TITLE

Continuous vs intermittent β-lactam antibiotic infusions in critically ill patients with sepsis: The BLING III randomized clinical trial

AUTHORS

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Key Points:

QUESTION:

Is there a difference in mortality between continuous and intermittent infusions of β-lactam antibiotics in critically ill patients with sepsis?

FINDINGS:

In this randomized clinical trial that included 7031 adult patients with sepsis, there was not a statistically significant difference in the proportion of patients who died within 90 days that received continuous (24.9%) compared with intermittent (26.8%) β-lactam antibiotic infusions (odds ratio 0.91, 95% confidence interval 0.81 to 1.01).

MEANING:

In critically ill patients with sepsis, continuous vs intermittent β-lactam antibiotic infusions did not significantly reduce 90-mortality in the primary analysis.

Abstract

IMPORTANCE

Whether β-lactam antibiotics administered by continuous compared with intermittent infusion reduces the risk of death in patients with sepsis is uncertain.

OBJECTIVE

To evaluate whether continuous vs intermittent infusion of a β-lactam antibiotic (piperacillin-tazobactam or meropenem) results in decreased all-cause mortality at 90 days in critically ill patients with sepsis.

DESIGN, SETTING, AND PARTICIPANTS

An international, open label, randomized clinical trial conducted in 104 intensive care units (ICUs) in Australia, Belgium, France, Malaysia, New Zealand, Sweden and the United Kingdom. Recruitment occurred from March 26, 2018 to January 11, 2023 with follow-up completed on April 12, 2023. Participants were critically ill adults (≥18 years) treated with piperacillin-tazobactam or meropenem for sepsis.

INTERVENTION

Eligible patients were randomized to receive an equivalent 24-hour dose of a β-lactam antibiotic by either continuous (n = 3498) or intermittent infusion (n = 3533) for a clinician-determined duration of treatment or until ICU discharge, whichever occurred first.

MAIN OUTCOMES AND MEASURES

The primary outcome was all-cause mortality within 90 days after randomization. Secondary outcomes were clinical cure up to 14 days after randomization; new acquisition, colonization or infection with a multi-resistant organism or *Clostridioides difficile* infection up to 14 days after randomization; ICU mortality and in-hospital mortality.

RESULTS

Among 7202 randomized participants, 7031 (mean age, 59 [standard deviation 16]; 2423 were women [35%]) met consent requirements for inclusion in the primary analysis (97.6%). Within 90 days, 864 of 3474 patients (24.9%) assigned to receive continuous infusion had died compared with 939 of 3507 (26.8%) assigned intermittent infusion (absolute difference [AD] -1.9%, 95% CI -4.9% to 1.1%; odds ratio 0.91, 95% CI, 0.81 to 1.01; *P* = 0.08). Clinical cure was higher in the continuous vs intermittent infusion group: 1930/3467 (55.7%) and 1744/3491 (50.0%), respectively (AD 5.7%, 95% CI 2.4% to 9.1%). Other secondary outcomes were not statistically different.

CONCLUSIONS AND RELEVANCE

The observed difference in 90-day mortality between continuous vs intermittent infusions of β-lactam antibiotics did not meet statistical significance in the primary analysis, however, the confidence interval around the effect estimate includes the possibility of both no important effect and a clinically important benefit in the use of continuous infusions in this group of patients.

TRIAL REGISTRATION

ClinicalTrials.gov Identifier: NCT03213990

Defined as life-threatening organ dysfunction due to a dysregulated response to infection,[1] sepsis is a major cause of mortality worldwide. Early antibiotic therapy directed at the likely infective microorganism is a cornerstone of treatment,[2-4] of which β-lactam antibiotics are an important class of antibiotics.[4] For patients treated in the intensive care unit (ICU), meropenem and piperacillin-tazobactam are commonly used drugs in this antibiotic class.[5,6] β-lactam antibiotics have been primarily administered as multiple, short (e.g. 30-minute) intermittent infusions. Due to time-dependent kill characteristics, there is a biological rationale that continuous infusion may be more effective than intermittent administration.[7-9]

Recent clinical trials have reported that the administration of β-lactam antibiotics by continuous infusion results in concentrations above the minimum inhibitory concentration of typical pathogens.[10,11] However, clinical trials and meta-analyses have not provided conclusive evidence of microbiological cure and improved patient-centered outcomes.[12-16] To address uncertainty about the optimal method of β-lactam antibiotic administration in the ICU setting,[17,18] we conducted a randomized clinical trial to determine whether continuous infusion of piperacillin-tazobactam or meropenem resulted in decreased all-cause mortality at 90 days in critically ill patients with sepsis compared to intermittent infusion.

Methods

TRIAL DESIGN AND OVERSIGHT

The Beta-Lactam Infusion Group (BLING) III trial was an international, open label, phase III, randomized clinical trial comparing continuous with intermittent infusions of β-lactam antibiotics on landmark 90-day mortality in critically ill patients with sepsis. The study protocol (Supplement 1) and statistical analysis plan (Supplement 2) have been published previously.[19,20] The trial was approved by the relevant human research ethics committee or

equivalent in each region; institutional approval was obtained as per site requirements. In some jurisdictions, approval was obtained for enrolment prior to consent in certain circumstances (eMethods, Supplement 3); in all countries, written informed consent was obtained from patients or their legal surrogate with documented verbal consent obtained in some regions during the SARS-CoV-2 (COVID-19) pandemic as per ethics committee approval (eMethods, Supplement 3).

The trial management committee was responsible for the design of the study. All authors participated in the conduct of the study and reporting of the results. The George Institute for Global Health sponsored the study, generated the allocation sequence and conducted the statistical analysis. An independent data and safety monitoring committee conducted a pre-specified mid-point safety analysis (Supplement 2). Study reporting adhered to the CONSORT 2010 Statement for randomized clinical trials.

The trial was conducted in 104 adult ICUs in Australia, Belgium, France, Malaysia, New Zealand, Sweden and the United Kingdom. Participants were enrolled between March 26, 2018 and January 11, 2023; 90-day follow-up was completed on April 12, 2023.

PARTICIPANTS

Eligible participants were adult (≥ 18 years) ICU patients with: (1) a documented site or strong suspicion of infection, (2) treatment with piperacillin-tazobactam or meropenem commenced within the previous 24 hours, and (3) one or more organ dysfunction criteria met in the previous 24 hours as defined in study inclusion criteria (eMethods, Supplement 3). Eligible participants were expected to remain in the ICU for at least the next calendar day and in whom the administration of either piperacillin-tazobactam or meropenem by intermittent or

continuous infusion was considered equally appropriate for the patient by the attending clinicians. Full details of inclusion and exclusion criteria are provided in eMethods (Supplement 3).

RANDOMIZATION

Participants were randomized in a 1:1 ratio to receive the prescribed antibiotic by either continuous (intervention group) or intermittent infusion (control group).[19] Randomization was generated using a minimization algorithm via a password-protected, encrypted web-based interface with stratification by study site.

INTERVENTIONS

In both groups, the total 24-hour β-lactam antibiotic dose was determined by the attending clinicians. A defined daily dose (DDD) of 14 g for piperacillin-tazobactam and 3 g for meropenem was used as a reference measure.[21] All participants received at least 1 β-lactam antibiotic infusion dose prior to open label randomized treatment. Randomized drug administration by continuous infusion (over 24 hours) or intermittent infusion (over 30 minutes) was continued for the duration of the treatment course or until ICU discharge, whichever occurred first. A switch between piperacillin-tazobactam and meropenem (or vice versa) was permitted in the same treatment group after receipt of a loading dose by intermittent infusion for participants in the continuous infusion group. Additional details on study drug administration appear in Supplement 3 (eMethods).

OUTCOME MEASURES

The primary outcome was all-cause mortality at 90 days from the date of randomization. Secondary outcomes were clinical cure, defined as the completion of the β-lactam antibiotic

treatment course by day 14 without recommencement of antibiotic therapy within 48 hours of cessation for the same infectious episode (eMethods, Supplement 3); new acquisition, colonization or infection with a multi-resistant organism or *Clostridioides difficile* infection up to 14 days after randomization (eMethods, Supplement 3); all-cause ICU mortality and all-cause hospital mortality. Tertiary outcomes were the number of days free of ICU, hospital, mechanical ventilation and renal replacement therapy up to 90 days after randomization.[19] Study days are defined in eMethods (Supplement 3). Drug reactions thought to have a causal relationship (i.e. possible, probable or definitely related) to the study assigned administration method were reported as adverse events. Protocol deviations related to administration of the β-lactam antibiotic, included pre-defined events (eMethods, Supplement 3).

TRIAL POPULATION

A sample size of 7000 patients provided 90% power to detect an absolute difference of 3.5% in all-cause mortality at 90 days from an estimated baseline mortality of 27.5%, at an alpha of 0.05.[20] This calculation allowed for a rate of withdrawal and loss to follow-up of up to 5% of participants. Recruitment proceeded for 6 months after the 7000th participant at 13 sites to facilitate recruitment in a pre-specified pharmacokinetic-pharmacodynamic sub-study.

STATISTICAL ANALYSIS

The effectiveness of the intervention was evaluated by a modified intention-to-treat analysis of all participants randomized to the trial where consent or approval to use their data was obtained, regardless of protocol compliance. This primary analysis consisted of logistic regression with treatment allocation as a fixed effect and trial site as a random effect. Results are presented as the odds ratio (OR) and 95% confidence interval (CI) and converted to an absolute difference (AD) in proportions.

The primary outcome was also examined in a pre-specified adjusted analysis with the following covariates added to the main logistic regression model: sex; Acute Physiology and Chronic Health Evaluation Score (APACHE) II score (a severity of illness score ranging from 0 to 71 with higher scores indicating an increased risk of death) at randomization,[22] source of admission (admitted following emergency or elective surgery vs other) and type of β-lactam antibiotic used pre-randomization (piperacillin-tazobactam or meropenem). Five pre-specified subgroup analyses were also carried out according to the following pre-randomization variables: presence vs absence of presumed pulmonary infection at baseline, type of β-lactam antibiotic first administered (piperacillin-tazobactam or meropenem), age (<65 years vs ≥65 years), sex (male vs female), and low vs high severity of illness (defined by an APACHE II score at randomization <25 or ≥25).[15,19,23]

Secondary binary outcomes were analyzed using a similar logistic regression to the primary analysis. Tertiary duration outcomes were analyzed using linear regression. Time to discharge or cessation were summarized using a cumulative incidence function treating death as a competing risk, censored at 90 days. Intervention effects were estimated as the hazard ratio and 95% CIs obtained from a cause-specific Cox model with a fixed effect of treatment and a random site effect. Proportions of patients with adverse events were compared using Fisher's exact test among patients who received 1 or more doses of the β-lactam antibiotic in the assigned treatment group.

There was no imputation of missing data across all analyses. All tests were two-sided with a nominal significance level at 5%. Analyses of the primary outcome are unadjusted for multiplicity; however, the family-wise error rate was controlled across secondary outcomes (one

family) and tertiary outcomes (one family) using a Holm-Bonferroni correction.[24] Analyses were performed using SAS Enterprise Guide 8.3, SAS version 9.4 (SAS Institute Inc).

Results

TRIAL POPULATION

A total of 7202 participants were randomized of which 7031 with consent or approval to use data were included in the primary analysis (Figure 1). Of these, 6950 received at least 1 dose of the β-lactam antibiotic by allocation group and were included in the safety analysis. Enrollment by country and site is shown in eTable 1 (Supplement 3). The intervention and control groups had similar baseline characteristics (Table 1 and eTable 2, Supplement 3).

The most common primary sites of infection were pulmonary in 4153/7026 (59.1%), intrabdominal in 865/7026 (12.3%), blood in 547/7026 (7.8%) and urinary in 379/7026 (5.4%) (Table 1). Infective organisms for the primary site of infection are listed in eTable 3 (Supplement 3). Secondary and tertiary sites of infection and associated infective organisms are shown in eTables 4-6 (Supplement 3). The median duration of randomized treatment was 5.8 days (inter-quartile range [IQR] 3.1-10.2) and 5.7 days (IQR 3.1-10.3) in the continuous and intermittent infusion groups, respectively (eTable 7, Supplement 3). The median DDD was 1.0 in both groups on the first whole day (Day 2) post-randomization with an inter-quartile range of 0.8-1.2 DDDs (eTable 7, Supplement 3). The daily dose of study drugs was similar in both groups over the post-randomization treatment period up to Day 16 (eFigures 1-2, Supplement 3). Reasons for cessation of the β-lactam antibiotic are listed in eTable 8 (Supplement 3). Prior to randomization, 2658 of 3415 patients (77.8%) in the continuous infusion group and 2809 of 3445 (81.5%) in the intermittent group were prescribed the study drug by intermittent infusion (eTable 7, Supplement 3). Other antibiotics administered in the

24 hours before randomization up to day 16 are listed in eTable 9 (Supplement 3); 16.2% (568/3498) and 14.0% (496/3533) in the continuous and intermittent infusion groups, respectively, did not receive any other antibiotics during this period.

PRIMARY OUTCOME

At 90 days after randomization, 864 of 3474 (24.9%) patients allocated to the continuous infusion group and 939 of 3507 (26.8%) allocated to the intermittent infusion group had died (AD -1.9%, 95% CI -4.9% to 1.1%; OR 0.91, 95% CI 0.81 to 1.01, *P* = 0.08); Day 90 status was missing for 0.7% of participants (50/7031) (Table 2). After adjusting for prespecified covariates, the AD was -2.2%, 95% CI -5.5% to 1.1%; OR, 0.89, 95% CI 0.79 to 0.99, *P* = 0.04. The cumulative incidence function of time to death is shown in eFigure 3 (Supplement 3). There was no significant heterogeneity in the effect of the intervention assignment on mortality at 90 days in any of the 5 predefined subgroup pairs (Figure 2). The place and cause of death are listed in eTable 10 (Supplement 3).

SECONDARY OUTCOMES

There was a statistically significant difference in rates of clinical cure at 14 days post randomization in favor of the continuous infusion group (AD 5.7%, 95% CI 2.4% to 9.1%; OR 1.26, 95% CI 1.15 to 1.38). There were no statistically significant differences between groups in the rates of new acquisition, colonization or infection with a multi-resistant organism or *Clostridioides difficile* infection (AD -0.3%, 95% CI -1.9% to 1.4%; OR 0.96, 95% CI 0.80 to 1.15); ICU mortality (AD -1.3%, 95% CI -4.0% to 1.4%); hospital mortality (AD -1.8%, 95% CI -4.8% to 1.2%).

TERTIARY OUTCOMES

There were no statistical differences in days alive and free of ICU, hospital, mechanical ventilation and renal replacement therapy (Table 2). Daily participant disposition is shown in Figure 3 and cumulative incidence functions of time to alive discharge from the index ICU and hospital admission are shown in eFigures 4-5 (Supplement 3).

ADVERSE EVENTS

There were 10 adverse events in the continuous infusion group (0.3%) and 6 adverse events in the interment infusion group (0.2%), including 1 serious adverse event in the continuous infusion group (eTable 11, Supplement 3). The serious adverse event was severe encephalopathy resulting in aspiration pneumonia, cardiac arrest and death in the setting of septic shock. The event was assessed by site clinicians as possibly related to meropenem treatment. Administration by continuous infusion was hypothesized as potentially contributing to a higher minimum meropenem blood concentration leading to a higher cerebrospinal fluid concentration.

PROTOCOL DEVIATIONS

There were no statistical differences in the proportions of protocol deviations in both groups (eTable 12, Supplement 3).

DISCUSSION

In this randomized clinical trial, the use of continuous compared with intermittent infusions of β-lactam antibiotics in critically ill patients with sepsis did not meet statistical significance in reducing mortality at 90 days. However, the confidence interval around the effect estimate includes a clinically important benefit. The observed absolute reduction in mortality of around 2 percentage points with the use of continuous infusion represents a number needed to treat of

50 patients to prevent 1 death. The clinical significance of this finding is further supported by increased rates of clinical cure in the continuous infusion group and consistent directional changes in point estimates across other secondary and tertiary outcomes.

This pragmatic trial has several strengths. An extensive body of work informed the design of the trial that include feasibility and phase II trials previously conducted by the BLING investigators.[10,18] This work facilitated the establishment of an international collaboration to conduct the trial in multiple ICUs in 7 countries under routine clinical conditions over a relatively short trial inception period. The effect of continuous infusion of β-lactam antibiotics was assessed using a robust, patient-centered primary outcome that was not susceptible to adjudication bias. The definition of clinical cure used in this trial was also not susceptible to adjudication bias. The size of this trial greatly exceeds all previous trials. The recent Continuous Infusion vs Intermittent Administration of Meropenem in Critically Ill Patients (MERCY) trial (n = 607) comparing continuous and intermittent infusions of meropenem with double-dummy administration reported a difference of 2.5 percentage points in mortality at 28 days in favor of continuous infusions that is consistent with the current trial despite differences in mortality, rates of drug-resistance and trial endpoints.[26]

Effective delivery of β-lactam antibiotics by continuous infusion present some practical considerations for patients treated in the ICU.[27,28] Pharmacokinetic and pharmacodynamic considerations mandate that the same daily doses are used for both continuous and intermittent infusions.[27] While overall drug costs may remain consistent, the time taken to prepare and administer drugs with continuous infusions may be shorter than intermittent infusions,[8,16,29] although this may be negated by a higher incidence of interruptions of continuous infusions for clinical reasons. Continuous infusions of carbapenems that require

multiple infusions in a 24-hour period for drug stability reasons and use of dedicated infusion pumps and intravenous portals pose additional pragmatic considerations, particularly in resource-limited environments. [8,28-30] Consistent with previous trials, there are no observed differences in adverse events between continuous and intermittent infusions of β-lactam antibiotics.[16,18,26,27]

LIMITATIONS

This study has some limitations. First, blinding was not feasible in a pragmatic trial of this size. This was mitigated by using a robust primary outcome and blinded outcome adjudication. Second, some participants may have been randomized despite having a non-infectious cause of organ dysfunction. Third, while this international study has high indices of external validity and generalizability, extrapolation of these results to regions with high levels of antibiotic resistance requires caution. Fourth, there was no adjustment for susceptibility to the β-lactam antibiotic or the impact of additional antibiotics and dosing strategies, although the groups were observed to have a high degree of baseline balance. Fifth, the difference in outcomes may have been reduced by the use of intermittent dosing prior to randomization in the continuous group and after ICU discharge. Sixth, these results relate to the use of continuous infusions primarily in a high-income ICU setting and extrapolation to low and middle-income settings in and outside the ICU cannot be inferred.

CONCLUSIONS

The observed difference in 90-day mortality between continuous vs intermittent infusions of β-lactam antibiotics did not meet statistical significance in the primary analysis, however, the confidence interval around the effect estimate includes the possibility of both no important

effect and a clinically important benefit in the use of continuous infusions in this group of patients.

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Author Contributions:

Dr Dulhunty and Mr Billot had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Lipman (lead), Brett, Cotta, Davis, De Waele, Dulhunty, Finfer, Knowles, McGuiness, Myburgh, Paterson, Peake, Rajbhandari, Rhodes, Roberts, Shirwadkar, Starr, Taylor.

Acquisition, analysis, or interpretation of data: Lipman, Billot, Brett, Cotta, Davis, De Waele, Dulhunty, Finfer, Hammond, Knowles, Liu, McGuinness, Myburgh, Mysore, Paterson, Peake, Rajbhandari, Rhodes, Roberts, Roger, Shirwadkar, Starr, Taylor.

Drafting of the manuscript: Dulhunty, Myburgh, Rajbhandari.

Critical revision of the manuscript: Lipman, Billot, Brett, Cotta, Davis, De Waele, Dulhunty, Finfer, Hammond, Knowles, Liu, McGuinness, Myburgh, Mysore, Paterson, Peake, Rajbhandari, Rhodes, Roberts, Roger, Shirwadkar, Starr, Taylor.

Statistical analysis: Billot, Liu, Mysore.

Obtained funding: Lipman, Brett, De Waele, Dulhunty, Finfer, McGuinness, Myburgh, Paterson, Peake, Rhodes, Roberts, Roger.

Administrative, technical, or material support: Lipman, Brett, Cotta, De Waele, Dulhunty, Hammond, Knowles, Myburgh, Rajbhandari, Rhodes, Roberts, Roger.

Supervision: Brett, De Waele, Billot, Myburgh, Lipman.

Conflict of Interest Disclosures:

Drs Dulhunty, Cotta, Paterson, Roberts and Lipman reported that The University of Queensland received payment from a National Health and Medical Research Council grant to conduct the trial. Dr Brett reported that Imperial College London received payment from a National Health and Medical Research Council grant to conduct the trial and receipt of an institutional consultancy fee from GSK. Dr De Waele reported that Ghent University Hospital received payment from a Belgian Health Care Knowledge Centre (KCE) grant to conduct the trial and attending Advisory Boards, acting as a consultant to, or giving lectures with honoraria from Accelerate, Grifols, MSD and Pfizer. Ms Rajbhandari, Mr Billot, Drs Finfer, Hammond, Knowles, Liu, Ms Mysore and Drs Taylor and Myburgh reported that The George Institute for Global Health received payment from a National Health and Medical Research Council grant to conduct the trial. Drs Finfer and Hammond reported receiving consulting fees from RevImmune Inc. unrelated to this work and paid to The George Institute for Global Health. Dr Finfer reported owning options in Sepsis Scout unrelated to this work. Dr McGuinness reported that the Medical Research Institute of New Zealand received payment from a Health Research Council of New Zealand grant to conduct the trial. Dr Paterson reported receipt of research grants from Shionogi, Pfizer, Merck, BioVersys, bioMerieux and Gilead and attending Advisory Boards, acting as a consultant to, or giving lectures with honoraria from Merck, GSK, bioMerieux, Cepheid, Aurobac, Arrepath, CARB-X and AMR Action Fund. Dr Roberts reported serving as a consultant for Qpex, Gilead, Advanz Pharma, Pfizer, Sandoz, MSD, Cipla and bioMerieux, receipt of research grants from Qpex, British Society of Antimicrobial Chemotherapy, Pfizer and bioMerieux and that bioMerieux provided ETEST® strips for bacterial susceptibility testing within the BLING III pharmacokinetic-pharmacodynamic sub-study. Dr Roger reported receipt of speaker's fees from Shionogi, bioMerieux, AOP Orphan, Advanz Pharma, Fresenius, Pfizer and MSD and attending

Advisory Boards with honoraria from bioMerieux and Viatris. Dr Taylor reported owning a company, Health Technology Analysts, which provides consulting services to pharmaceutical companies, medical device companies and the Australian Government. No other disclosures were reported.

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Role of the Funder/Sponsor:

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Group Information:

The collaborating investigators for the BLING III trial are listed in Supplement 4.

Meeting Presentations:

The study will be presented at the Critical Care Reviews Meeting 2024; June 12, 2024; Belfast, United Kingdom.

Data Sharing Statement:

See Supplement 5.

Additional Contributions:

We thank the trial participants and their families, the trial teams, and the independent data safety and monitoring committee: Professor J. Duncan Young (Chair), MD, University of Oxford, Oxford, United Kingdom, Professor John Marshall, MD, St Michael's Hospital and University of Toronto, Toronto, Canada, and Professor Tom van der Poll, MD, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands; the project support, data monitoring, data management and legal teams at The George Institute for Global Health (Supplement 3); The University of Queensland project support team (Supplement 3); Farah Al-Beidh, BSc, PhD, and Janis Best-Lane, BSc, MRes, (United Kingdom), Daisy Vermeiren, RN, (Belgium and Europe), Sally Hurford, RN, (New Zealand), Loubna Elotmani, MSc, (France), Mohd Hafiz Abdul-Aziz, BPharm(Hons), PhD, (Malaysia) and Frederik Sjövall, MD, PhD (Sweden) for regional coordination; Greg Barton, BSc,

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Table 1. Baseline Characteristics

Characteristic	Continuous Infusion (n = 3498)[a]	Intermittent Infusion (n = 3533)[a]
Age, mean (SD), y	59.3 (16.4)	59.6 (16.1)
Median (IQR)	62 (49, 72)	63 (50, 72)
Sex, No. (%)		
Female	1190 (34.0)	1233 (34.9)
Male	2308 (66.0)	2300 (65.1)
Weight, mean (SD) [N], kg	82.7 (22.6) [3493]	82.7 (22.9) [3530]
Median (IQR)	80 (68, 94)	80 (67, 94)
Height, mean (SD) [N], cm	170.5 (9.9) [3468]	170.3 (10.2) [3509]
Median (IQR)	170 (164, 178)	170 (164, 178)
Source of ICU admission, n/N (%)		
Accident and Emergency Department	1203/3495 (34.4)	1178/3532 (33.4)
Hospital floor (i.e. wards)	982/3495 (28.1)	1047/3532 (29.6)
Operating theatre following emergency surgery	732/3495 (20.9)	720/3532 (20.4)
Operating theatre following elective surgery	254/3495 (7.3)	265/3532 (7.5)
Transfer from another hospital (except from another ICU)	179/3495 (5.1)	173/3532 (4.9)
Transfer from another ICU[b]	145/3495 (4.1)	149/3532 (4.2)

Characteristic	Continuous Infusion (n = 3498)[a]	Intermittent Infusion (n = 3533)[a]
Time from ICU admission to randomization, mean (SD) [N], h	80.2 (135.2) [3496]	78.9 (148.3) [3532]
Median (IQR)	25.2 (12.6, 102.9)	24.8 (12.1, 104.1)
APACHE II score,[c] mean (SD) [N]	19.6 (7.6) [3495]	19.5 (7.4) [3529]
Median (IQR)	19 (14, 25)	19 (14, 24)
Lowest PaO_2/FiO_2 ratio in the 24 h prior to randomization, mean (SD) [N]	190.5 (102.5) [3322]	192.4 (103.6) [3371]
Median (IQR)	169 (111, 252)	172 (113, 252)
Highest creatinine, mean (SD) [N], µmol/L	122.6 (95.2) [3481]	123.6 (106.5) [3519]
Median (IQR)	92 (64, 150)	91 (63, 148)
Highest bilirubin, mean (SD) [N], µmol/L	25.9 (45.8) [3308]	24.7 (43.9) [3346]
Median (IQR)	14 (8, 24)	13 (8, 24)
Lowest platelet count, mean (SD) [N], $x10^9$/L	232.3 (141.0) [3460]	228.6 (137.6) [3492]
Median (IQR)	208 (138, 298)	204 (136, 295)
Lowest MAP in the 24 h prior to randomization, mean (SD) [N], mmHg	63.8 (12.4) [3485]	64.0 (12.1) [3512]
Median (IQR)	63 (57, 70)	63 (57, 70)
Worst Glasgow Coma Score (non-sedated),[d] mean (SD) [N]	12.2 (4.1) [2776]	12.3 (4.0) [2814]
Median (IQR)	14 (10, 15)	14 (11, 15)
Received inotropes/vasopressors in the 24 h prior to randomization, n/N (%)	2481/3496 (71.0)	2482/3532 (70.3)

Characteristic	Continuous Infusion (n = 3498)[a]	Intermittent Infusion (n = 3533)[a]
Received antibiotics in the 24 h prior to randomization,[e] n/N (%)	2340/3496 (66.9)	2460/3532 (69.6)
Primary site of infection, No. (%)		
Pulmonary	2062 (59.0)	2119 (60.0)
Intra-abdominal	469 (13.4)	447 (12.7)
Blood	268 (7.7)	294 (8.3)
Urinary	214 (6.1)	166 (4.7)
Skin	184 (5.3)	186 (5.3)
Gut	98 (2.8)	120 (3.4)
Central nervous system	65 (1.9)	74 (2.1)
Intravenous catheter	18 (0.5)	20 (0.6)
Endocarditis	13 (0.4)	4 (0.1)
Other[f]	103 (2.9)	102 (2.9)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, inter-quartile range; MAP, mean arterial pressure; OT, operating theatre; SD, standard deviation.

[a]Descriptive statistics are reported for all participants with available data by group. The group denominator for each characteristic is reported.

[b]From the same or a different hospital.

[c]The Acute Physiology and Chronic Health Evaluation (APACHE) II score is a severity of illness scoring system that ranges from 0 to 71; higher scores correspond to more severe disease and a higher risk of death.[22] A median APACHE II score of 19 equates to a 90-day mortality of approximately 22% in critically ill patients.[25]

[d]The Glasgow Coma Score (GCS) ranges from 3 to 15 with lower scores indicating a greater degree of neurological dysfunction. A GCS of 14 most commonly indicates a patient who opens their eyes spontaneously, follows verbal commands, but is confused.

[e]Other than piperacillin-tazobactam or meropenem.

[f]Other includes musculoskeletal,18 (0.5%) vs 20 (0.6%); oro-nasopharyngeal, 20 (0.6%) vs. 15 (0.4%); intrathoracic, 15 (0.4%) vs 13 (0.4%); soft tissue, 13 (0.4%) vs 13 (0.4%); gynecological, 3 (0.1%) vs 2 (0.1%); ear/eye infection, 2 (0.1%) vs 2 (0.1%), infected graft/hardware, 2 (0.1%) vs 2 (0.1%); unknown, 30 (0.9%) vs 35 (1.0%); for continuous and intermittent infusion, respectively.

Table 2. Reporting of Primary, Secondary and Tertiary Outcomes

Outcome	Continuous Infusion (n = 3498)[a]	Intermittent Infusion (n = 3533)[a]	Absolute difference, % (95% CI)	Odds Ratio or mean difference (95% CI)	*P* value[b]
Primary outcome:					
All-cause mortality at Day 90, n/N (%)	864/3474 (24.9)	939/3507 (26.8)	-1.9 (-4.9 to 1.1)	0.91 (0.81 to 1.01)	0.08
Adjusted analysis			-2.2 (-5.5 to 1.1)	0.89 (0.79 to 0.99)	0.04
Secondary outcomes:					
Clinical cure at Day 14, n/N (%)	1930/3467 (55.7)	1744/3491 (50.0)	5.7 (2.4 to 9.1)	1.26 (1.15 to 1.38)	<0.001
New acquisition, colonization or infection with an MRO or *C. difficile*,[c] n/N (%)	253/3498 (7.2)	266/3533 (7.5)	-0.3 (-1.9 to 1.4)	0.96 (0.80 to 1.15)	0.65
All-cause ICU mortality, n/N (%)	595/3474 (17.1)	645/3507 (18.4)	-1.3 (-4.0 to 1.4)	0.92 (0.81 to 1.04)	0.35
All-cause hospital mortality, n/N (%)	808/3474 (23.3)	878/3507 (25.0)	-1.8 (-4.7 to 1.2)	0.91 (0.81 to 1.02)	0.27
Tertiary outcomes:					
Days alive and free of ICU up to Day 90, mean (SD) [N]	59.4 (33.9) [3481]	57.8 (34.2) [3516]	NA	1.5 (-0.1 to 3.0)	0.18
Median (IQR)	78 (31, 84)	76 (22, 84)			

Outcome	Continuous Infusion (n = 3498)[a]	Intermittent Infusion (n = 3533)[a]	Absolute difference, % (95% CI)	Odds Ratio or mean difference (95% CI)	*P* value[b]
Days alive and free of hospital up to Day 90, mean (SD) [N]	42.4 (32.2) [3476]	40.6 (32.5) [3515]	NA	1.8 (0.3 to 3.3)	0.08
Median (IQR)	52 (0, 73)	48 (0, 72)			
Days alive and free of mechanical ventilation up to Day 90, mean (SD) [N]	64.2 (34.5) [3486]	62.9 (34.8) [3520]	NA	1.2 (-0.4 to 2.8)	0.28
Median (IQR)	84 (41, 89)	83 (32, 89)			
Days alive and free of RRT up to Day 90, mean (SD) [N]	71.2 (32.8) [3489]	70.2 (33.1) [3521]	NA	0.9 (-0.6 to 2.4)	0.25
Median (IQR)	90 (70, 90)	90 (54, 90)			

Abbreviations: CI, confidence interval; ICU, intensive care unit; MRO, multi-resistant organism; MV, mechanical ventilation; NA, not applicable; Q, quartile; RRT, renal replacement therapy; SD, standard deviation.

[a]Descriptive statistics and odds ratio or mean difference are reported for all participants with available data by group. The group denominator for each outcome is reported.

[b]*P* values for secondary and tertiary outcomes corrected with a Holm-Bonferroni adjustment.

[c]The number and per cent of new acquisition, colonization or infection with a multi-resistant organism, excluding *C. difficile*, was 6.1% (213/3498) in the continuous infusion group and 6.6% (232/3533) in the intermittent infusion group.

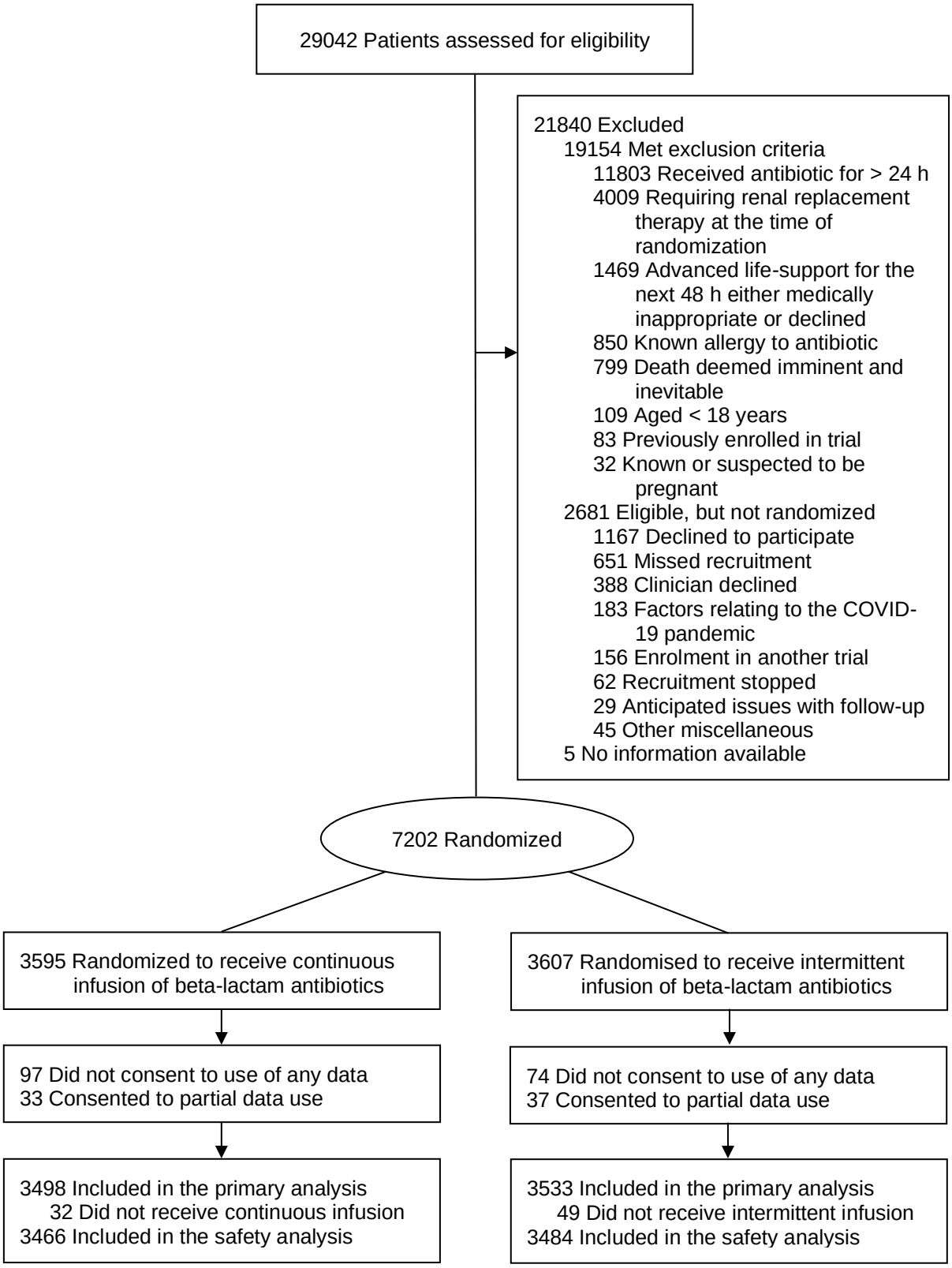
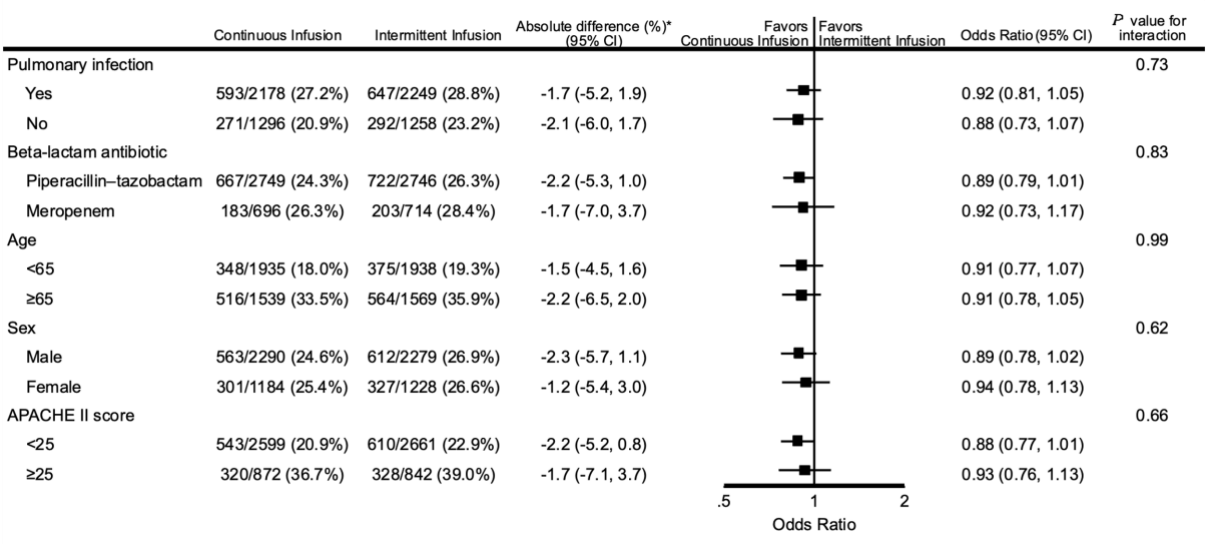


Figure 1. Screening, Randomization and Analysis of Study Participants in the BLING III Trial



Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

The APACHE II score is a severity of illness scoring system that ranges from 0 to 71; higher scores correspond to more severe disease and a higher risk of death.[22] A median APACHE II score of 19 equates to a 90-day mortality of approximately 22% in critically ill patients.[25]

Figure 2. Dot and Whisker Plot for Subgroup Analysis of Mortality at Day 90

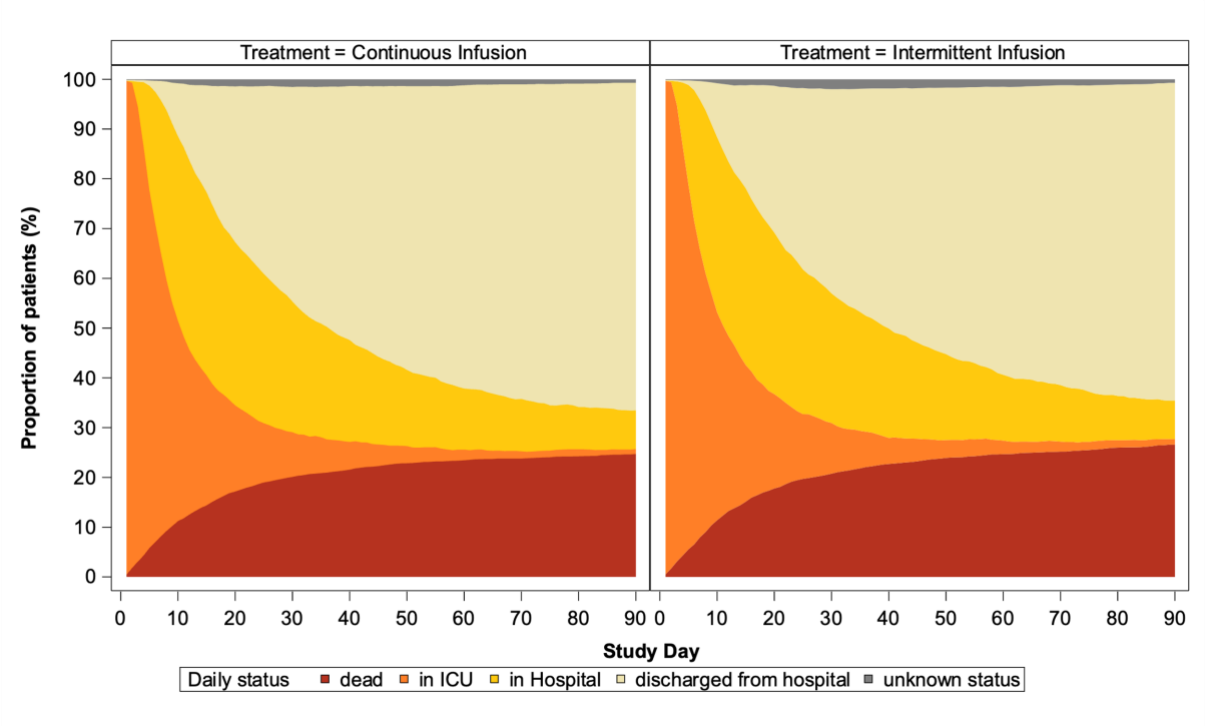


Figure 3. Daily Participant Disposition