam exposures in the intervention arm, a single loading dose infused over 30 min was given at initiation of antibiotic therapy meaning that the continuous infusion group received a larger antibiotic dose on day 1 post-randomisation compared to those in the control arm (Supplementary Table 1). The study antibiotic was administered until (1) the treating intensivist decided to cease the drug; (2) the participant withdrew from the study; (3) ICU discharge; or (4) ICU death. All subsequent patient management including addition of other antibiotics and non-study drugs was at the treating intensivist's discretion.

### Outcomes and measurements

The primary endpoint investigated in this study was clinical cure at 14 days after antibiotic cessation. Clinical outcome was rated as either (1) resolution: complete disappearance of all signs and symptoms related to infection; (2) improvement: a marked or moderate reduction in disease severity and/or number of signs and symptoms related to infection; or (3) failure: insufficient lessening of the signs and symptoms of infection to qualify as improvement, death or indeterminate for any reason. Clinical cure was scored as a "Yes" for resolution and a "No" for all other findings (i.e. sum of 2 and 3 above). Secondary endpoints investigated in this study include (1) PK/PD target attainment; (2) ICU-free days at day 28; (3) ventilator-free days at day 28; (4) survival at day 14; (5) survival at day 30; (6) time to white cell count (WCC) normalisation. The definitions used to assess these endpoints are described in Supplementary Table 2.

For the secondary endpoint of PK/PD target attainment, assessment was made by comparing the unbound (free) beta-lactam concentrations against the "surrogate MIC" of the pathogen. This MIC was inferred from the European Committee on Antimicrobial Susceptibility

Testing (EUCAST) database. PK/PD target attainment was evaluated as a dichotomous variable and scored as a "Yes" if measured drug concentration exceeded pathogen "surrogate MIC". Only participants with complete PK data were included in the analysis (i.e. those who had both trough and mid-interval drug concentrations collected on days 1 and 3 post-randomisation). Participants who were infected with beta-lactam-resistant pathogens were excluded from the PK/PD analysis.

Independent investigators who were blinded to treatment allocation, patient care and management assessed the endpoints of interest. These investigators were not working in the participating ICUs during this study.

Demographic, clinical and treatment-related variables were collected. Microbiological cultures were collected from the most likely infection site immediately before or during antibiotic treatment. Creatinine clearance was estimated using the Cockcroft–Gault formula [22]. Acute Physiology and Chronic Health Evaluation II (APACHE II) [23] and Sequential Organ Failure Assessment (SOFA) [24] scores were calculated and recorded within 24 h of ICU admission. Comorbidity was scored using the Charlson comorbidity index [25]. Adverse events during the study period were recorded and evaluated as "almost certainly", "probably", "possibly", or "unlikely" to be caused by study antibiotics [26]. Data were collected until participants were discharged from hospital or death.

### Pharmacokinetic sampling and bioanalysis

Pharmacokinetic sampling was coordinated by unblinded investigators and was performed on days 1 and 3 post-randomisation. Blood (5 mL) was collected into lithium-heparinised tubes. For participants in the IB arm, mid-dosing interval and trough concentrations were collected. For participants in the CI arm, two blood samples were taken at least 12 h apart. All blood samples were immediately refrigerated at 4 °C and within 1 h, then centrifuged at 3000 rpm for 10 min to separate plasma. Plasma samples were frozen at –80 °C within 24 h of collection. Frozen plasma samples were shipped on dry ice by a commercial courier and assayed at the Burns, Trauma and Critical Care Research Centre (BTCCRC), the University of Queensland, Australia.

Beta-lactam plasma concentrations were measured, after protein precipitation, by a validated high-performance liquid chromatography (HPLC) method with ultraviolet detection [27], on a Shimadzu Prominence (Shimadzu Corporation, Kyoto, Japan) instrument. Samples were assayed in batches, alongside calibration standards and quality control replicates at high, medium and low concentrations. All bioanalysis techniques were conducted in accordance with regulatory standards [28]. Observed concentrations were corrected for protein binding using published protein binding values (20 % for

cefepime, 2 % for meropenem and 30 % for piperacillin) [29].

### Sample size calculations

A sample size of 120 participants (60 in each treatment arm) was estimated to demonstrate a statistical significant difference in the primary endpoint (power 0.8, alpha 0.05). For clinical cure, 75 % of patients in the intervention arm versus 45 % in the control arm were estimated to achieve clinical cure [17]. The final study sample size was increased to 140 participants (70 in each arm) factoring in a 15–20 % dropout rate.

### Statistical analysis

Statistical analyses were primarily performed on the intention-to-treat (ITT) population. A modified intention-to-treat (mITT) analysis was also performed in all participants who received at least one dose of study antibiotic. A per-protocol (PP) analysis was performed in all participants who received study antibiotic for  $\geq 4$  days.

Data are presented as median values with interquartile ranges (IQR) for continuous variables and number and percentage for categorical variables. Differences in free plasma antibiotic concentration and free plasma antibiotic concentration to MIC ratio in the ITT population were analysed using a Mann–Whitney *U* test and are graphically presented as box (median and IQR) and whisker (10th–99th percentile) plots. Primary and secondary endpoints were compared between the two treatment arms using a Pearson's Chi-square test or a Mann–Whitney *U* test as appropriate. For the primary endpoint, subgroup analyses (determined a priori) were performed according to the beta-lactams prescribed, concomitant antibiotic treatment, infection sites and presence of *Acinetobacter baumannii* or *Pseudomonas aeruginosa* infection. For ICU-free days and ventilator-free days, results are presented for ICU survivors. A Kaplan–Meier survival curve was constructed to compare survival trends at day 14 and day 30 in the ITT population. Comparison of survival between the two treatment arms was performed using a log-rank test with the hazard ratio (HR) and 95 % confidence interval (CI) reported. A multivariate logistic regression was constructed to identify significant predictors associated with cure, with odds ratio (OR) and 95 % CI reported. Biologically plausible variables with a *p* value  $\leq 0.15$  on univariate analysis were considered for model building. A two-sided *p* value of  $< 0.05$  was considered statistically significant in all analyses. Statistical analysis was performed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, New York).

## Results

### Baseline demographics and clinical characteristics

Participants were recruited from April 2013 to July 2014. The sites enrolled 55 and 85 participants, respectively. Two hundred and twenty patients were assessed for eligibility of whom 140 were randomised and 134 received at least one dose of the study antibiotic. One hundred and twenty-six participants received  $\geq 4$  days of randomised treatment. The BLISS study CONSORT flow diagram is presented in Supplementary Fig. 1 and details that the most common reason for patient exclusion was presence of RRT on assessment ( $n = 32$ ). The baseline characteristics of the ITT population are presented in Table 1.

The allocation of beta-lactam antibiotics was comparable between the treatment arms except for cefepime where 11 participants were allocated to the intervention arm and only two to the control arm. The median 24-h antibiotic dose was not different between the intervention and control arms: cefepime 6 g (IQR 6–6) versus 6 g (2 participants), meropenem 3 g (IQR 3–3) versus 3 g (IQR 3–3) and piperacillin/tazobactam 18 g (IQR 18–18) versus 18 g (IQR 9–18), respectively. The median antibiotic treatment course was 7 days (IQR 5–9) in both treatment arms. Thirty-three participants (47 %) in both treatment arms received concomitant antibiotic therapy as part of their treatment. The median ICU stay was 8 days (IQR 5–10) for participants in the intervention arm and 6 days (IQR 4–13) in the control arm ( $p = 0.544$ ). The median ventilator days were 6 (IQR 3–7) and 5 (IQR 3–11) for participants in the intervention and control arms ( $p = 0.662$ ), respectively. There was no difference between the groups in terms of proportion of patients with appropriate initial therapy.

Microbiological characteristics of the intention-to-treat population are shown in Supplementary Table 3. Forty-eight participants (69 %) in the CI arm and 56 participants (80 %) in the IB arm had at least one causative pathogen identified before or during the course of treatment. Eighteen participants (38 %) in the CI arm and 26 participants (46 %) in the IB arm had polymicrobial infections during the course of treatment. The most prevalent Gram-negative pathogens in the intervention arm were *P. aeruginosa* (37 %) and *A. baumannii* (25 %) and for the control arm, *A. baumannii* (31 %) and *Klebsiella pneumoniae* (23 %). There were nine participants (6 %) who had a non-susceptible pathogen identified as the primary causative organism: intervention arm six participants (9 %) versus control arm three participants (4 %). The median “surrogate MIC” values were similar in both treatment arms: 8 mg/L (IQR 4–8) for cefepime, 2 mg/L (IQR 2–2) for meropenem, and 16 mg/L (IQR 8–16) for piperacillin/tazobactam.



**Table 1** Baseline demographic and clinical characteristics of the intention-to-treat population

Characteristic	Intervention ( <i>n</i> = 70)	Control ( <i>n</i> = 70)
Age, (years)	54 (42–63)	56 (41–68)
Male, <i>n</i> (%)	46 (66)	50 (71)
Body weight (kg)	70 (59–80)	65 (59–75)
Body mass index (kg/m <sup>2</sup> )	27 (23–30)	24 (22–29)
APACHE II	21 (17–26)	21 (15–26)
SOFA	8 (6–10)	7 (5–9)
Charlson comorbidity index	3 (1–5)	4 (2–6)
Serum creatinine concentration (μmol/L)	111 (73–118)	92 (59–158)
Cockcroft–Gault creatinine clearance (mL/min)	64 (43–98)	72 (41–122)
Pre-randomisation ICU stay (days)	2 (2–5)	3 (2–6)
Pre-randomisation antibiotic therapy, <i>n</i> (%)	52 (74)	56 (80)
Pre-randomisation appropriate antibiotic therapy, <i>n</i> (%) <sup>a</sup>	38 (79)	41 (73)
Post-randomisation ICU stay (days)	8 (5–10)	6 (4–13)
Duration of randomised treatment (days)	7 (5–9)	7 (5–9)
Mechanically ventilated, <i>n</i> (%)	66 (52)	61 (48)
Post-randomisation renal replacement therapy, <i>n</i> (%)	15 (21)	12 (17)
White cell count (×10 <sup>9</sup> /L)	17 (13–25)	15 (13–20)
Study antibiotic, <i>n</i> (%)		
Piperacillin/tazobactam	38 (54)	47 (67)
Meropenem	21 (30)	21 (30)
Cefepime	11 (16)	2 (3.0)
Pharmacokinetic sampling, <i>n</i> (%) <sup>b</sup>		
Piperacillin/tazobactam	35 (92)	37 (79)
Meropenem	19 (91)	17 (81)
Cefepime	9 (82)	2 (100)
Concomitant antibiotic, <i>n</i> (%)	33 (47)	33 (47)
Azithromycin	13 (19)	12 (17)
Vancomycin	6 (9)	12 (17)
Metronidazole	6 (9)	10 (6)
Clindamycin	2 (3)	4 (6)
Aminoglycosides	3 (4)	3 (4)
Colistin	1 (1)	1 (1)
Other <sup>c</sup>	7 (10)	5 (7)
Primary infection site, <i>n</i> (%)		
Lung	46 (66)	36 (51)
Intra-abdominal	11 (16)	15 (21)
Blood	4 (6)	6 (9)
Urinary tract	2 (3)	3 (4)
Skin or skin structure	6 (9)	7 (10)
Central nervous system	1 (1)	3 (4)
Organ dysfunction, <i>n</i> (%)		
Respiratory	46 (66)	44 (63)
Cardiovascular	40 (57)	37 (53)
Haematologic	18 (26)	12 (17)
Renal	17 (24)	10 (14)
Metabolic acidosis	4 (6)	3 (4)

Data are presented as median (interquartile range) or number (percentage)

APACHE Acute Physiology and Chronic Health Evaluation, SOFA Sequential Organ Failure Assessment, ICU intensive care unit

<sup>a</sup> Appropriate antibiotic therapy was assumed if a participant received at least one antibiotic (24 h before study inclusion) which was effective against the isolated pathogen(s). Only participants

who had at least one organism identified was assessed (*n* = 104, intervention = 48, control = 56)

<sup>b</sup> Participants who had complete pharmacokinetic data i.e. those who had mid-dose and trough concentrations on both sampling occasions

<sup>c</sup> Includes cloxacillin (*n* = 7), doxycycline (*n* = 2), co-trimoxazole (*n* = 2) and ciprofloxacin (*n* = 1)

## Outcome measures

Primary and secondary endpoints in the ITT population and the clinical outcome for the subgroups of interest are presented in Table 2. Participants in the intervention arm had higher clinical cure rates and shorter median time to WCC normalisation. The number needed to treat with continuous

infusion to improve the likelihood of clinical cure is three patients. Additionally, CI administration demonstrated higher clinical cure rates than IB dosing in participants who had respiratory infection, participants who received piperacillin/tazobactam and in those without concomitant antibiotic treatment (Table 2). Differences in PK/PD target attainment rates were significantly higher in the

**Table 2** Primary and secondary endpoints by treatment arm in the intention-to-treat population and the subgroups of interest

Primary endpoint	Intervention (n = 70)	Control (n = 70)	Absolute difference (95 % CI)	Significance (p value) <sup>a,b</sup>
Clinical cure for ITT population, n (%)	39 (56)	24 (34)	22 (-0.4 to -0.1)	<b>0.011</b>
Clinical cure by antibiotic, n (%) <sup>c</sup>				
Piperacillin/tazobactam	22 (58)	15 (32)	26 (-0.4 to -0.1)	<b>0.016</b>
Meropenem	14 (67)	8 (38)	29 (-0.5 to 0.1)	0.064
Cefepime	3 (27)	1 (50)	23 (-0.3 to 0.7)	1.000
Clinical cure by concomitant antibiotic treatment, n (%) <sup>d</sup>				
Yes	14 (42)	13 (39)	3 (-0.3 to 0.2)	0.802
No	25 (68)	11 (30)	38 (-0.6 to -0.2)	<b>0.001</b>
Clinical cure by site of infection, n (%) <sup>e</sup>				
Lung	27 (59)	12 (33)	25 (-0.4 to -0.1)	<b>0.022</b>
Clinical cure by <i>A. baumannii</i> or <i>P. aeruginosa</i> infection, n (%) <sup>f</sup>				
Yes	13 (52)	6 (25)	27 (-0.5 to 0.1)	0.052
No	10 (44)	12 (38)	6 (-0.3 to 0.2)	0.655
Secondary endpoints	Intervention (n = 70)	Control (n = 70)	Absolute difference (95 % CI)	Significance (p value) <sup>a,b</sup>
PK/PD target attainment, n (%) <sup>g</sup>				
50 % $fT_{>MIC}$ on day 1	56 (98)	49 (93)	5 (-0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 1	55 (97)	37 (70)	27 (-0.4 to -0.1)	<b>&lt;0.001</b>
50 % $fT_{>MIC}$ on day 3	56 (98)	49 (93)	5 (-0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 3	55 (97)	36 (68)	29 (-0.4 to -0.1)	<b>&lt;0.001</b>
ICU-free days	20 (12–23)	17 (0–24)	3 (-3 to 9)	0.378
ICU survivors <sup>h</sup>	21 (19–23)	21 (14–24)	0 (-3 to 3)	0.824
Ventilator-free days	22 (0–24)	14 (0–24)	8 (-2 to 18)	<b>0.043</b>
ICU survivors <sup>i</sup>	23 (21–25)	21 (0–25)	2 (-3 to 7)	0.076
14-day survival, n (%)	56 (80)	50 (71)	9 (-0.2 to 0.1)	0.237
30-day survival, n (%)	52 (74)	44 (63)	11 (-0.3 to 0.1)	0.145
WCC normalisation days	3 (2–7)	8 (4–15)	5 (1 to 5)	<b>&lt;0.001</b>

CI confidence interval, PK/PD pharmacokinetic/pharmacodynamic, 50 %  $fT_{>MIC}$  unbound (free) plasma concentration at 50 % of the dosing interval (mid-interval concentration) was above the causative pathogens MIC, 100 %  $fT_{>MIC}$  unbound (free) plasma concentration at 100 % of the dosing interval (trough concentration) was above the causative pathogens MIC, ICU intensive care unit, WCC white cell count

<sup>a</sup> Represents the *p* value between the intervention arm versus the control arm and values in bold indicate significant difference between the two treatment arms (*p* < 0.05)

<sup>b</sup> Continuous variables were compared using Mann–Whitney *U* test as data were non-normally distributed as indicated by Kolmogorov–Smirnov test. Dichotomous variables were compared using Pearson's Chi-square test or Fisher's exact test as appropriate

<sup>c</sup> Number of participants analysed: (1) piperacillin/tazobactam (*n* = 85; intervention = 38, control = 47), (2) meropenem (*n* = 42; intervention = 21, control = 21), and (3) cefepime (*n* = 13; intervention = 11, control = 2)

<sup>d</sup> Number of participants analysed: (1) patients who received concomitant antibiotics (*n* = 66; intervention = 33, control = 33)

intervention group at 100 %  $fT_{>MIC}$  on day 1 and day 3 post-randomisation. At 28 days, there was no difference in median ICU-free days but median ventilator-free days were significantly higher in the participants of the intervention arm. There was no difference in survival at 14 days or 30 days between the treatment arms (Fig. 1).

Findings in the mITT and PP population were similar to those reported in the ITT population and the primary and secondary endpoints for these groups are presented in Supplementary Tables 4 and 5.

and (2) patients who did not receive concomitant antibiotics (*n* = 74; intervention = 37, control = 37)

<sup>e</sup> Number of participants analysed: lung (*n* = 82; intervention = 46, control = 36)

<sup>f</sup> Number of participants analysed: (1) *A. baumannii* or *P. aeruginosa* infection (*n* = 49; intervention = 25, control = 24) and (2) other infections (*n* = 55; intervention = 23, control = 32)

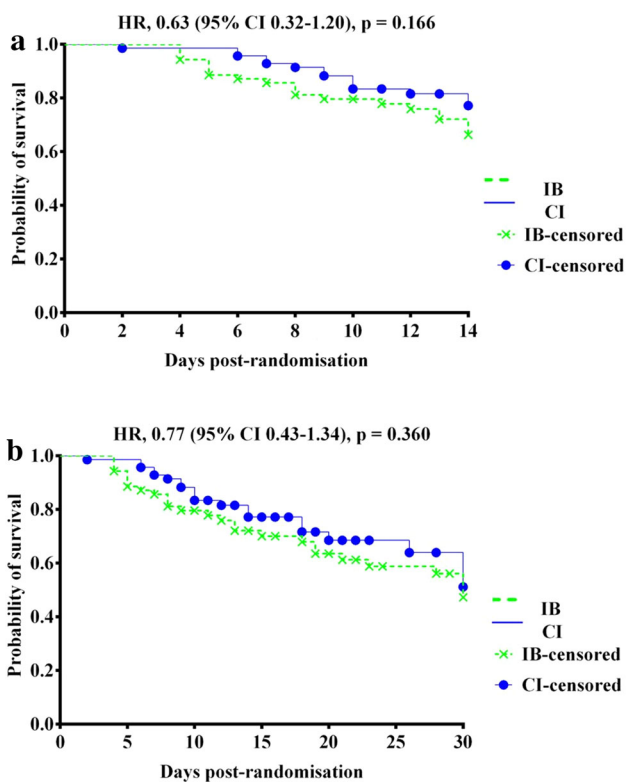
<sup>g</sup> Only participants with complete pharmacokinetic data (*n* = 119; intervention = 63, control = 56) and those who were infected with beta-lactam susceptible pathogens (*n* = 110; intervention = 57, control = 53) were included in the analysis

<sup>h</sup> Only participants who survived at ICU discharge was included in this subanalysis (57 and 53 participants in the intervention and control arm, respectively)

<sup>i</sup> Only mechanically ventilated participants who survived at ICU discharge was included in this subanalysis (53 and 46 participants in the intervention and control arm, respectively)

## Outcome measures predictors

Significant predictors associated with clinical cure in the ITT population are presented in Supplementary Tables 6 and 7. On the basis of the most parsimonious logistic regression model, CI administration of beta-lactam antibiotics (OR 3.21, 95 % CI 1.48–6.94, *p* = 0.003), pre-randomisation antibiotic therapy (OR 2.85, 95 % CI 1.12–7.23, *p* = 0.028), non-bacteraemia-related infection (OR 11.73, 95 % CI 1.30–105.94, *p* = 0.028), lower



**Fig. 1** Kaplan–Meier survival curves for the intention-to-treat population censored at **a** 14 days and **b** 30 days post-randomisation. *HR* hazard ratio, *CI* confidence interval

APACHE II score (OR 0.95, 95 % CI 0.90–0.99,  $p = 0.036$ ), and meropenem (OR 6.54, 95 % CI 1.48–28.90,  $p = 0.013$ ) or piperacillin/tazobactam administration (OR 4.21, 95 % CI 1.06–16.64,  $p = 0.041$ ) (as opposed to cefepime administration) were all statistically significant predictors for clinical cure.

#### Pharmacokinetic/pharmacodynamic data

Plasma antibiotic concentrations measured at 50 and 100 % of the dosing interval were relatively higher in the intervention group on day 1 and day 3 post-randomisation (Fig. 2). The ratio of plasma antibiotic concentration to surrogate MIC was also higher in the intervention group on both sampling days for all study antibiotics (Supplementary Fig. 2).

#### Adverse events

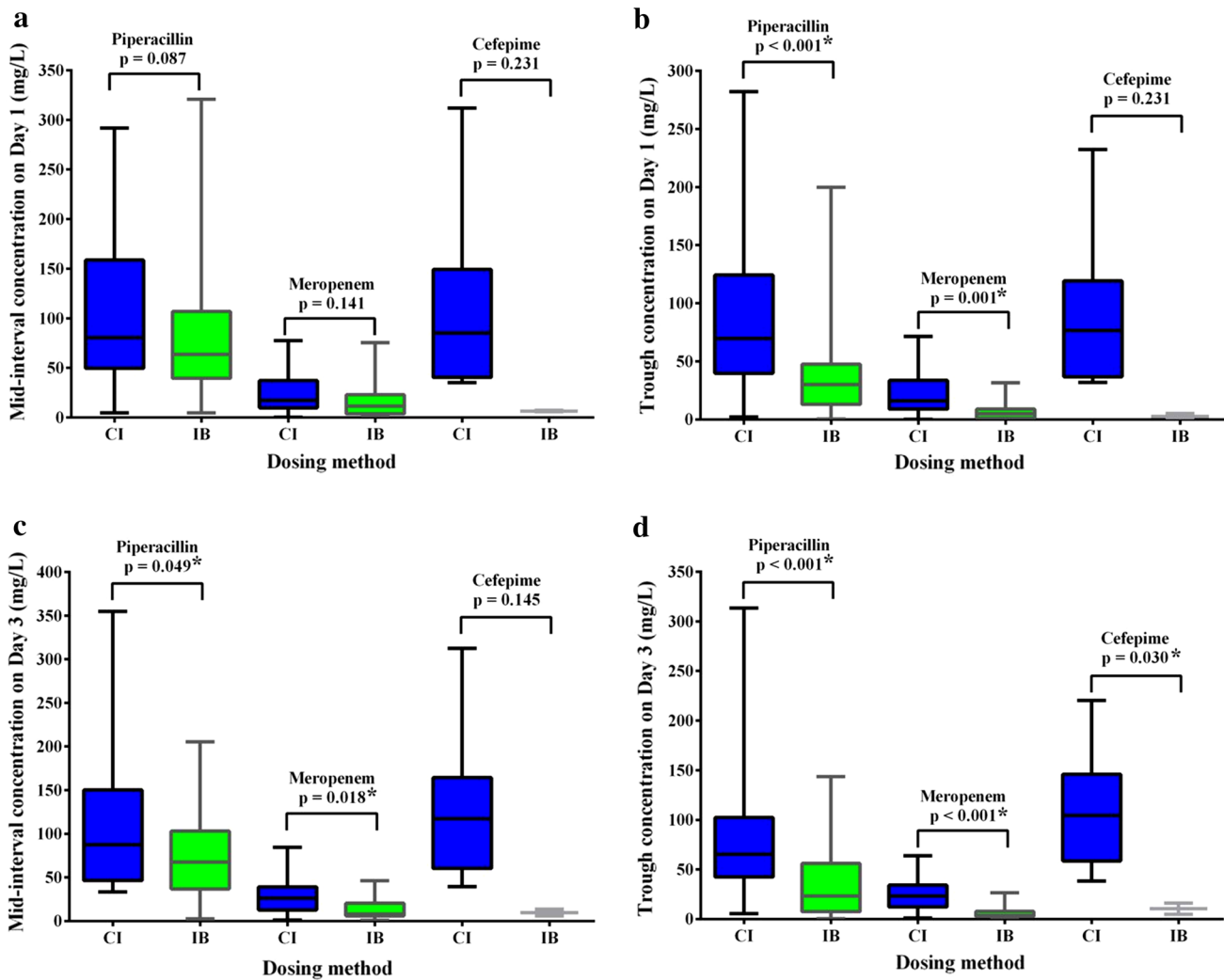
No adverse events occurred during study participation. A total of 18 deaths occurred during receipt of the study drug: seven participants in the CI arm versus 11 participants in the IB arm.

## Discussion

In this RCT, we found that continuous beta-lactam infusion demonstrated higher clinical cure rates and better PK/PD target attainment compared to IB dosing in critically ill patients with severe sepsis. Other significant benefits for CI participants in two other surrogate clinical endpoints were increased ventilator-free days and a reduced time to WCC normalisation. Given that these results were derived from a population of ICU patients with severe sepsis, who were not on extracorporeal renal support, our findings provide further evidence that CI of beta-lactam antibiotics is likely to be beneficial for patients with a high level of illness severity not receiving RRT. Although three recent RCTs have also reported similar findings [17–19], our current work remains unique considering that we recruited patients from a different geographical region, one which is rarely investigated but commonly associated with higher illness severity, than those commonly reported.

Clinical evidence supporting improved patient outcome with CI of beta-lactams has been mixed, varying from no significant effect [6, 8–10, 12, 30] to significant patient benefits [7, 11, 13, 17–19]. We note that there is yet to be a report suggesting inferior patient outcomes when CI is used. Meta-analyses of the above prospective clinical studies have failed to comprehensively demonstrate the superiority of CI over IB dosing in terms of clinical cure and patient survival [14–16]. However, a particularly noteworthy feature in most of these studies has been the inclusion of non-critically ill patients, whereas the patients who may be most likely to benefit from CI dosing are critically ill patients with high illness severity [17, 18]. Critically ill patients, particularly those with severe sepsis, commonly develop extreme physiological derangements, which may severely reduce antibiotic exposure, particularly when IB dosing is employed [2, 31]. Patients that received beta-lactams via CI dosing in our study were ten times more likely to achieve 100 %  $fT_{>MIC}$  on day 1 ( $p < 0.001$ ) and nine times more likely to achieve 100 %  $fT_{>MIC}$  on day 3 ( $p < 0.001$ ). As maintaining 100 %  $fT_{>MIC}$  in critically ill patients is associated with improved patient outcomes [32], we believe that the observed clinical cure difference in the ITT analysis (absolute difference of 22 %) favouring CI dosing may be partly explained by the relative ability of CI dosing to achieve the target PK/PD exposure more consistently than IB dosing in patients with severe sepsis [31, 33]. Importantly, CI participants in this study were three times more likely to achieve clinical cure when compared with IB participants, even after controlling for confounding variables (OR 3.21, 95 % CI 1.48–6.94,  $p = 0.003$ ).

Significant advantages of CI over IB for beta-lactam antibiotics were also observed in two recent RCTs of



**Fig. 2** Free plasma antibiotic concentration by beta-lactam antibiotics and treatment groups measured at **a** 50 % of the dosing interval on day 1, **b** 100 % of the dosing interval on day 1, **c** 50 % of the dosing interval on day 3 and, **d** 100 % of the dosing interval

on day 3. *CI* continuous infusion, *IB* intermittent bolus. Median, interquartile range and range are presented. An *asterisk* indicates a significant difference between continuous infusion and intermittent bolus dosing ( $p < 0.05$ )

critically ill patients with severe sepsis. In a prospective, multicentre, double-blind RCT (BLING I;  $n = 60$ ), Dulhunty et al. [17] showed that participants in the CI treatment arm demonstrated greater  $fT_{>MIC}$  (82 versus 29 %,  $p = 0.001$ ) and higher clinical cure rates (77 versus 50 %,  $p = 0.032$ ) compared to the IB arm. In a single-centre RCT which recruited 240 critically ill Czech participants, Chytra et al. [18] reported higher microbiological cure rates in the CI treatment arm as opposed to the IB arm (91 versus 78 %,  $p = 0.020$ ). Neither study demonstrated significant mortality advantages.

Despite these results, disease severity is only one of the many variables which can influence the outcome of CI versus IB dosing in critically ill patients. This was

recently highlighted in a multicentre, double-blind RCT (BLING II;  $n = 420$ ) [30]. Despite recruiting only patients with severe sepsis, Dulhunty et al. found no significant difference between participants in both treatment arms, in all five clinical endpoints evaluated. In their study, the absolute difference in clinical cure between CI and IB participants was 3 % in favour of CI dosing compared with the 22 % in the present BLISS study. In contrast to BLISS, the BLING II trial included patients receiving RRT (ca. 25 % of participants) and this inclusion criterion may reduce PK/PD exposure differences between CI and IB dosing because patients with reduced drug clearances are less likely to manifest subtherapeutic antibiotic exposures [34, 35] and, consequently, are less likely to benefit from altered dosing approaches such as



CI administration. Interestingly, all five clinical studies which demonstrated patient benefits with CI dosing only recruited critically ill patients with conserved renal function [7, 13, 17–19].

Other than recruiting participants with a low burden of disease, most clinical studies have also isolated pathogens which are highly susceptible to the study antibiotics [6–11, 13, 17–19, 30]. PK/PD principles state that IB dosing will be just as likely as CI to achieve target exposures when MICs are low [4] with treatment failures more likely with IB dosing when less susceptible pathogens are present [12, 36, 37]. In the present study, although actual MIC values were not available, 41 % of the causative pathogens were either *A. baumannii* or *P. aeruginosa* which mostly have higher MICs than the study antibiotics [38], thereby reducing the likelihood of achieving therapeutic concentrations with IB dosing. However, it should also be highlighted that benefits of CI may not be apparent in some geographical regions with different microbiology and antibiotic resistance patterns. Importantly, use of combination therapy to treat infections caused by Gram-negative pathogens was infrequent in this study, which may differ from practices in other centres.

This study has several limitations. Participants were only recruited from two centres in one country which may limit the generalizability of the findings to other treatment settings. Despite the baseline characteristics of the treatment arms being relatively well balanced, CI participants manifested higher median SOFA scores on admission compared to IB participants. Even though this typically translates into a reduced likelihood of survival, it is possible that CI participants may have been selectively provided with additional monitoring in the ICU to account for their illness severity, which may influence clinical outcomes. Furthermore, clinical outcomes were evaluated by an independent investigator and, unlike a specialised review committee, the former strategy may be more likely to introduce biased observations toward one of the treatment allocations. However, the possibility of bias in this study should be very low as the assessor had no knowledge of treatment allocation nor role in patient management and was not working in the participating centres during the study period. We also acknowledge the limitation of the Cockcroft–Gault formula in estimating renal function in this cohort and that measured creatinine clearance would be more accurate [39]. Neither unbound plasma concentrations nor concentrations at the sites of infections were measured in this study, although all drugs have relatively low protein binding [29]. As MIC reporting is rare in Malaysia, we have used “surrogate MIC” values, using EUCAST MIC breakpoints, in our primary endpoint analyses. Accordingly, this approach will exaggerate the magnitudes of PK/PD target non-attainment in the IB treatment arm relative to the CI arm if

actual MIC values were used. Although actual MIC values would have been preferable, we believe that our approach resembles the real-life clinical approach where the MIC of a pathogen is rarely available upon antibiotic commencement [40]. Although data on concomitant antibiotics were available, we did not evaluate the PK/PD of those antibiotics. This study was not powered to test the effect of CI versus IB dosing on survival but has provided useful information that can be used for sample size determination of a larger multicentre RCT seeking to quantify any survival benefits of CI dosing.

## Conclusion

In critically ill patients with severe sepsis not receiving RRT, CI administration was associated with higher clinical cure rates and better PK/PD target attainment compared to IB dosing for three common beta-lactam antibiotics. Our findings suggest that beta-lactam CI may be most beneficial for critically ill patients with a high level of illness severity, who are infected with less susceptible microorganisms and that are not receiving RRT. A large-scale, prospective, multinational clinical study is required to ascertain whether the potential benefits of continuous beta-lactam infusion do indeed translate into survival benefit in critically ill patients with severe sepsis.

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## Compliance with ethical standards

**Conflicts of interest** All of the other authors declare that there are no conflicts of interest.

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