

A protocol for a phase 3 multicentre randomised controlled trial of continuous versus intermittent β -lactam antibiotic infusion in critically ill patients with sepsis: BLING III

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β -Lactam antibiotics are the most common class of antibiotics used to treat life-threatening infections in the intensive care unit (ICU) setting.¹⁻⁵ The mechanism of action for β -lactam antibiotics is time-dependent, with optimal bactericidal effect observed when plasma antibiotic concentrations remain above the minimum inhibitory concentration for 100% of the dosing interval.⁶ Despite improved maintenance of plasma antibiotic concentrations with continuous infusion,^{7,8} there is current uncertainty as to whether there are survival benefits when compared with standard intermittent infusion in critically ill patients with sepsis admitted to the ICU.^{9,10} Recent meta-analyses demonstrate survival benefit with the use of continuous or prolonged infusion in critically ill patients;¹¹⁻¹³ however, there is no evidence from phase 3 randomised controlled trials (RCTs) to support this. The aim of the β -Lactam Infusion Group (BLING) III study is to determine whether continuous infusion of a β -lactam antibiotic (piperacillin-tazobactam or meropenem) results in decreased all-cause Day 90 mortality compared with intermittent β -lactam antibiotic infusion in critically ill patients with sepsis. This article describes the BLING III study protocol.

Trial registration

The BLING III trial has been registered with the ClinicalTrials.gov Registry: NCT03213990.

Study design

The BLING III study is a prospective, multicentre, open, phase 3 RCT that will be conducted in about 70 ICUs, including study sites in Australia, New Zealand, the United Kingdom, Belgium and selected other countries, from 2018 to 2021.

Participants

Patients in the ICU being treated with either piperacillin-tazobactam or meropenem for a documented site or strong suspicion of infection, and who are expected to stay in the ICU beyond the following calendar day and meet at least one organ dysfunction criterion will be eligible for enrolment. Patients will be excluded if they have received greater than

ABSTRACT

Background and rationale: β -Lactam antibiotics display a time-dependent mechanism of action, with evidence suggesting improved outcomes when administering these drugs via continuous infusion compared with standard intermittent infusion. However, there is no phase 3 randomised controlled trial (RCT) evidence to support one method of administration over another in critically ill patients with sepsis.

Design and setting: The β -Lactam Infusion Group (BLING) III study is a prospective, multicentre, open, phase 3 RCT to compare continuous infusion with standard intermittent infusion of β -lactam antibiotics in critically ill patients with sepsis. The study will be conducted in about 70 intensive care units (ICUs) in Australia, New Zealand, the United Kingdom, Belgium and selected other countries, from 2018 to 2021.

Participants and interventions: BLING III will recruit 7000 critically ill patients with sepsis being treated with one of two β -lactam antibiotics (piperacillin-tazobactam or meropenem) to receive the β -lactam antibiotic by either continuous or intermittent infusion.

Main outcome measures: The primary outcome is all-cause mortality within 90 days after randomisation. Secondary outcomes are clinical cure at Day 14 after randomisation, new acquisition, colonisation or infection with a multiresistant organism or *Clostridium difficile* diarrhoea up to 14 days after randomisation, all-cause ICU mortality and all-cause hospital mortality. Tertiary outcomes are ICU length of stay, hospital length of stay and duration of mechanical ventilation and duration of renal replacement therapy up to 90 days after randomisation.

Results and conclusions: The BLING III study will compare the effect on 90-day mortality of β -lactam antibiotics administered via continuous versus intermittent infusion in 7000 critically ill patients with sepsis.

Trial registration: ClinicalTrials.gov Registry (NCT03213990).

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Table 1. Inclusion criteria for the β -Lactam Infusion Group (BLING) III study

- The patient has a documented site of infection or strong suspicion of infection
- The patient is expected to be in the ICU the day after tomorrow
- The patient has been commenced on piperacillin–tazobactam or meropenem to treat the episode of infection
- Giving piperacillin–tazobactam or meropenem by intermittent infusion or continuous infusion is considered equally appropriate for the patient
- One or more organ dysfunction criteria in the previous 24 hours:
 - ▶ MAP < 60 mmHg for at least 1 hour
 - ▶ Vasopressors required for > 4 hours
 - ▶ Respiratory support using supplemental high flow nasal prongs, continuous positive airway pressure, bilevel positive airway pressure or invasive mechanical ventilation for at least 1 hour
 - ▶ Serum creatinine concentration > 220 μ mol/L or < 2.49 mg/dL

ICU = intensive care unit. MAP = mean arterial pressure.

Table 2. Exclusion criteria for the β -Lactam Infusion Group (BLING) III study

- The patient's age is less than 18 years
- The patient has received piperacillin–tazobactam or meropenem for more than 24 hours during the current infectious episode
- The patient is known or suspected to be pregnant
- The patient has a known allergy to piperacillin–tazobactam, meropenem or penicillin
- The patient is requiring renal replacement therapy at the time of randomisation, including renal replacement therapy for chronic renal failure
- The attending physician or patient or surrogate legal decision maker is not committed to advanced life support, including mechanical ventilation, dialysis and vasopressor administration, for at least the next 48 hours
- The patient's death is deemed imminent and inevitable
- The patient has previously been enrolled in BLING III

24 hours of β -lactam antibiotic treatment, are pregnant, aged less than 18 years or require renal replacement therapy at the time of randomisation. The inclusion and exclusion criteria are shown in Table 1 and Table 2.

Study outcomes

Primary, secondary and tertiary outcomes are summarised in Table 3. Clinical cure will be defined as the completion of

the β -lactam antibiotic treatment course on or before Day 14, without recommencement of antibiotic therapy within 48 hours of cessation. For the purposes of evaluating clinical cure, change of antibiotic therapy, including escalation or de-escalation, for the same indication for which the β -lactam antibiotic was commenced is considered part of the antibiotic treatment course. Participants discharged from hospital within 14 days after randomisation will be considered to meet the definition of clinical cure, unless readmitted with ongoing antibiotic treatment for the same infectious episode within 14 days of randomisation. Participants who die while receiving the antibiotic treatment course, or for whom antibiotic therapy is ceased in the setting of death being deemed imminent and inevitable, will be assessed as not meeting the criteria for clinical cure.

New acquisition, colonisation or infection with a multiresistant organism will be defined as newly identified methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum β -lactamase, carbapenem-resistant Enterobacteriaceae or multidrug-resistant *Pseudomonas* on any routine swabs (eg, nose, perineum or wounds) or clinically indicated specimens (eg, blood, urine or endotracheal aspirates) taken between Day 1 and Day 14 inclusive. Multidrug-resistant *Pseudomonas* will be defined as a *Pseudomonas* species resistant to three or more of the following antibiotics: ceftazidime, ciprofloxacin, meropenem, gentamicin or piperacillin–tazobactam. *Clostridium difficile* diarrhoea will be defined as a stool sample sent to the laboratory and testing as *C. difficile* toxin positive between Day 1 and Day 14 inclusive.

Study interventions

The administration of β -lactam antibiotic therapy will be commenced before randomisation. Following successful randomisation, each participant will be assigned an administration method of either continuous infusion or intermittent infusion over 30 minutes. The choice of β -lactam antibiotic and the 24-hour dose of β -lactam antibiotic will be determined by the treating physician before randomisation. Dose changes in response to clinical changes in the participant are permitted after randomisation.

Participants randomly allocated to receive the β -lactam antibiotic via continuous infusion must receive at least one bolus dose before receiving the prescribed dose over 24 hours. An intermittent or extended infusion dose given before randomisation will qualify as a bolus dose. Participants previously receiving an intermittent dosing regimen who have been randomly allocated to the continuous infusion arm, or following a bolus dose if prescribed a continuous infusion before randomisation, will commence the continuous infusion at a time equivalent to half the intended intermittent dosing interval ($t_{50\%}$) for the β -lactam antibiotic.

Table 3. Primary, secondary and tertiary study outcomes

Outcomes	
Primary outcome	▪ All-cause mortality within 90 days after randomisation
Secondary outcomes	<ul style="list-style-type: none"> ▪ Clinical cure at Day 14 after randomisation ▪ New acquisition, colonisation or infection with an MRO or <i>Clostridium difficile</i> diarrhoea up to 14 days after randomisation ▪ All-cause ICU mortality ▪ All-cause hospital mortality
Tertiary outcomes	<ul style="list-style-type: none"> ▪ ICU length of stay ▪ Hospital length of stay ▪ Duration of mechanical ventilation in ICU up to 90 days after randomisation ▪ Duration of renal replacement therapy up to 90 days after randomisation

ICU = intensive care unit. MRO = multiresistant organism.

Participants randomly assigned to receive the β -lactam antibiotic via intermittent infusion over 30 minutes will receive the prescribed dose at intermittent dosing intervals determined by the treating clinician. Participants previously receiving a continuous infusion dosing regimen who have been randomly allocated to the intermittent infusion arm will have the continuous infusion ceased and receive the next scheduled dose by intermittent infusion over 30 minutes at $t_{50\%}$.

The β -lactam antibiotic (piperacillin–tazobactam or meropenem) will continue to be administered according to the allocated study administration method until either the β -lactam antibiotic is ceased by the treating physician, ICU discharge (including death), or at Day 14 after randomisation, whichever is sooner. For participants for whom the β -lactam antibiotic is subsequently changed from piperacillin–tazobactam to meropenem or vice versa for ongoing treatment of the infectious episode, the new prescription will continue to be administered in the allocated method.

Randomisation and data management

Randomisation will be conducted via a password-protected, secure web-based interface. Data collection will occur via a web-based case report form. The schedule of assessments is shown in Table 4.

Study preparation and logistics

The study sponsor and central trial coordinating centre is The George Institute for Global Health, Sydney, Australia, which will provide direct oversight of study initiation and monitoring during the study. The Study Management Committee provides oversight of the scientific integrity and conduct of the study. Regional coordination will be done by the Imperial College London, for the United Kingdom, and

Ghent University Hospital, Belgium, for continental Europe.

A Data Safety Monitoring Committee (DSMC) independent from the study sponsor and investigators will perform an ongoing review of study outcomes and overall study conduct. The DSMC will review study progress, including loss to follow-up, study withdrawal, mortality and all adverse reactions at predetermined intervals during the study or as deemed appropriate by the DSMC. The primary responsibility of the DSMC is to review interim analyses of outcome data and to recommend to the Study Management Committee whether the study needs to be changed or terminated based on these analyses.

Ethics approval

In Australia, the study has received ethics approval from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/17/QRBW/155). Additional jurisdictional ethics review board approval will be obtained as per study site requirements. The approved consent model in general will be for entry into the study under a waiver of consent if the participant is not able to provide initial consent and all avenues to seek consent from a legally recognised substitute decision maker or consultee have been exhausted. For participants enrolled under this provision, consent to continue with study participation will be obtained from the participant or legally recognised substitute decision maker or consultee as soon as practicable after study enrolment. Study sites will follow jurisdictional ethics committee requirements.

Sample size and power

The sample size for this study is based on data derived from the previous phase 2b trial and a subsequent individual patient meta-analysis,^{10,13} referenced to 90-day mortality

Table 4. Schedule of assessments

Task	Screening	Randomisation	Baseline	Day 1 to Day 90	Day 90 follow-up
Assess ability to gain consent and follow-up	X				
Assess eligibility to enter study	X				
Demographics and eligibility checklist		X			
Record date and time of randomisation		X			
Administer study treatment			X		
Patient characteristics (estimated/actual weight and height)			X		
ICU admission diagnosis			X		
Admission APACHE II (severity of illness) score components			X		
Site or sites of presumed or known infection			X		
Baseline SOFA scores			X		
Planned 24-hour dose and dosing interval of the β -lactam antibiotic at randomisation			X		
Microbiological confirmation of infection			X		
Assess for concurrent antibiotic use up to Day 14				X	
Assessment for clinical cure, Day 14				X	
Colonisation with an MRO or <i>Clostridium difficile</i> at 14 days after randomisation				X	
All β -lactam antibiotic doses				X	
Reason for cessation of β -lactam antibiotic				X	
Consent		X	X	X	X
Duration of mechanical ventilation				X	
Duration of RRT				X	
Date of ICU discharge up to Day 90				X	
Vital status at ICU discharge				X	
Date of hospital discharge up to Day 90				X	
Vital status at hospital discharge				X	
Vital status at Day 90 (including date and cause of death if deceased)					X
Adverse reactions			X	X	X
Protocol violations			X	X	X

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. MRO = multiresistant organism. RRT = renal replacement therapy. SOFA = Sequential Organ Failure Assessment.

in patients with sepsis in an international setting.¹⁴ A sample size of 7000 participants (3500 in each group) is required to achieve 90% power to detect an absolute risk reduction of 3.5% (ie, a 12.7% relative risk reduction) in 90-day mortality in the continuous infusion group from baseline mortality of 27.5%, with a significance level (α) of 0.05. From the calculated sample size (6558), an estimated 5% loss to follow-up (345) was added with rounding up to 7000.

Statistical analysis

The effectiveness of the intervention will be evaluated by an analysis of all randomised participants (excluding those who withdraw consent for use of health information) according to their allocated treatment group, irrespective of compliance. Initial range and logic tests will be performed and discrepancies corrected with the original site and data source where applicable. The primary outcome (all-cause

mortality within 90 days after randomisation), as well as the secondary outcomes, will be analysed using either log-binomial or logistic regression. The main intervention effect will be estimated as the relative risk or odds ratio of death and its 95% confidence interval, with intermittent infusion used as the reference. Time-to-death will be described using Kaplan–Meier plots with differences in survival estimated using a Cox proportional hazard model. Tertiary outcomes will be analysed both as the number of days alive and free of outcome (eg, days alive and free of mechanical ventilation) and as time from randomisation to resolution or discharge (eg, time to cessation of mechanical ventilation). A two-sided $P < 0.05$ will be considered evidence of a significant difference in the study outcomes, with the family-wise error rate controlled within each outcome level (primary, secondary and tertiary). All statistical analyses will be conducted in accordance with a detailed pre-specified statistical analysis plan, which will be finalised before database lock.

Pre-specified subgroup analysis

A subgroup analysis for the study outcomes will be performed for participants with or without lung infection at baseline and according to the type of β -lactam antibiotic commenced, either piperacillin–tazobactam or meropenem.

Pre-specified substudies

Three pre-specified substudies will be conducted: a pharmacokinetic and pharmacodynamic (PK-PD) substudy, a cost-effectiveness analysis and, in participants with an identified infective organism, outcomes will be examined across the distribution of minimum inhibitory concentration values.

A PK-PD substudy will be conducted at sites able to support collection and storage of three blood samples between Day 2 and Day 5 of β -lactam antibiotic therapy. The aim of the PK-PD substudy will be to explore the relationship between plasma antibiotic concentration targets and study outcomes.

A cost-effectiveness analysis at 90 days after randomisation will be conducted as a nested cohort in a limited number of country-specific regions, including Australia and New Zealand. Cost data will be derived from health care utilisation to Day 90, estimated through standard per diem ICU and hospital costs. The analysis will be conducted from a health care payer perspective, comparing health care utilisation costs and quality-adjusted life years gained (measured by the five-level EuroQol five dimensions [EQ-5D-5L] questionnaire) between treatment arms.¹⁵

Funding

The study is funded by the National Health and Medical Research Council (APP1121481) in Australia and the Belgian Health Care Knowledge Centre (KCE) in Belgium, with additional funding sourced in other regions. Funding bodies have no input into the design, management or reporting of the trial.

Endorsement

The study is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australasian Society for Infectious Diseases Clinical Research Network and the European Society of Clinical Microbiology and Infectious Diseases. The study has been reviewed and supported by the Infection Section of the European Society for Intensive Care Medicine (ESICM).

Current status

The study commenced recruitment in March 2018. It is estimated that recruitment will be completed by June 2021.

Summary

The BLING III study will provide phase 3 RCT evidence of whether administration of piperacillin–tazobactam or meropenem by continuous infusion will result in improved outcomes for patients with sepsis compared with intermittent antibiotic infusion. The potential significance of this research is that it will reduce clinician uncertainty and standardise the mode of administration for β -lactam antibiotics if there is evidence to support one mode of administration over another in this group of patients.

Competing interests

Menino Cotta, Joshua Davis, Simon Finfer, Parisa Glass, Serena Knowles, Shay McGuinness, Sandra Peake, Dorrilyn Rajbhandari, Andrew Rhodes, Charudatt Shirwadkar, Therese Starr, Laurent Billot and Joel Dulhunty declare no competing interests. Jeffrey Lipman has served as a board member for the Bayer ESICM and MSD Antibacterials Advisory Boards and given lectures with honoraria from Pfizer and MSD. Stephen Brett has received a speaker's fee and attended an Advisory Board from Orion Pharma. Jan De Waele has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from Accelerate Diagnostics, Bayer HealthCare, MSD and Pfizer. John Myburgh has received travel and speaker fees in relation to investigator-initiated research projects from Fresenius Kabi. David Paterson has received research grants from AstraZeneca and has attended Advisory Boards, acted as a consultant to, or given lectures with honoraria from Three Rivers Pharmaceuticals, Merck, AstraZeneca, Sanofi–Aventis, Pfizer, Johnson & Johnson, Shionogi and Leo Pharma. Jason Roberts has served as a consultant for MSD, Bayer, Astellas, bioMerieux and Accelerate Diagnostics and has received

research grants from MSD, The Medicines Company, Pfizer, Astellas and Cardeas Pharma. Colman Taylor owns a company, Health Technology Analysts, which provides consulting services to pharmaceutical companies, medical device companies and the Australian Government.

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