The Beta Lactam InfusionN Group

A phase III randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients

Overview

We aim to conduct an international multicentre randomised, controlled trial (RCT) to determine whether continuous infusion of a beta-lactam antibiotic (piperacillin-tazobactam or meropenem) results in decreased all-cause Day 90 mortality compared with intermittent beta-lactam antibiotic infusion in critically ill patients with sepsis.

The trial is being sponsored by the George Institute, Sydney, Australia, and the UK sites will be managed by Imperial College London (UK CI Prof Steve Brett, UK trial Manager Dr Farah Al-Beidh). The BLING III Trial has been deemed a non-CTIMP and should be adopted on the NIHR portfolio.

Regardless of the outcome, this study will provide vital evidence to answer the clinically important question of whether there is a difference in patient-centred outcomes in critically ill patients with sepsis administered beta-lactam antibiotics by continuous infusion versus intermittent infusion. If a 3.5% absolute reduction in hospital mortality is observed, then this intervention has the potential to save over 750 lives each year in Australia and New Zealand alone (based on severe sepsis incidence data). This research will provide pivotal evidence on the optimal method of delivery of commonly used beta-lactam antibiotics via a phase III RCT of global relevance.

Design

Participants initiated on one of two beta-lactam antibiotics (piperacillin-tazobactam or meropenem) will be randomised to receive the beta-lactam antibiotic via either continuous infusion or intermittent infusion over 30 minutes for the treatment course for up to 14 days after randomisation while in the ICU. For participants where the beta-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 (continuous infusion or intermittent infusion over 30 minutes).

Participants

This study will be conducted in approximately 70 ICUs worldwide, with approximately 40 sites anticipated in the UK.

Inclusion criteria

1. The patient has a documented site of infection or strong suspicion of infection
2. The patient is expected to be in the ICU the day after tomorrow

3. The patient has been started on piperacillin-tazobactam or meropenem to treat the episode of infection
4. Giving piperacillin-tazobactam or meropenem by intermittent infusion or continuous infusion is considered equally appropriate for the patient
5. One or more organ dysfunction criteria in the previous 24 hours
   i. MAP < 60 mmHg for at least 1 hour
   ii. Vasopressors required for > 4 hours
   iii. 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
   iv. Serum creatinine concentration at randomisation > 220 µmol/L

Exclusion criteria

1. Patient age is less than 18 years
2. Patients who have received piperacillin-tazobactam or meropenem for more than 24 hours during current infectious episode
3. Patients who are known or suspected to be pregnant
4. Patients requiring renal replacement therapy at the time of randomisation, including renal replacement therapy for chronic renal failure
5. 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
6. Patients in whom death is deemed imminent and inevitable
7. Patients who have previously been enrolled in BLING III

Intervention

The administration of beta-lactam antibiotic will be randomised to either continuous infusion or intermittent infusion over 30 minutes for the treatment course for up to 14 days after randomisation while the patient is in the ICU. The choice of beta-lactam antibiotic, either piperacillin-tazobactam or meropenem, and the dose and dosing interval (i.e. the dose the patient will receive in 24 hours) will be determined by the treating physician prior to randomisation.

Primary outcome

All-cause mortality within 90 days after randomisation.

Secondary outcomes

1. Clinical cure at Day 14 post randomisation
2. New acquisition, colonisation or infection with an multi-resistant organism (MRO) or *Clostridium difficile* diarrhoea up to 14 days post randomisation

3. All-cause ICU mortality
4. All-cause hospital mortality

Tertiary outcomes

1. ICU length of stay
2. Hospital length of stay
3. Duration of mechanical ventilation in ICU up to 90 days after randomisation
4. Duration of renal replacement therapy up to 90 days after randomisation