Beta-lactam Infusion Group
BLING II Study

INDUCTION SESSION

Presenters:
Dr Joel Dulhunty¹ & Ms Therese Starr²

¹Principal Investigator & Research Fellow, ²Project Manager (Trial Coordination Centre) & Research Coordinator, Department of Intensive Care Medicine, Royal Brisbane & Women’s Hospital
Purpose of the session

• To introduce the project management team
• To provide an overview of the BLING II study
• To familiarise site investigators & research coordinators with study methods
• To outline site responsibilities
• To provide contact details for the Trial Coordination Centre
• Opportunity to ask questions
Welcome to the team!

Project Management team (RBWH/UQ)

The George Institute for Global Health (study monitors)

Participants

You
Background to the study

• β-lactam antibiotics are commonly used in the treatment of severe sepsis

• β-lactams act via time-dependent pharmacokinetics

• Continuous infusion of β-lactams more consistently achieve pharmacodynamic endpoints than the standard practice of bolus dosing

• Human trials have been inconclusive as to which dosing strategy results in better outcomes for patients with severe sepsis
Aim

To determine if continuous β-lactam infusion results in improvement in surrogate outcomes compared with standard intermittent β-lactam dosing in critically ill patients with severe sepsis prior to proceeding with a definitive Phase III trial.
Study Design

- Multicentre
- Double-blinded
  - Concealed (double-dummy) delivery
- Randomised controlled trial
- Study medications (analysed as a group):
  - Ticarcillin-clavulanate
  - Piperacillin-tazobactam
  - Meropenem

Note: includes de-escalation to flucloxacillin & dicloxacillin
Blinding to administration method

- Persons blinded
  - Participant
  - Treating clinical team
  - Research staff involved in data collection

- Persons unblinded
  - Pharmacist, research coordinator or nurse involved in preparing blinded study medications
  - Project Manager, Trial Coordination Centre (access to randomisation code if required)
  - UQ Clinical Trials & Biostatistics Centre (data analysis)
Intervention

- Concealed administration (both forms given)
  - β-lactam antibiotic in either infusion bag OR syringe bolus
  - Placebo: sodium chloride 0.9% (infusion bag) or water for injection (syringe)

- Physician-determined dosing (same in both arms)
  - Modifiable dose if changing clearance
Sites

28 participating ICUs:
- Australia (21)
- New Zealand (6)
- Hong Kong (1)
Endpoints

Primary outcome:
1. ICU-free days up to Day 28

Secondary outcomes:
1. 90-day survival
2. Clinical cure at test of cure date
3. Cardiovascular, respiratory & renal organ failure free days at Day 14
4. Time to culture negative growth at 48 hours post collection
Inclusion criteria

1. Severe sepsis: confirmed or suspected infection with new organ dysfunction
   – Note: there are defined organ entry criteria

2. The treating clinician has chosen one of the study antibiotics to treat this sepsis

3. The treating clinician is uncertain if administration of the chosen antibiotic by bolus administration or by infusion is superior

4. At the time of the assessment of suitability for the study, the treating physician expects the patient will require treatment in the ICU that extends beyond the next calendar day
Exclusion criteria

1. Receipt of any potential study drug for more than 24 hours prior to randomisation during this admission to the ICU
2. Age less than 18 years
3. Allergy or potential allergy to the study medications
4. Pregnancy
5. No central venous catheter access with 3+ lumens
6. Receiving palliative or supportive treatment only at the time of assessment for eligibility
7. Treating physician is not committed to provision of advanced life-support including any of mechanical ventilation, dialysis, & vasopressor administration for at least the next 48 hours
8. Death is deemed imminent & inevitable
9. The patient has an underlying process that is likely to result in death before 90 days of follow up
10. Consent has not been gained for study participation
Timelines

• Stage 1 (Jan-Dec 2012):
  – Site finalisation, ethics approval & baseline preparation

• Stage 2 (July 2012-July 2014):
  – Recruitment (first patient recruited: 2 July 2012)
  – Anticipated interim analysis by DSMB: Oct 2013

• Stage 3 (Aug-Dec 2014):
  – Data analysis, write-up & dissemination of results
Screening

• Who:
  – All ICU admissions with evidence of SIRS/infection

• When:
  – Only during periods when randomisation & enrolment is able to occur

• How:
  – Record details on screening log to allow future reporting
Consent

• Important site responsibility

• Consent hierarchy:
  – Participant
  – Person responsible
  – Waiver of consent (“delayed consent”) if above not possible, then seek consent from participant / person responsible as soon as able
  – Note: seek participant consent as soon as able

• Follow local HREC approval provisions
Site responsibilities in regard to consent

- Ensure the Patient Information Sheet & Consent Form is up to date & the version approved by the HREC
- Ensure the HREC approved consent process is followed, including processes for waiver of consent / delayed consent; if a waiver of consent process is followed, ensure documentation is obtained in regard to subsequent consent obtained
- Ensure the person or persons taking the informed consent have an adequate understanding of the project & of the informed consent process
- Ensure that before informed consent is obtained the participant or person responsible is provided ample time & opportunity to inquire about details of the project & to decide whether or not to participate in the research. All questions about the study should be answered to the satisfaction of the participant or the person responsible
- Ensure that the written informed consent form is *personally signed & dated* by the participant or by the person responsible, & by the person who conducted the informed consent discussion (record the time & date of verbal consent if obtained prior to written consent)
- Ensure if a participant is unable to read or if the person responsible is unable to read, that an impartial witness be present during the entire informed consent discussion, & that discussion be held in an appropriate language
- Ensure that the study participant or the person responsible is given a copy of the signed informed consent form, & any other written information provided to the participants.
Randomisation

• Each site will receive a series of sealed opaque envelopes containing the allocation status for sequential participants randomised

• Study number: three digit site code + three digit participant number
  – For example, the RBWH site code is 401 & the first patient randomised at RBWH is 401001

• Only unblinded staff should open randomisation envelopes & have access to the randomisation log

• The Trial Coordination Centre can be contacted in the event urgent unblinding is required:
  – Ph: +61 (0)421 273 063
Study drug preparation

(see demonstration video)
Dose per bag/syringe

• If randomised to continuous infusion:
  – Meropenem is administered in 100 ml infusion bags changed 8-hourly (note: calculate 24 hour dose & divide by 3 to determine individual bag dose; equal to bolus dose if prescribed tds)
  – Piperacillin-tazobactam & ticarcillin-clavulanate administered in 250 ml infusion bags changed 24-hourly (note: calculate 24 hour dose to determine individual bag dose)

• If randomised to intermittent bolus:
  – Prepare blinded syringe with prescribed bolus dose
Labels

• Study labels will be distributed by the Trial Coordination Centre
Dosing & duration of blinded treatment

- Treating clinician orders β-lactam antibiotic; dose clinician determined as per standard practice

- First dose administered as ‘open label’

- If study drug is ‘switched’ to another β-lactam study drug (e.g. meropenem, flucloxacillin or dicloxacilin) the patient can remain on blinded treatment for a total of 14 days treatment, length of ICU admission or treatment course (whichever is sooner)
Timing of study drug commencement

- The first dose of the study medication (which may be prior to randomisation) must be via open label.
- Commence the continuous infusion at half the dosing interval between scheduled bolus doses.
- Continue blinded bolus doses at the scheduled interval from the last open label bolus dose.
- Switching to flucloxacillin, dicloxacillin or meropenem: follow above procedure.
Timing of study drug cessation

- Cease as per treating clinician, patient withdrawal, ICU discharge, or Day 14 or blinded study drug administration (whichever is sooner)
- If changing back to open label administration:
  - Commence open label bolus at the next scheduled bolus dose or at half the time interval of the scheduled bolus dosing (see protocol for guidance, pp.12-13)
Storage

• Meropenem
  – Bags at room temperature must be changed every 8 hours
  – Can be stored at 2-8ºC for 72 hours

• Ticarcillin-clavulanate, piperacillin-tazobactam, flucloxacillin & dicloxacillin
  – Bags/syringes may be kept at room temperature for up to 24 hours
  – Can be stored at 2-8ºC for 72 hours
Blood cultures

• Time to culture negative growth is a surrogate endpoint based on the likely mechanism of benefit that continuous infusion is able to kill bacteria more efficiently

• Blood cultures to be performed daily until no growth of a pathogenic organism in a blood culture 48 hours after collection

• 1st blood culture: collected as per unit policy (e.g. venepuncture or new line collection) on day of randomisation/pre-infusion &/or pre-ICU admission

• Subsequent samples can be collected from arterial line unless otherwise clinically indicated
Blood Culture Collections

- Review blood culture results on Day 3 for growth of a pathogenic organism
- *If No:* cease
- *If Yes:* continue until 48 hours of no growth post collection
Augmented Renal Clearance

• Once only 8 hour urine collection for a measured creatinine clearance for centres participating in the embedded sub-study
  – Commence an 8 hour urine collection within the first 24 hours of study drug commencement
  – Send to your local laboratory for evaluation
  – Record height (cm), weight (kg) & creatinine clearance (mL/min) via eCRF
Data Collection

Data entry via eCRF (OpenClinica) – see training materials

Study participants to be followed up until death or hospital discharge & day 90 if alive at hospital discharge

Baseline variables
- Inclusion criteria
- Consent details
- Randomisation details
- ICU admission details (date/time, admission diagnosis, APACHE II, presumed/known site of infection)
- Study drug details
Data collection (cont.)

- Microbiology (blood culture details)
- Daily SOFA scores up to Day 15 or ICU discharge (whichever is sooner)
- Test of cure (14 days post study drug cessation)
- ICU/hospital discharge
- 90 day follow-up

(see Case Report Form Completion Guidelines)
Overview of site responsibilities

Responsibilities in keeping with Good Clinical Practice guidelines apply to:

• Principal Investigator/s
• Sub/Associate-Investigator/s
• Clinical Research Coordinators
• Other staff delegated to be involved in trial-related activities by the Principal investigator
Data management responsibilities

- Ensure the accuracy, completeness, legibility, & timeliness of data collection is adhered to according to the protocol.

- Ensure that data reported on the e-CRF (or paper CRF), which is derived from source documents, is consistent with the source documents. Any discrepancies should be explained.

- Ensure that any change or correction to a paper CRF is made with a single stroke through the incorrect information, dated, initialled, & explained (if necessary). The original entry should not be obscured (i.e. an audit trail should be maintained). Changes & corrections (e.g. data queries) should be recorded in the eCRF via the inbuilt correction & audit process.

- Keep original source documents (where the data was first recorded) & take measures to prevent accidental or premature destruction of these documents.

- Ensure that a copy of the signed & completed Participant Information Sheet & Consent form has been filed in the appropriate place in the hospital chart (follow local Medical Records guidelines).

- Maintain the trial documents (e.g. the Study Site Master File and Essential Documents) as required by the applicable regulatory requirement(s) & take measures to prevent accidental or premature destruction of these documents.

- For clinical trials, data should be retained for a minimum of 15 years after formal notification is received that all study procedures are completed and the study is closed.
Adverse Events

• Any untoward medical occurrence in a participant administered the study intervention which does not necessarily have to have a causal relationship with the study treatment.

  – It is recognised that the patient population with severe sepsis will experience a number of common aberrations in laboratory values, & signs & symptoms due to the severity of the underlying disease & the impact of standard therapies.

  – These will not necessarily constitute an AE unless they require significant intervention or are considered to be of concern in the investigator’s (or treating clinician’s) clinical judgement.

  – Report higher levels of intervention (e.g. diuretics or renal replacement therapy) or changes to clinical practice where study involvement was perceived to be a contributing factor.
Serious Adverse Events

- Death
- Life-threatening
- Hospitalisation (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly/Birth Defect
- Required Intervention to Prevent Permanent Impairment or Damage
- Other Serious (Important Medical Events)
SAEs (cont.)

• In this study all SAEs must be reported regardless of suspected causality
• Events already defined & reported as study outcomes (e.g. mortality) will not be labelled & reported a second time as SAEs (unless the following criteria are met)
• SAEs which occur from the time of commencement of study treatment to 48 hours post cessation of study treatment must be reported to the Trial Coordination Centre by faxing the supplied SAE report form
• All SAEs must be reported to the Trial Coordination Centre (via fax) & local HREC/Governance Office within 24 hours of study staff becoming aware of the event
• SAEs may also be discussed with the Trial Coordination Centre staff or Chief Investigator, if necessary.
Responsibilities in regard to AE/SAE reporting

- Report immediately to the Trial Coordination Centre all serious adverse events (SAEs) except for those SAEs that the protocol or other document identifies as not needing immediate reporting.

- Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the regulatory authority(ies) & the HREC / Governance Office.

- Ensure that the immediate & follow-up reports identify Participants by unique code numbers assigned to the trial Participants rather than by the Participants' names, personal identification numbers, &/or addresses.

- Record non-serious & expected adverse reactions & adverse events as part of GCP (in the eCRF). In accordance with GCP principles, this will allow an internal statistical analysis of these data to be performed. The TGA will be advised of any safety issues which emerge during this process.
Reporting requirements (cont.)

• Minimum information to report for AE/SAEs will include:
  – Patient initials & study number
  – Nature of the event
  – Commencement & cessation of the event
  – An investigator’s opinion of the relationship between study involvement & the event (unrelated, possibly, probably or definitely related).
  – Whether treatment was required for the event & what action was taken

• It is the responsibility of Principal Investigators to inform the site Research Governance Office and/or jurisdictional HREC of all SAEs which occur at their site, in accordance with local requirements. The Chief Investigator is required to report all SAEs to the lead HREC & the TGA.

• Report protocol deviations via the eCRF & fax to the Trial Coordination Centre.
Managing complaints

- Complaints, issues or queries should be directed to & managed in the first instance by the Principal Investigator or site study team (guidance may be sought from the Trial Coordination Centre)

- If a person wishes to talk to someone not directly involved in the study they should be referred to the local HREC/Governance office as per PICF details

- The Trial Coordination Centre should be notified of all complaints which impact on the successful conduction of the study.
Study monitoring

- To be undertaken by The George Institute
- Initial visit expected after 2\textsuperscript{nd} randomised patient
- 100% monitoring of first 2 patients
- Two further visits planned over life of study unless otherwise required (proportional data verification)
- Study team at RBWH available to assist (email/call)
Invoicing

• Quarterly invoicing as per Clinical Trial Agreement
• The University of Queensland hold the study funds
• Vendor request form to be completed and to be returned to:

  Sia Athanasas  Research Manager
  Burns Trauma & Critical Care Research Centre, Level 9, UQ Health Sciences Bldg, Royal Brisbane and Women's Hospital QLD 4029
  E-mail: s.athanasas@uq.edu.au
Questions
Contact details for the Trial Coordination Centre

• Ph: +61 7 3646 8894
• Afterhours Ph: +61 (0)421 273 063
• Fax: +61 7 3646 3542
• E-mail: BLING_II@health.qld.gov.au
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<tr>
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<td>Prof Steve Webb</td>
<td>Royal Perth Hospital</td>
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<td>Dr Jason Roberts</td>
<td>Royal Brisbane &amp; Women’s Hospital</td>
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<td>Dr Joshua Davis</td>
<td>Royal Darwin Hospital</td>
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<td>Prof David Paterson</td>
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<td>Dr Charudatt Shirwadkar</td>
<td>Blacktown Hospital</td>
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<td>Mr Glenn Eastwood</td>
<td>Austin Hospital</td>
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<td>Ms Therese Starr</td>
<td>Royal Brisbane &amp; Women’s Hospital</td>
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Acknowledgements

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Collaborative partner:

The George Institute for Global Health

Endorsed by:

ANZICS Clinical Trials Group

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Clinical Research Network
Question 1

When completing the eCRF, calculate & record the APACHE II score for the following time period:

A. First 24 hours post ICU admission
B. First 24 hours post study drug commencement
C. First 24 hours post randomisation
D. Not required
Question 2

The following organisms are identified on blood culture:

Day 1 – *Pseudomonas aeruginosa*
Day 2 – No organism grown
Day 3 – Coagulase-negative staphylococci

Would you:

A. Repeat a blood culture on Day 4, then cease further blood cultures on Day 5
B. Repeat blood cultures on Days 4 & 5 – cease if the Day 4 blood culture was negative at 48 hours
C. Cease the blood culture on Day 4 if the Day 2 blood culture was negative at 48 hours
D. Determine whether the Coagulase-negative staphylococci was pathogenic before proceeding
Question 3

A study participant, randomised to continuous infusion, is commenced on open-label meropenem 1 g 8-hourly. What study drug dose should be made up in each infusion bag?

A. 0 g (placebo)
B. 1 g
C. 2 g
D. 3 g
Question 4

A newly randomised study participant, prescribed ticarcillin-clavulanate 3.1 g 6-hourly, received the previous open-label bolus at 11 am. At what time should the blinded continuous infusion commence?

A. Immediately
B. 14:00
C. 17:00
D. 23:00
Question 5

(As previously) a newly randomised study participant, prescribed ticarcillin-clavulanate 3.1 g 6-hourly, received the previous open-label bolus at 11 am. At what time should the blinded intermittent bolus commence?

A. Immediately
B. 14:00
C. 17:00
D. 23:00
Question 6

A study participant, receiving Day 3 of blinded study medications (piperacillin-tazobactam 4.5 g 8-hourly), is ready for discharge to the ward (study drug to continue). The last intermittent bolus dose was given at 6 am; the time is currently 8.15 am. When should open-label piperacillin-tazobactam be prescribed to recommence?

A. 10:00
B. 12:15
C. 14:00
D. 16:15
Question 7

The HREC has approved a waiver of consent (‘delayed consent’). A sedated & ventilated patient is eligible for study participation. The patient’s wife is traveling en-route from the USA. There is no other substitute decision maker. What do you do?

A. Record the patient as ineligible in the screening log (reason: unable to obtain consent)
B. Randomise & commence blinded study medications – consent is not required
C. Randomise & commence blinded study medications – seek consent from the participant’s wife to continue
D. Seek consent from the relevant tribunal to commence blinded study medications
Question 8

When is the test of cure endpoint evaluated?

A. 7 days following randomisation
B. 7 days following study drug cessation
C. 14 days following randomisation
D. 14 days following study drug cessation
Question 9

On the morning ward round, it is discovered that a patient randomised to the study yesterday evening has received a blinded continuous infusion overnight, but not the blinded intermittent boluses. What do you do?

A. Monitor the patient for Adverse Events
B. Withdraw the patient from the study & continue open label treatment
C. Record the protocol violation in the eCRF
D. Contact the Trial Coordination Centre & determine corrective actions
Question 10

Which of the following is NOT correct:

A. Meropenem study medications can be stored at 2-8°C for 72 hours

B. Syringes with meropenem (or placebo) can be stored at the bedside for up to 24 hours

C. Syringes with piperacillin-tazobactam (or placebo) can be stored at the bedside for up to 24 hours

D. Piperacillin-tazobactam study medications can be stored at 2-8°C for 72 hours