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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/pharmacodynamic (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 primary 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 survival, 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 participants. 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 difference in 14-day or 30-day survival between the treatment arms. *Conclusions:* 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 (≥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 μmol/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 pathogens "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 ≥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 ≤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 ≥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 ($n = 70$)	Control ($n = 70$)
Age, (years)	54 (42–63)	56 (41–68)
Male, *n* (%)	46 (66)	50 (71)
Body weight (kg)	70 (59–80)	65 (59–75)
Body mass index (kg/m^2)	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, *n* (%)	52 (74)	56 (80)
Pre-randomisation appropriate antibiotic therapy, *n* (%)[a]	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, *n* (%)	66 (52)	61 (48)
Post-randomisation renal replacement therapy, *n* (%)	15 (21)	12 (17)
White cell count ($\times 10^9$/L)	17 (13–25)	15 (13–20)
Study antibiotic, *n* (%)		
Piperacillin/tazobactam	38 (54)	47 (67)
Meropenem	21 (30)	21 (30)
Cefepime	11 (16)	2 (3.0)
Pharmacokinetic sampling, *n* (%)[b]		
Piperacillin/tazobactam	35 (92)	37 (79)
Meropenem	19 (91)	17 (81)
Cefepime	9 (82)	2 (100)
Concomitant antibiotic, *n* (%)	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[c]	7 (10)	5 (7)
Primary infection site, *n* (%)		
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, *n* (%)		
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

[a] 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)

[b] Participants who had complete pharmacokinetic data i.e. those who had mid-dose and trough concentrations on both sampling occasions

[c] 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)[a,b]
Clinical cure for ITT population, n (%)	39 (56)	24 (34)	22 (−0.4 to −0.1)	**0.011**
Clinical cure by antibiotic, *n* (%)[c]				
Piperacillin/tazobactam	22 (58)	15 (32)	26 (−0.4 to −0.1)	**0.016**
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* (%)[d]				
Yes	14 (42)	13 (39)	3 (−0.3 to 0.2)	0.802
No	25 (68)	11 (30)	38 (−0.6 to −0.2)	**0.001**
Clinical cure by site of infection, *n* (%)[e]				
Lung	27 (59)	12 (33)	25 (−0.4 to −0.1)	**0.022**
Clinical cure by *A. baumannii* or *P. aeruginosa* infection, *n* (%)[f]				
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)[a,b]
PK/PD target attainment, *n* (%)[g]				
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)	**<0.001**
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)	**<0.001**
ICU-free days	20 (12–23)	17 (0–24)	3 (−3 to 9)	0.378
ICU survivors[h]	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)	**0.043**
ICU survivors[i]	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)	**<0.001**

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

[a] Represents the p value between the intervention arm versus the control arm and values in bold indicate significant difference between the two treatment arms ($p < 0.05$)

[b] 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

[c] 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)

[d] Number of participants analysed: (1) patients who received concomitant antibiotics ($n = 66$; intervention = 33, control = 33) and (2) patients who did not receive concomitant antibiotics ($n = 74$; intervention = 37, control = 37)

[e] Number of participants analysed: lung ($n = 82$; intervention = 46, control = 36)

[f] 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)

[g] 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

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

[i] 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)

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.

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

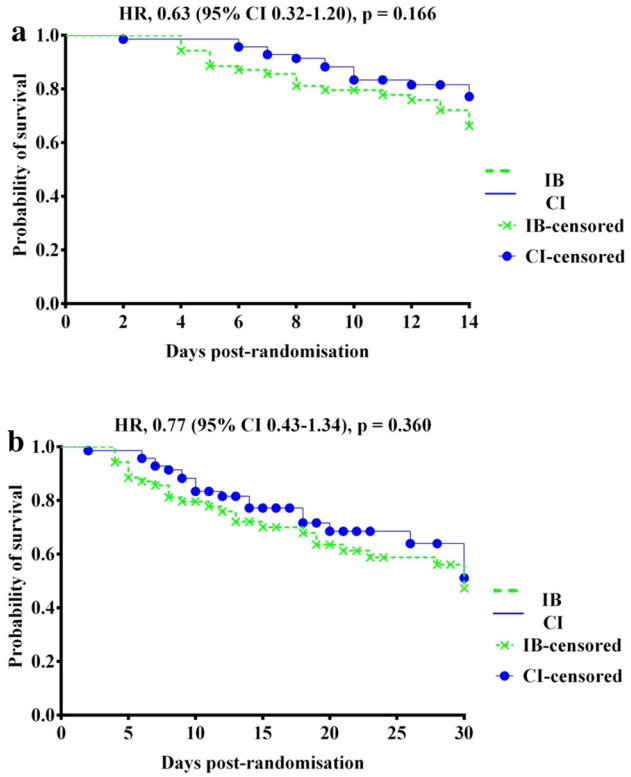

Fig. 1 Kaplan–Meier survival curves for the intention-to-treat population censored at **a** 14 days and **b** 30 days post-randomisation. *HR* hazard ratio, *CI* confidence interval

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

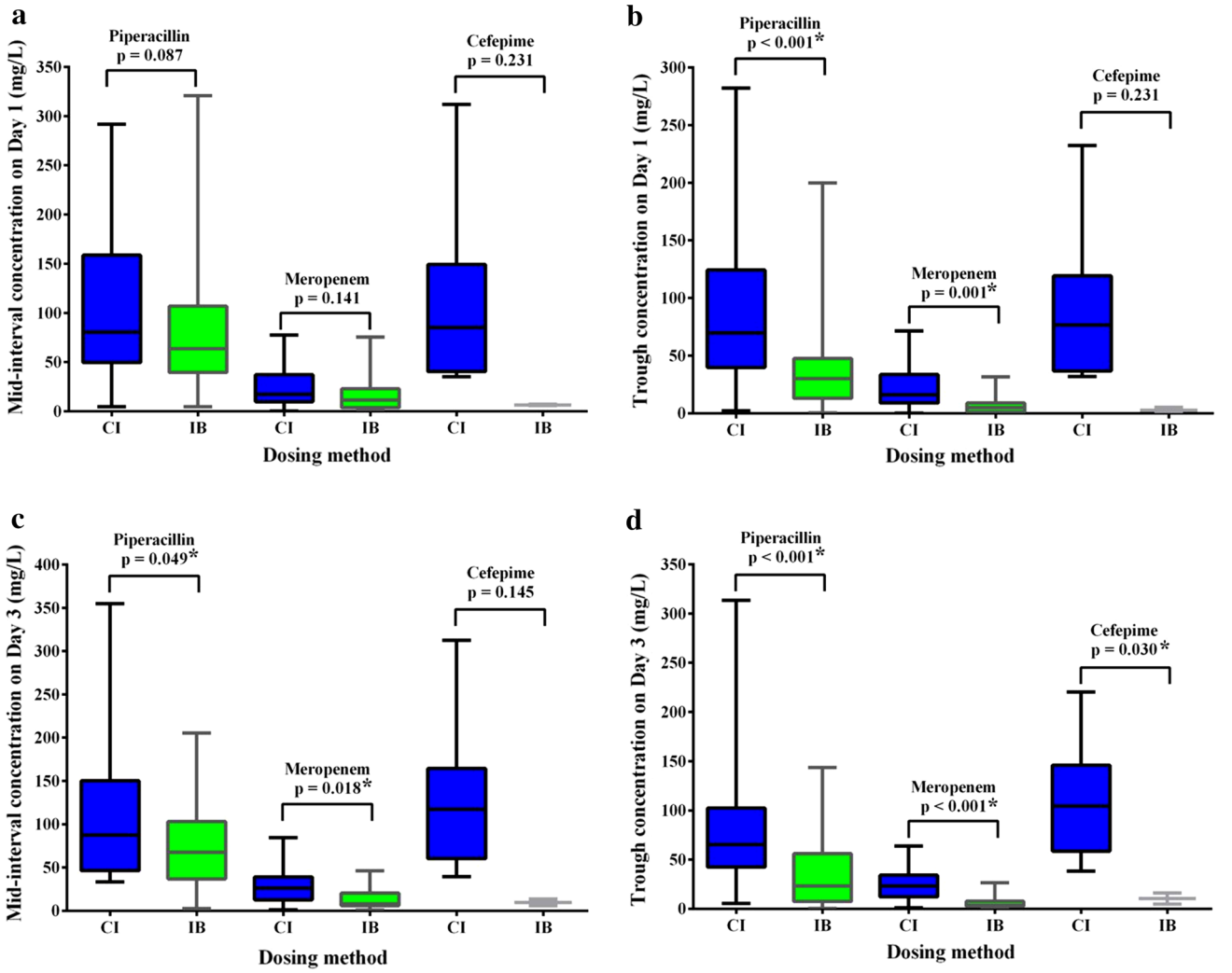

Fig. 2 Free plasma antibiotic concentration by beta-lactam antibiotics and treatment groups measured at **a** 50 % of the dosing interval on day 1, **b** 100 % of the dosing interval on day 1, **c** 50 % of the dosing interval on day 3 and, **d** 100 % of the dosing interval on day 3. *CI* continuous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

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41:580–637
2. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14:498–509
3. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26:1–10 (**quiz 11–12**)
4. Abdul-Aziz MH, Dulhunty JM, Bellomo R, Lipman J, Roberts JA (2012) Continuous beta-lactam infusion in critically ill patients: the clinical evidence. Ann Intensive Care 2:37
5. Abdul-Aziz MH, Lipman J, Mouton JW, Hope WW, Roberts JA (2015) Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: optimizing efficacy and reducing resistance development. Semin Respir Crit Care Med 36:136–153
6. van Zanten AR, Oudijk M, Nohlmans-Paulssen MK, van der Meer YG, Girbes AR, Polderman KH (2007) Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. Br J Clin Pharmacol 63:100–109
7. Rafati MR, Rouini MR, Mojtahedzadeh M, Najafi A, Tavakoli H, Gholami K, Fazeli MR (2006) Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. Int J Antimicrob Agents 28:122–127
8. Lau WK, Mercer D, Itani KM, Nicolau DP, Kuti JL, Mansfield D, Dana A (2006) Randomized, open-label, comparative study of piperacillin-tazobactam administered by continuous infusion versus intermittent infusion for treatment of hospitalized patients with complicated intra-abdominal infection. Antimicrob Agents Chemother 50:3556–3561
9. Georges B, Conil JM, Cougot P, Decun JF, Archambaud M, Seguin T, Chabanon G, Virenque C, Houin G, Saivin S (2005) Cefepime in critically ill patients: continuous infusion vs. an intermittent dosing regimen. Int J Clin Pharmacol Ther 43:360–369
10. Lubasch A, Luck S, Lode H, Mauch H, Lorenz J, Bolcskei P, Welte T (2003) Optimizing ceftazidime pharmacodynamics in patients with acute exacerbation of severe chronic bronchitis. J Antimicrob Chemother 51:659–664
11. Nicolau DP, McNabb J, Lacy MK, Quintiliani R, Nightingale CH (2001) Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. Int J Antimicrob Agents 17:497–504
12. Angus BJ, Smith MD, Suputtamongkol Y, Mattie H, Walsh AL, Wuthiekanun V, Chaowagul W, White NJ (2000) Pharmacokinetic-pharmacodynamic evaluation of ceftazidime continuous infusion vs intermittent bolus injection in septicaemic melioidosis. Br J Clin Pharmacol 50:184–191
13. Hanes SD, Wood GC, Herring V, Croce MA, Fabian TC, Pritchard E, Boucher BA (2000) Intermittent and continuous ceftazidime infusion for critically ill trauma patients. Am J Surg 179:436–440
14. Shiu J, Wang E, Tejani AM, Wasdell M (2013) Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. Cochrane Database Syst Rev 3:CD008481
15. Roberts JA, Webb S, Paterson D, Ho KM, Lipman J (2009) A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med 37:2071–2078
16. Kasiakou SK, Sermaides GJ, Michalopoulos A, Soteriades ES, Falagas ME (2005) Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect Dis 5:581–589
17. Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Lipman J (2013) Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis 56:236–244
18. Chytra I, Stepan M, Benes J, Pelnar P, Zidkova A, Bergerova T, Pradl R, Kasal E (2012) Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial. Crit Care 16:R113
19. Roberts JA, Boots R, Rickard CM, Thomas P, Quinn J, Roberts DM, Richards B, Lipman J (2007) Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study. J Antimicrob Chemother 59:285–291
20. Kiratisin P, Chongthaleong A, Tan TY, Lagamayo E, Roberts S, Garcia J, Davies T (2012) Comparative in vitro activity of carbapenems against major Gram-negative pathogens: results of Asia–Pacific surveillance from the COMPACT II study. Int J Antimicrob Agents 39:311–316
21. Abdul-Aziz M, Sulaiman H, Mat-Nor M, Rai V, Wong K, Hasan M, Wallis S, Lipman J, Staatz C, Roberts J (2015) The BLISS Study: beta-lactam infusion in severe sepsis-randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis in a Malaysian ICU setting. In: 55th interscience conference of antimicrobial agents and chemotherapy (ICAAC), San Diego, 18–21 September 2015
22. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
24. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL (2001) Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286:1754–1758
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
26. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239–245
27. McWhinney BC, Wallis SC, Hillister T, Roberts JA, Lipman J, Ungerer JP (2010) Analysis of 12 beta-lactam antibiotics in human plasma by HPLC with ultraviolet detection. J Chromatogr B Analyt Technol Biomed Life Sci 878:2039–2043

28. Food and Drug Administration (2001) Guidance for industry: bioanalytical method validation. FDA, Rockville
29. Wong G, Briscoe S, Adnan S, McWhinney B, Ungerer J, Lipman J, Roberts JA (2013) Protein binding of beta-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? Antimicrob Agents Chemother 57:6165–6170
30. Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Starr T, Paul SK, Lipman J, BLING II Investigators for the ANZICS Clinical Trials Group (2015) A multicenter randomized trial of continuous versus intermittent beta-lactam infusion in severe sepsis. Am J Respir Crit Care Med 192:1298–1305
31. Abdul-Aziz MH, Lipman J, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Dulhunty J, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Roberts JA, DALI Study Group (2016) Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. J Antimicrob Chemother 71(1):196–207
32. McKinnon PS, Paladino JA, Schentag JJ (2008) Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 31:345–351
33. De Waele JJ, Lipman J, Akova M, Bassetti M, Dimopoulos G, Kaukonen M, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Udy AA, Starr T, Wallis SC, Roberts JA (2014) Risk factors for target non-attainment during empirical treatment with beta-lactam antibiotics in critically ill patients. Intensive Care Med 40:1340–1351
34. Jamal JA, Roberts DM, Udy AA, Mat-Nor MB, Mohamad-Nor FS, Wallis SC, Lipman J, Roberts JA (2015) Pharmacokinetics of piperacillin in critically ill patients receiving continuous venovenous haemofiltration: a randomised controlled trial of continuous infusion versus intermittent bolus administration. Int J Antimicrob Agents 46:39–44
35. Jamal JA, Mat-Nor MB, Mohamad-Nor FS, Udy AA, Wallis SC, Lipman J, Roberts JA (2015) Pharmacokinetics of meropenem in critically ill patients receiving continuous venovenous haemofiltration: a randomised controlled trial of continuous infusion versus intermittent bolus administration. Int J Antimicrob Agents 45:41–45
36. Hsaiky L, Murray KP, Kokoska L, Desai N, Cha R (2013) Standard versus prolonged doripenem infusion for treatment of gram-negative infections. Ann Pharmacother 47:999–1006
37. Bauer KA, West JE, O'Brien JM, Goff DA (2013) Extended-infusion cefepime reduces mortality in patients with Pseudomonas aeruginosa infections. Antimicrob Agents Chemother 57:2907–2912
38. Mustafa M, Chan WM, Lee C, Harijanto E, Loo CM, Van Kinh N, Anh ND, Garcia J (2014) A PROspective study on the usage patterns of doripenem in the Asia–Pacific region (PROUD study). Int J Antimicrob Agents 43:353–360
39. Carlier M, Dumoulin A, Janssen A, Picavet S, Vanthuyne S, Van Eynde R, Vanholder R, Delanghe J, De Schoenmakere G, De Waele JJ, Hoste EA (2015) Comparison of different equations to assess glomerular filtration in critically ill patients. Intensive Care Med 41:427–435
40. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J (2014) DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 58:1072–1083

Supplementary Table 1: Antibiotic dosing protocol according to treatment arm in the BLISS study

Antibiotic and treatment arm	Dosing regimen
Cefepime	
Intervention arm (continuous infusion)	• Day 1: 2 g IV loading dose (infused over 30 minutes) followed by 2 g IV (infused over 480 minutes) every 8 hours • Day 2 onwards: 2 g IV (infused over 480 minutes) every 8 hours
Control arm (intermittent bolus dosing)	• 2 g IV (infused over 30 minutes) every 8 hours
Meropenem	
Intervention arm (continuous infusion)	• Day 1: 1 g IV loading dose (infused over 30 minutes) followed by 1 g IV (infused over 480 minutes) every 8 hours • Day 2 onwards: 1 g IV (infused over 480 minutes) every 8 hours
Control arm (intermittent bolus dosing)	• 1 g IV (infused over 30 minutes) every 8 hours
Piperacillin/tazobactam	
Intervention arm (continuous infusion)	• Day 1: 4 g/0.5 g IV loading dose (infused over 30 minutes) followed by 4 g/0.5 g IV (infused over 360 minutes) every 6 hours • Day 2 onwards: 4 g/0.5 g IV (infused over 360 minutes) every 6 hours
Control arm (intermittent bolus dosing)	• 4 g/0.5 g IV (infused over 30 minutes) every 6 hours

IV = intravenous

Supplementary Table 2: Definitions used for primary and secondary clinical end-points

Primary end-point[a]	**Definition and description**
Clinical cure	Clinical outcome was evaluated at 14 days after cessation of study antibiotic and was rated as: 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. 3. Failure: insufficient lessening of the signs and symptoms of infection to qualify as improvement, including death or indeterminate (i.e. no evaluation possible, 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 end-points[b,c,d]	**Definition and description**
PK/PD – 50% $fT_{>MIC}$	Free (unbound) drug concentration maintained above the MIC of the causative pathogen for at least 50% of dosing interval (i.e. mid-interval drug concentration). For CI participants, this was the first sample taken over a 24-hour interval.
PK/PD – 100% $fT_{>MIC}$	Free (unbound) drug concentration maintained above the MIC of the causative pathogen for at least 100% of dosing interval (i.e. trough drug concentration or steady-state drug concentration). For CI participants, this was the second sample taken over a 24-hour interval.
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 days post-randomisation. ICU-free days were 0 if a patient died or stayed in the ICU for ≥28 days.
Ventilator-free days at day 28	The number of days the participant was ventilator-free (for at least 48 consecutive hours) in the first 28 days post-randomisation. Ventilator-free days were 0 if a patient died or required mechanical ventilation for ≥28 days.
14-day survival	Survival at day 14 post-randomisation.
30-day survival	Survival at day 30 post-randomisation
Time to WCC normalisation	The number of days from randomisation to the first identified date when WCC was $\geq 4.0 \times 10^9$/L and $\leq 10.0 \times 10^9$/L (for at least 48 consecutive hours) in participants who had values outside this range.

PK/PD = pharmacokinetic/pharmacodynamic; MIC = minimum inhibitory concentration; CI = continuous infusion; ICU = intensive care unit; WCC = white cell count

[a]Clinical cure was evaluated by a blinded clinician if the participant was still in the ICU or by blinded review of the medical records if the participant was discharged from the ICU.

[b]Pharmacokinetic/pharmacodynamic (PK/PD) analysis only included participants with complete pharmacokinetic data (i.e. those who had both trough and mid-interval concentrations collected on both sampling days).

[c]PK/PD analysis was performed on days 1 and 3 post-randomisation.

[d]Where a pathogen was isolated, the "surrogate MIC" was defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC_{90} data. Where no pathogen was formally identified, the MIC breakpoints for *P. aeruginosa* (8 mg/L for cefepime, 2 mg/L for meropenem and 16 mg/L for piperacillin/tazobactam) were inferred as the "surrogate MIC". Participants who were infected with beta-lactam resistant pathogens were excluded from PK/PD analysis.

Supplementary Table 3: Microbiological characteristics of the intention-to-treat population

Characteristic	Intervention (n = 70)	Control (n = 70)
Participants who had organisms identified, n (%)	48 (69)	56 (80)
Gram-positive, n (%)	12 (20)	25 (33)
Staphylococcus aureus	5 (42)	11 (44)
Staphylococcus epidermidis	4 (33)	6 (24)
Enterococcus faecalis	0 (0)	3 (12)
Streptococcus intermedius	1 (8)	2 (8)
Streptococcus pneumoniae	2 (17)	1 (4)
Mycoplasma pneumoniae	0 (0)	2 (8)
Enterococcus faecium	0 (0)	1 (4)
Streptococcus anginosus	0 (0)	1 (4)
Streptococcus constellatus	0 (0)	1 (4)
Gram-negative, n (%)	49 (80)	52 (68)
Acinetobacter baumanii	12 (25)[a]	16 (31)[b]
Pseudomonas aeruginosa	18 (37)	10 (19)
Klebsiella pneumoniae	9 (18)[c]	12 (23)
Escherichia coli	5 (10)[d]	5 (10)
Proteus mirabilis	2 (4)	2 (4)
Bulkholderia cepacia	1 (2)	1 (2)
Chlamydophila pneumoniae	0 (0)	2 (4)
Stenotrophomonas maltophilia	1 (2)	1 (2)
Bulkholderia pseudomallei	1 (2)	0 (0)
Enterobacter aerogenes	0 (0)	1 (2)
Morganella morganii	0 (0)	1 (2)
Serratia marcescens	0 (0)	1 (2)
Polymicrobial infection, n (%)	18 (38)	26 (46)

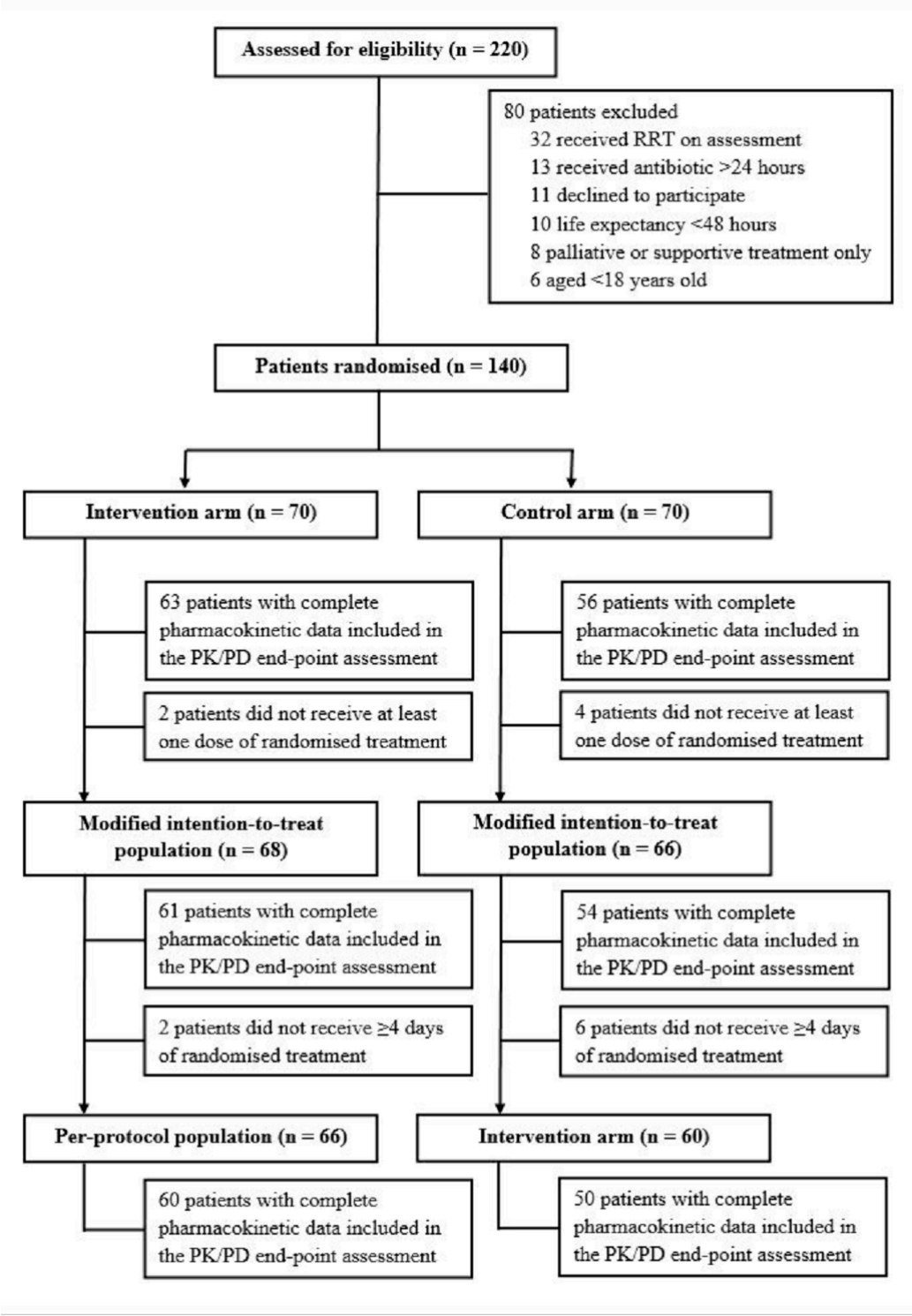
[a]Four isolates were multi-drug resistant *Acinetobacter baumanii*.

[b]Three isolates were multi-drug resistant *Acinetobacter baumanii*.

[c]One isolate was extended-spectrum beta-lactamase (ESBL) *Klebsiella pneumoniae*.

[d]One isolate was carbapenem-resistant *Escherichia coli*.

Supplementary Figure 1: The BLISS study CONSORT flow diagram



Supplementary Table 4: Primary and secondary end-points by treatment arm in the modified intention-to-treat population

Primary end-point	**Intervention (n = 68)**	**Control (n = 66)**	**Absolute difference (95% CI)**	**Significance (p-value)**[a,b]
Clinical cure, n (%)	39 (57.4)	23 (34.8)	22.5 (-0.4 to -0.1)	**0.009**
Secondary end-points	**Intervention (n = 68)**	**Control (n = 66)**	**Absolute difference (95% CI)**	**Significance (p-value)**[a,b]
PK/PD target attainment, n (%)[c]				
50% $fT_{>MIC}$ on day 1	54 (98.2)	48 (94.1)	4.1 (-0.1 to 0.1)	0.350
100% $fT_{>MIC}$ on day 1	53 (96.4)	37 (72.5)	23.9 (-0.4 to -0.1)	**0.001**
50% $fT_{>MIC}$ on day 3	54 (98.2)	48 (94.1)	4.1 (-0.1 to 0.1)	0.350
100% $fT_{>MIC}$ on day 3	53 (96.4)	36 (70.6)	25.8 (-0.4 to -0.1)	**<0.001**
ICU-free days	20 (11-23)	16 (0-23)	4 (-4 to 0)	0.287
ICU survivors[d]	21 (19-23)	21 (12-24)	0 (-3 to 1)	0.565
Ventilator-free days	22 (0-24)	14 (0-24)	8 (-7 to 1)	**0.045**
ICU survivors[e]	23 (21-25)	20 (0-25)	3 (-6 to 0)	**0.050**
14-day survival, n (%)	54 (79.4)	47 (71.2)	8.2 (-0.2 to 0.1)	0.271
30-day survival, n (%)	50 (73.5)	42 (63.6)	9.9 (-0.2 to 0.1)	0.217
WCC normalisation days	3 (2-7)	8 (4-15)	5 (1-5)	**<0.001**

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

[a]Represents the p-value between the intervention arm versus the control arm and values in bold indicate significant difference between the two treatment arms ($p < 0.05$).

[b]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 chi-square test or Fisher's exact test as appropriate.

[c]Only participants with complete pharmacokinetic data (n = 115; intervention = 61, control = 54) and those who were infected with beta-lactam susceptible pathogens (n = 106; intervention = 55, control = 51) were included in the analysis.

[d]Only participants who survived at ICU discharge was included in this sub-analysis (55 and 50 participants in the intervention and control arm, respectively).

[e]Only mechanically-ventilated participants who survived at ICU discharge was included in this sub-analysis (52 and 43 participants in the intervention and control arm, respectively).

Supplementary Table 5: Primary and secondary end-points by treatment arm in the per-protocol population

Primary end-point	**Intervention (n = 66)**	**Control (n = 60)**	**Absolute difference (95% CI)**	**Significance (p-value)**[a,b]
Clinical cure, n (%)	39 (59.1)	20 (33.3)	25.8 (-0.4 to -0.1)	**0.004**
Secondary end-points	**Intervention (n = 66)**	**Control (n = 60)**	**Absolute difference (95% CI)**	**Significance (p-value)**[a,b]
PK/PD target attainment, n (%)				
50% $fT_{>MIC}$ on day 1	54 (98.2)	42 (93.6)	4.6 (-0.2 to 0.1)	0.332
100% $fT_{>MIC}$ on day 1	53 (96.4)	34 (72.3)	24.1 (-0.4 to -0.1)	**0.001**
50% $fT_{>MIC}$ on day 3	54 (98.2)	42 (93.6)	4.6 (-0.2 to 0.1)	0.332
100% $fT_{>MIC}$ on day 3	53 (96.4)	34 (72.3)	24.1 (-0.4 to -0.1)	**0.001**
ICU-free days	20 (12-23)	17 (0-23)	3 (-4 to 0)	0.276
ICU survivors[d]	21 (19-23)	21 (14-24)	0 (-3 to 1)	0.662
Ventilator-free days	22 (0-24)	14 (0-24)	8 (-7 to 0)	**0.025**
ICU survivors[e]	23 (21-25)	19 (1-25)	4 (-7 to 0)	**0.027**
14-day survival, n (%)	53 (80.3)	42 (70.0)	10.3 (-0.3 to 0.1)	0.180
30-day survival, n (%)	49 (74.2)	38 (63.3)	10.9 (-0.3 to 0.1)	0.186
WCC normalisation days	3 (2-6)	8 (5-15)	5 (2 to 5)	**<0.001**

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

[a]Represents the p-value between the intervention arm versus the control arm and values in bold indicate significant difference between the two treatment arms ($p < 0.05$).

[b]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 chi-square test or Fisher's exact test as appropriate.

[c]Only participants with complete pharmacokinetic data (n = 110; intervention = 60, control = 50) and those who were infected with beta-lactam susceptible pathogens (n = 102; intervention = 55, control = 47) were included in the analysis.

[d]Only participants who survived at ICU discharge was included in this sub-analysis (54 and 45 participants in the intervention and control arm, respectively).

[e]Only mechanically-ventilated participants who survived at ICU discharge was included in this sub-analysis (51 and 40 participants in the intervention and control arm, respectively).

Supplementary Table 6: Differences in clinical characteristics and treatment-related variables between participants who demonstrated clinical cure and clinical failure in the ITT population

Variable	**Cure (n =63)**	**Failure (n = 77)**	**p-value**[a,b]
Age (years)	55 (45-63)	53 (40-68)	0.774
Male, n (%)	46 (73.0)	50 (64.9)	0.306
Body weight (kg)	70 (56-80)	68 (60-75)	0.875
Body mass index (kg/m^2)	25 (22-30)	25 (22-29)	0.793
APACHE II	19 (16-22)	23 (17-28)	**0.009***
SOFA	7 (6-9)	8 (5-10)	0.695
Charlson comorbidity index	3 (2-5)	4 (2-6)	0.126*
Serum albumin (g/dL)	26 (21-30)	22 (17-28)	**0.037***
Serum creatinine concentration (µmol/L)	94 (63-176)	120 (66-165)	0.697
Cockcroft-Gault creatinine clearance (mL/min)	68 (50-115)	59 (38-97)	0.268
Pre-randomisation ICU stay (days)	2 (2-5)	3 (2-6)	0.580
Pre-randomisation antibiotic therapy, n (%)	24 (28.1)	34 (44.2)	0.469
Pre-randomisation appropriate antibiotic therapy, n (%)	34 (82.9)	45 (71.4)	0.180
Duration of randomised treatment (days)	7 (6-9)	6 (4-8)	**0.040***
Mechanically-ventilated, n (%)	57 (90.5)	70 (90.9)	0.930
Post-randomisation renal replacement therapy, n (%)	7 (11.1)	20 (26.0)	**0.027***
Surgery within 24 hours of study inclusion, n (%)	24 (38.1)	34 (44.2)	0.469
White cell count (x 10^9/L)	16 (13-21)	16 (14-21)	0.769
Pre-randomisation antibiotic therapy, n (%)	44 (69.8)	64 (83.1)	0.063*
Study antibiotic, n (%)			
Piperacillin/tazobactam	37 (58.7)	48 (62.3)	0.357
Meropenem	22 (34.9)	20 (26.0)	
Cefepime	4 (6.3)	9 (11.7)	

Concomitant antibiotic use, n (%)	27 (42.9)	39 (50.6)	0.358
Treatment			
Continuous infusion	39 (61.9)	31 (40.3)	**0.011***
Intermittent bolus	24 (38.1)	46 (59.7)	
Primary infection site, n (%)			
Lung	39 (61.9)	43 (55.8)	0.469
Intra-abdominal	13 (20.6)	13 (16.9)	0.570
Blood	1 (1.6)	9 (11.7)	**0.023***
Urinary tract	3 (4.8)	2 (2.6)	0.657
Skin or skin structure	6 (9.5)	7 (9.1)	0.930
Central nervous system	1 (1.6)	3 (3.9)	0.627
Organ dysfunction, n (%)			
Respiratory	40 (63.5)	50 (64.9)	0.859
Cardiovascular	37 (58.7)	40 (51.9)	0.422
Hematologic	13 (20.6)	17 (22.1)	0.836
Renal	13 (20.6)	14 (18.2)	0.714
Metabolic acidosis	4 (6.3)	3 (3.9)	0.701
Participants who had organisms identified, n (%)	41 (65.1)	63 (81.8)	**0.024***
Gram-negative infections, n (%)	35 (85.4)	45 (71.4)	0.099*
PK/PD ratio			
Concentration at 50% of the dosing interval to MIC D1	5.8 (3.4-15.0)	6.5 (3.6-16)	0.547
Concentration at 100% of the dosing interval to MIC D1	4.5 (2.1-12.4)	4.7 (2.1-10.1)	0.823
Concentration at 50% of the dosing interval to MIC D3	7.9 (3.8-17.0)	6.9 (13.2-16.1)	0.583

Concentration at 100% of the dosing interval to MIC D3	6.3 (2.2-13.8)	4.2 (1.7-12.8)	0.282

*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.

[a]Bold values indicate statistical significance ($p < 0.05$).

[b]Represents variable that was included in the multivariate logistic regression model.

Supplementary Table 7: Factors predicting clinical cure in the ITT population

Variable	All factors included in the model		Final model	
	Odds ratio (95% CI)	Significance (p-value)	Odds ratio (95% CI)	Significance (p-value)
Factors predicting clinical cure				
Continuous infusion[a]	3.08 (1.38-6.94)	**0.007**	3.21 (1.48-6.94)	**0.003**
Bacteremia[b]	0.10 (0.01-0.92)	**0.042**	0.09 (0.09-0.770)	**0.028**
Pre-randomisation antibiotic therapy[c]	2.74 (1.02-7.32)	**0.045**	2.85 (1.12-7.23)	**0.028**
APACHE II score (per 1-point increase)	0.95 (0.90-1.00)	0.060	0.95 (0.90-0.99)	**0.036**
Study drug[d]		0.075		**0.047**
Piperacillin/tazobactam	4.15 (1.01-17.01)	0.049	4.21 (1.06-16.64)	0.041
Meropenem	6.04 (1.28-28.47)	0.023	6.54 (1.48-28.90)	0.013
Cefepime	1.0	-	1.0	-
Causative organism identified[e]	0.54 (0.22-1.33)	0.180	-	-
Duration of randomised treatment (per 1-day increase)	1.04 (0.98-1.09)	0.208	-	-
Albumin (per 1 g/dL increase)	1.02 (0.96-1.08)	0.597	-	-
Charlson comorbidity index (per 1-point increase)	0.98 (0.85-1.13)	0.781	-	-
Goodness-of-fit				
Hosmer-Lemeshow test	$X^2 = 6.96$, $df = 8$	0.541	$X^2 = 3.843$, $df = 8$	0.871

APACHE = Acute Physiology and Chronic Health Evaluation

[a]OR compares continuous infusion relative to IB dosing of beta-lactam antibiotics.

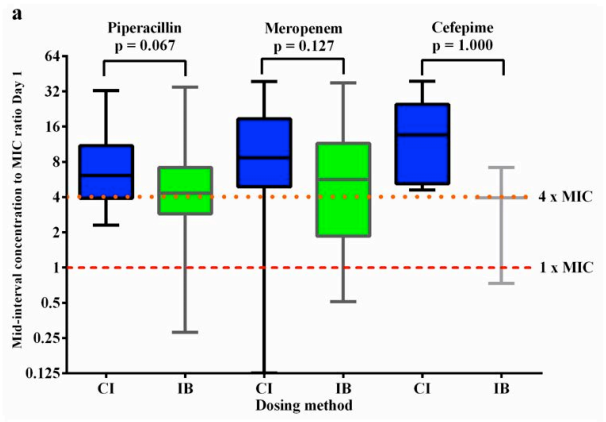
[b]OR compares bacteremia relative to other sites of infections.

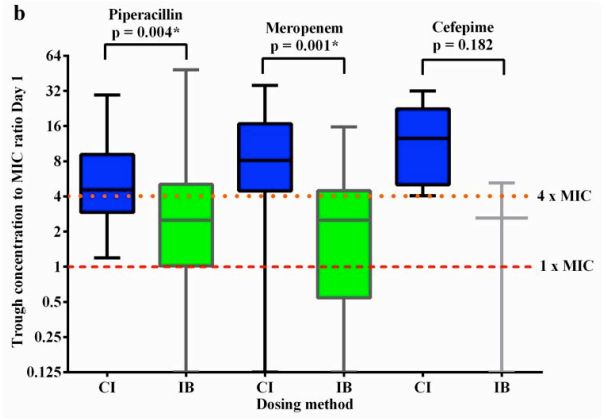
[c]OR compares those who received pre-randomisation antibiotic therapy relative to those who did not.

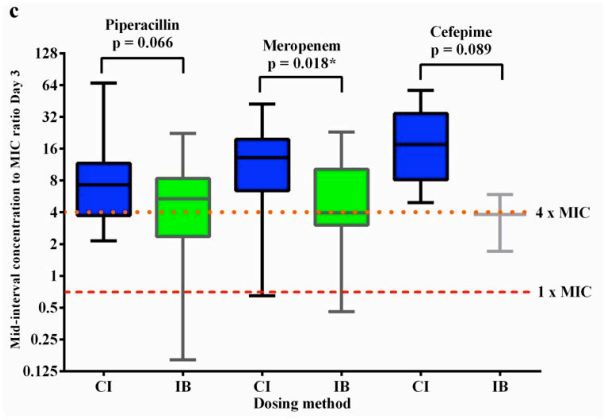
[d]OR compares piperacillin/tazobactam and meropenem relative to cefepime.

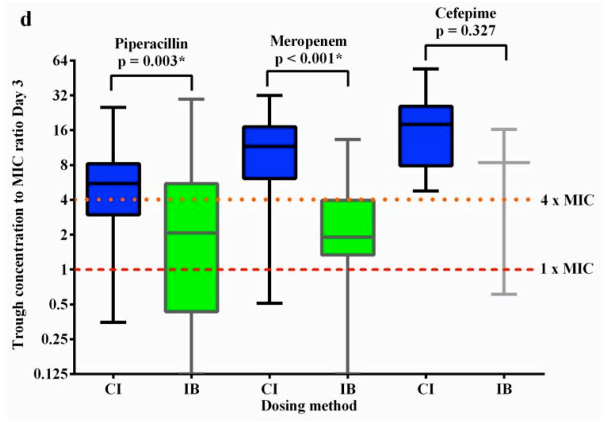
[e]OR compares those who had at least one causative organism identified relative to those who did not

Supplementary Figure 2: Free plasma antibiotic concentration to minimum inhibitory concentration (MIC) ratio 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









Legends:

Supplementary Table 4: Primary and secondary end-points by treatment arm in the modified intention-to-treat population

Primary end-point	**Intervention (n = 68)**	**Control (n = 66)**	**Absolute difference (95% CI)**	**Significance (p-value)**[a,b]
Clinical cure, n (%)	39 (57.4)	23 (34.8)	22.5 (-0.4 to -0.1)	**0.009**
Secondary end-points	**Intervention (n = 68)**	**Control (n = 66)**	**Absolute difference (95% CI)**	**Significance (p-value)**[a,b]
PK/PD target attainment, n (%)[c]				
50% $fT_{>MIC}$ on day 1	54 (98.2)	48 (94.1)	4.1 (-0.1 to 0.1)	0.350
100% $fT_{>MIC}$ on day 1	53 (96.4)	37 (72.5)	23.9 (-0.4 to -0.1)	**0.001**
50% $fT_{>MIC}$ on day 3	54 (98.2)	48 (94.1)	4.1 (-0.1 to 0.1)	0.350
100% $fT_{>MIC}$ on day 3	53 (96.4)	36 (70.6)	25.8 (-0.4 to -0.1)	**<0.001**
ICU-free days	20 (11-23)	16 (0-23)	4 (-4 to 0)	0.287
ICU survivors[d]	21 (19-23)	21 (12-24)	0 (-3 to 1)	0.565
Ventilator-free days	22 (0-24)	14 (0-24)	8 (-7 to 1)	**0.045**
ICU survivors[e]	23 (21-25)	20 (0-25)	3 (-6 to 0)	**0.050**
14-day survival, n (%)	54 (79.4)	47 (71.2)	8.2 (-0.2 to 0.1)	0.271
30-day survival, n (%)	50 (73.5)	42 (63.6)	9.9 (-0.2 to 0.1)	0.217
WCC normalisation days	3 (2-7)	8 (4-15)	5 (1-5)	**<0.001**

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

[a]Represents the p-value between the intervention arm versus the control arm and values in bold indicate significant difference between the two treatment arms ($p < 0.05$).

[b]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 chi-square test or Fisher's exact test as appropriate.

[c]Only participants with complete pharmacokinetic data (n = 115; intervention = 61, control = 54) and those who were infected with beta-lactam susceptible pathogens (n = 106; intervention = 55, control = 51) were included in the analysis.

[d]Only participants who survived at ICU discharge was included in this sub-analysis (55 and 50 participants in the intervention and control arm, respectively).

[e]Only mechanically-ventilated participants who survived at ICU discharge was included in this sub-analysis (52 and 43 participants in the intervention and control arm, respectively).

Supplementary Table 5: Primary and secondary end-points by treatment arm in the per-protocol population

Primary end-point	**Intervention (n = 66)**	**Control (n = 60)**	**Absolute difference (95% CI)**	**Significance (p-value)**[a,b]
Clinical cure, n (%)	39 (59.1)	20 (33.3)	25.8 (-0.4 to -0.1)	**0.004**
Secondary end-points	**Intervention (n = 66)**	**Control (n = 60)**	**Absolute difference (95% CI)**	**Significance (p-value)**[a,b]
PK/PD target attainment, n (%)				
50% $fT_{>MIC}$ on day 1	54 (98.2)	42 (93.6)	4.6 (-0.2 to 0.1)	0.332
100% $fT_{>MIC}$ on day 1	53 (96.4)	34 (72.3)	24.1 (-0.4 to -0.1)	**0.001**
50% $fT_{>MIC}$ on day 3	54 (98.2)	42 (93.6)	4.6 (-0.2 to 0.1)	0.332
100% $fT_{>MIC}$ on day 3	53 (96.4)	34 (72.3)	24.1 (-0.4 to -0.1)	**0.001**
ICU-free days	20 (12-23)	17 (0-23)	3 (-4 to 0)	0.276
ICU survivors[d]	21 (19-23)	21 (14-24)	0 (-3 to 1)	0.662
Ventilator-free days	22 (0-24)	14 (0-24)	8 (-7 to 0)	**0.025**
ICU survivors[e]	23 (21-25)	19 (1-25)	4 (-7 to 0)	**0.027**
14-day survival, n (%)	53 (80.3)	42 (70.0)	10.3 (-0.3 to 0.1)	0.180
30-day survival, n (%)	49 (74.2)	38 (63.3)	10.9 (-0.3 to 0.1)	0.186
WCC normalisation days	3 (2-6)	8 (5-15)	5 (2 to 5)	**<0.001**

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

[a]Represents the p-value between the intervention arm versus the control arm and values in bold indicate significant difference between the two treatment arms ($p < 0.05$).

[b]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 chi-square test or Fisher's exact test as appropriate.

[c]Only participants with complete pharmacokinetic data (n = 110; intervention = 60, control = 50) and those who were infected with beta-lactam susceptible pathogens (n = 102; intervention = 55, control = 47) were included in the analysis.

[d]Only participants who survived at ICU discharge was included in this sub-analysis (54 and 45 participants in the intervention and control arm, respectively).

[e]Only mechanically-ventilated participants who survived at ICU discharge was included in this sub-analysis (51 and 40 participants in the intervention and control arm, respectively).

Supplementary Table 6: Differences in clinical characteristics and treatment-related variables between participants who demonstrated clinical cure and clinical failure in the ITT population

Variable	**Cure (n =63)**	**Failure (n = 77)**	**p-value**[a,b]
Age (years)	55 (45-63)	53 (40-68)	0.774
Male, n (%)	46 (73.0)	50 (64.9)	0.306
Body weight (kg)	70 (56-80)	68 (60-75)	0.875
Body mass index (kg/m^2)	25 (22-30)	25 (22-29)	0.793
APACHE II	19 (16-22)	23 (17-28)	**0.009***
SOFA	7 (6-9)	8 (5-10)	0.695
Charlson comorbidity index	3 (2-5)	4 (2-6)	0.126*
Serum albumin (g/dL)	26 (21-30)	22 (17-28)	**0.037***
Serum creatinine concentration (µmol/L)	94 (63-176)	120 (66-165)	0.697
Cockcroft-Gault creatinine clearance (mL/min)	68 (50-115)	59 (38-97)	0.268
Pre-randomisation ICU stay (days)	2 (2-5)	3 (2-6)	0.580
Pre-randomisation antibiotic therapy, n (%)	24 (28.1)	34 (44.2)	0.469
Pre-randomisation appropriate antibiotic therapy, n (%)	34 (82.9)	45 (71.4)	0.180
Duration of randomised treatment (days)	7 (6-9)	6 (4-8)	**0.040***
Mechanically-ventilated, n (%)	57 (90.5)	70 (90.9)	0.930
Post-randomisation renal replacement therapy, n (%)	7 (11.1)	20 (26.0)	**0.027***
Surgery within 24 hours of study inclusion, n (%)	24 (38.1)	34 (44.2)	0.469
White cell count (x 10^9/L)	16 (13-21)	16 (14-21)	0.769
Pre-randomisation antibiotic therapy, n (%)	44 (69.8)	64 (83.1)	0.063*
Study antibiotic, n (%)			
Piperacillin/tazobactam	37 (58.7)	48 (62.3)	0.357
Meropenem	22 (34.9)	20 (26.0)	
Cefepime	4 (6.3)	9 (11.7)	

Concomitant antibiotic use, n (%)	27 (42.9)	39 (50.6)	0.358
Treatment			
Continuous infusion	39 (61.9)	31 (40.3)	**0.011***
Intermittent bolus	24 (38.1)	46 (59.7)	
Primary infection site, n (%)			
Lung	39 (61.9)	43 (55.8)	0.469
Intra-abdominal	13 (20.6)	13 (16.9)	0.570
Blood	1 (1.6)	9 (11.7)	**0.023***
Urinary tract	3 (4.8)	2 (2.6)	0.657
Skin or skin structure	6 (9.5)	7 (9.1)	0.930
Central nervous system	1 (1.6)	3 (3.9)	0.627
Organ dysfunction, n (%)			
Respiratory	40 (63.5)	50 (64.9)	0.859
Cardiovascular	37 (58.7)	40 (51.9)	0.422
Hematologic	13 (20.6)	17 (22.1)	0.836
Renal	13 (20.6)	14 (18.2)	0.714
Metabolic acidosis	4 (6.3)	3 (3.9)	0.701
Participants who had organisms identified, n (%)	41 (65.1)	63 (81.8)	**0.024***
Gram-negative infections, n (%)	35 (85.4)	45 (71.4)	0.099*
PK/PD ratio			
Concentration at 50% of the dosing interval to MIC D1	5.8 (3.4-15.0)	6.5 (3.6-16)	0.547
Concentration at 100% of the dosing interval to MIC D1	4.5 (2.1-12.4)	4.7 (2.1-10.1)	0.823
Concentration at 50% of the dosing interval to MIC D3	7.9 (3.8-17.0)	6.9 (13.2-16.1)	0.583

Concentration at 100% of the dosing interval to MIC D3	6.3 (2.2-13.8)	4.2 (1.7-12.8)	0.282

*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.

[a]Bold values indicate statistical significance ($p < 0.05$).

[b]Represents variable that was included in the multivariate logistic regression model.

Supplementary Table 7: Factors predicting clinical cure in the ITT population

Variable	All factors included in the model		Final model	
	Odds ratio (95% CI)	Significance (p-value)	Odds ratio (95% CI)	Significance (p-value)
Factors predicting clinical cure				
Continuous infusion[a]	3.08 (1.38-6.94)	**0.007**	3.21 (1.48-6.94)	**0.003**
Bacteremia[b]	0.10 (0.01-0.92)	**0.042**	0.09 (0.09-0.770)	**0.028**
Pre-randomisation antibiotic therapy[c]	2.74 (1.02-7.32)	**0.045**	2.85 (1.12-7.23)	**0.028**
APACHE II score (per 1-point increase)	0.95 (0.90-1.00)	0.060	0.95 (0.90-0.99)	**0.036**
Study drug[d]		0.075		**0.047**
Piperacillin/tazobactam	4.15 (1.01-17.01)	0.049	4.21 (1.06-16.64)	0.041
Meropenem	6.04 (1.28-28.47)	0.023	6.54 (1.48-28.90)	0.013
Cefepime	1.0	-	1.0	-
Causative organism identified[e]	0.54 (0.22-1.33)	0.180	-	-
Duration of randomised treatment (per 1-day increase)	1.04 (0.98-1.09)	0.208	-	-
Albumin (per 1 g/dL increase)	1.02 (0.96-1.08)	0.597	-	-
Charlson comorbidity index (per 1-point increase)	0.98 (0.85-1.13)	0.781	-	-
Goodness-of-fit				
Hosmer-Lemeshow test	$X^2 = 6.96$, $df = 8$	0.541	$X^2 = 3.843$, $df = 8$	0.871

APACHE = Acute Physiology and Chronic Health Evaluation

[a]OR compares continuous infusion relative to IB dosing of beta-lactam antibiotics.

[b]OR compares bacteremia relative to other sites of infections.

[c]OR compares those who received pre-randomisation antibiotic therapy relative to those who did not.

[d]OR compares piperacillin/tazobactam and meropenem relative to cefepime.

[e]OR compares those who had at least one causative organism identified relative to those who did not

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.

***PK/PD ratio is defined as the ratio between the measured plasma antibiotic concentration at 50% or 100% of the dosing interval and the causative pathogen's "surrogate MIC" (i.e. not actual MIC values), as defined in Supplementary Table 2. Note that a ratio of 1 at 100% of the dosing interval is generally considered to be a minimum PK/PD target during beta-lactam therapy.