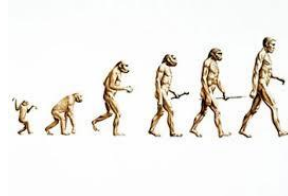


## The **ADP-TRAUMA** Trial



A randomised controlled clinical trial of **A**ugmented **D**osing  
of **P**iperacillin-tazobactam in **TRAUMA** patients with  
suspected or confirmed infection

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## **ABBREVIATIONS**

AE - adverse event

ARC – augmented renal clearance

CL<sub>CR</sub> – creatinine clearance

$f_{T>MIC}$  - fraction of the dosing interval the antibiotic concentration is greater than MIC

ICU – intensive care unit

IV – intravenous

LD – loading dose

MIC – minimum inhibitory concentration

PD – pharmacodynamics

PK - pharmacokinetics

SAE - serious adverse event

TTE – transthoracic echocardiogram

SIRS – systemic inflammatory response

V<sub>d</sub> – volume of distribution

## BACKGROUND & RATIONALE

### Introduction

Treatment of infection in the intensive care unit (ICU) represents an ongoing challenge for critical care clinicians. The critically ill represent a unique population, either presenting with infection complicated by systemic inflammation (sepsis), or being predisposed to such complications by virtue of the underlying disease process. Multi-trauma represents a relevant example; where organ function is already significantly disturbed, while subsequent infection is common.

Successful therapy relies on early recognition of infection, and the timely application of antibiotics against the contributing pathogen. Modest evidence supports this as an effective intervention that will improve outcomes (1). However, mortality rates in this setting remain high, while antibiotic resistance is becoming more prevalent, suggesting further improvements are urgently needed. Optimization of antibiotic dosing, such that predefined targets for maximal bacterial killing are achieved, has been proposed as one such approach (2). This premise is based on the growing body of literature demonstrating grossly altered antibiotic pharmacokinetics in the critically ill (3), in addition to the increasing prevalence of microbial isolates with decreased susceptibility.

#### *Impact of Infection in Trauma*

Trauma victims are at high risk for developing infection (4), due to disruption in tissue integrity and impaired host defence mechanisms (5, 6). Traumatic injury is the leading cause of death in people under 45, a leading cause of morbidity, mortality and permanent disability, and a major source of healthcare costs in Australia. Hospital acquired infections in this population is associated with increased in-hospital mortality, longer hospital length of stay, and greater costs (7). Routinely beta-lactam antibacterial agents are prescribed empirically in this setting (8). Whether optimising drug exposure in this setting will improve patient centered outcomes requires additional research.

#### *Antibacterial Pharmacokinetics-Pharmacodynamics*

Pharmacokinetics (PK) refers to the change in drug concentration (ideally at the effect site) over time, and is primarily a reflection of the agents' physicochemical properties, protein binding, and the elimination pathways involved. Pharmacodynamics (PD) involves measuring drug effect, typically illustrated by a dose-response relationship. In the case of antibacterial agents, this describes the ability to kill or inhibit the growth of an infecting organism following a given dose. There are important interactions between these parameters, referred to as the PK/PD characteristic, which describes the optimal drug exposure required for maximal bacterial killing. Broad PK/PD classes include concentration-dependent, time-dependent, and concentration/time-dependent killing.

Beta-lactams are the most frequently prescribed time-dependent agents (8-10), with animal studies suggesting a target time above the minimum inhibitory concentration (MIC) of at least 40-70% of the dosing interval ( $40-70\% fT_{>MIC}$ ), to ensure adequate bacterial killing (11). In the critically ill, previous data has suggested that even higher drug exposures ( $90-100\% fT_{>4-5xMIC}$ ) are required to increase the likelihood of clinical success (12, 13). More recently Roberts et al. in a large multi-national point prevalence study of antibacterial concentrations in critical illness, demonstrated that clinical failure was three times more likely when beta-lactam exposure was less than  $50\% fT_{>MIC}$  (14). Although currently there are no large-scale clinical trial data quantifying the clinical effect of achieving antibiotic PK/PD targets in the critically ill, they do represent logical end-points for pharmacologically robust empirical dosing.

#### *Augmented Renal Clearance (ARC)*

Many commonly prescribed antibiotics are primarily cleared from the body by renal elimination, including beta-lactams (15), aminoglycosides (16), and glycopeptides (17). Altered renal function will therefore greatly impact the CL of these agents, and the corresponding PK profile. Augmented renal clearance (ARC), defined as the enhanced renal elimination of circulating solute (such as waste products and drugs), represents an evolving concept in critical care pharmacology (18). This is based in part on PK studies demonstrating elevated clearances of beta-lactams (15, 19, 20), aminoglycosides (16), and glycopeptides (21), in different subsets of patients.

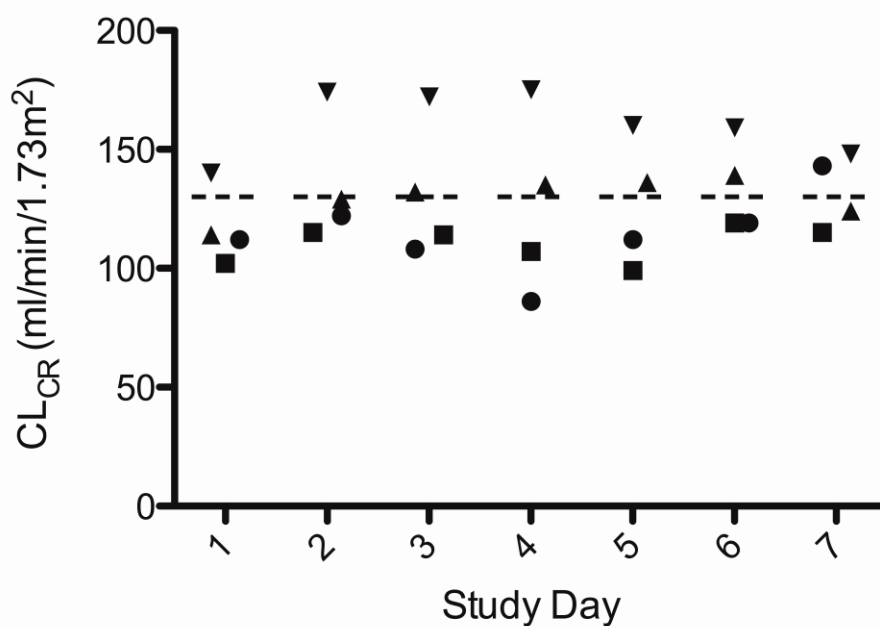
A clinically useful measure of this phenomenon is a timed urinary creatinine clearance ( $CL_{CR}$ ). Use of this surrogate in ICU is reinforced by its' significance as a PK covariate for renally eliminated agents (18), and the observed association between elevated measures ( $\geq 130\text{ml}/\text{min}/1.73\text{m}^2$ ) and sub-optimal antibiotic concentrations (22-24). Numerous 'at-risk' populations have been reported including; multi-trauma (25), traumatic brain injury (26), post-operative patients (27), burns injury (28), and ventilator associated pneumonia (29). Overall, the prevalence of ARC varies considerably (30 to 85% of study participants), although is heavily influenced by case-mix, and definitions.

Younger age, admission post-trauma, and lower illness severity scores have been repeatedly identified as risk factors for ARC (25, 30-32). As such, the interaction between physiological reserve (most marked in younger patients), and systemic inflammation, appears to a key component. This was recently substantiated by Shimamoto et al., in which an increasing number of SIRS criteria were strongly associated with higher drug clearance, and consequently lower plasma concentrations, in non-ventilated critically ill patients receiving standard doses of vancomycin (33).

While outcome data are limited, a recent prospective, single-center observational study, has demonstrated an association between ARC ( $24\text{-hr } CL_{CR} > 130\text{ml}/\text{min}/1.73\text{m}^2$ ), and therapeutic failure (defined by a poor clinical response and the need for an alternative antibiotic) in critically ill patients receiving anti-infective therapy (32). The implications for future clinical study of

new or emerging antibiotics are therefore significant (2). Specifically, interim data analyses of a recent clinical study, revealed greater mortality and lower clinical cure in patients with ventilator associated pneumonia treated with a fixed course of doripenem, compared with imipenem/cilastatin (34). These findings were most marked in the sub-group with an estimated  $CL_{CR} \geq 150$  ml/min. Of note, separate PK/PD modelling has suggested that significantly higher daily doripenem doses (up to 2 g 8-hourly) might have been required for adequate drug exposure in these patients (35).

The epidemiology of ARC has recently been investigated by Udy et al. In a multi-national observational study of  $CL_{CR}$  in critically ill patients with normal plasma creatinine concentrations, 65% of the study cohort manifested ARC on at least one occasion (36) in the first seven study days. 83% of trauma patients displayed ARC, and  $CL_{CR}$  measures in this sub-group were significantly elevated, and remained so over the study period (see Figure 1). 78% of this sub-group were prescribed an antibacterial agent.



Elective	26	15	11	8	6	5	5
Emergency	93	77	58	47	41	38	33
Surgical Emergency	126	110	84	67	59	46	42
Trauma	36	29	24	21	17	17	13

Legend: Mean  $CL_{CR}$  in elective (●), emergency (■), surgical emergency (▲), and trauma (▼) patients to study day 7. The dashed line represents the cut-off for ARC (130ml/min/1.73m<sup>2</sup>). The number of patients of each admission type remaining in the study per day is provided (36).

*Novel dosing strategies: Methods to improve antibiotic exposure.*

Much of the data supporting newer approaches to antibiotic dosing in critical illness are based on PK/PD end-points, reinforcing the need for ongoing well-designed clinical investigation.

Loading doses (LD) are primarily employed to ensure therapeutic concentrations are achieved rapidly, promoting fast, efficient bacterial killing. Mathematically this is expressed as the product of the desired plasma concentration and the apparent volume of distribution ( $V_d$ ). After bolus IV administration, plasma antibiotic concentrations fall rapidly, primarily as a consequence of drug distribution. As such, in the setting of a larger than anticipated  $V_d$ , standard doses are likely to result in sub-optimal drug exposure. Insufficient beta-lactam concentrations, in association with a larger  $V_d$ , have been demonstrated in the critically ill (37), although arguably more attention has focused on the role of continuous infusion with these agents.

Maintaining sufficient drug concentrations throughout the dosing interval represents a logical approach when prescribing time-dependent antibiotics, such as beta-lactams (minimum target  $fT_{>MIC} > 50\%$ ). Options include more frequent administration, or use of continuous or extended infusions. Adequate loading doses should still be employed, particularly with continuous infusions, in order to prevent prolonged exposure to sub-therapeutic concentrations. In this respect, numerous small studies have demonstrated a distinct PK advantage to continuous infusions (20, 38, 39), although a clear clinical benefit remains to be fully established.

Lodise and colleagues examined the role of extended infusions of piperacillin-tazobactam in a retrospective cohort of critically ill patients with *Pseudomonas aeruginosa* infection. Extended infusions were associated with a significant improvement in 14-day survival in those patients with higher illness severity (40). Similar retrospective analyses have been performed in patients with ventilator associated pneumonia due to gram-negative bacilli, with continuous infusions of meropenem (41), ceftazidime (42), and piperacillin-tazobactam (43), all associated with improved rates of clinical cure, particularly with more difficult to treat organisms. In a small prospective study, Roberts et al. also reported a clinical advantage to continuous infusion of ceftriaxone, when patients received four or more days of therapy (44).

Confounding these results was a systematic review and meta-analysis performed in 2009, which reported no significant clinical advantage to continuous infusion of beta-lactams in hospitalized patients (45). More recently, Falagas and colleagues repeated this analysis focusing on piperacillin-tazobactam and

carbapenem administration. Overall, lower mortality was demonstrated with extended or continuous infusions, although only 3 of 14 included studies were randomized controlled trials (46). Contrasting findings were recently reported from a single-center before and after study, in which extended infusions of beta-lactams offered no advantage over intermittent dosing (47).

In the largest prospective study to date, a multicenter double-blind randomized controlled trial of continuous infusion of beta-lactams reported improved  $fT_{>MIC}$  and clinical cure, in critically ill patients with severe sepsis (48). No significant difference was noted in ICU-free days or survival to hospital discharge (48), although further studies are ongoing.

Use of continuous or extended infusions of antibiotics in patients manifesting ARC represents an attractive approach, although to date there are no prospective data comparing dosing regimens in this setting. However, a recent observational study by Carlier et al. suggests that despite the use of such strategies, elevated  $CL_{CR}$  remains strongly associated with sub-optimal beta-lactam drug exposure (49). This in combination with the inferior clinical outcomes demonstrated in patients manifesting ARC (32), indicates that higher daily doses are also likely to be required. This is supported by dosing simulations reported for doripenem (35), meropenem (50), cefepime (51), and piperacillin-tazobactam (52), in which adjustments in total dose, in addition to use of extended or continuous infusions are demonstrated.

### *Summary*

In summary, critically ill trauma patients are at high risk for infection, the development of which has a significant impact on patient centered outcomes. These patients are also likely to manifest significantly distorted beta-lactam PK, such that sufficient drug exposure is frequently unlikely. A major clinical driver appears to be ARC, resulting in significantly elevated drug CL. Extended or continuous infusions, in addition to higher total daily doses are empirical solutions that may improve the frequency of target attainment. The proposed study aims to ascertain whether this is the case, by performing a controlled clinical trial of augmented piperacillin-tazobactam dosing optimised by  $CL_{CR}$  measures compared with standard practice in trauma patients with suspected or confirmed infection.



## **AIMS**

### Primary Aim

To demonstrate the efficacy and safety of augmented piperacillin-tazobactam dosing optimised according to CL<sub>CR</sub> measures, in comparison to standard piperacillin-tazobactam prescription, in trauma patients with suspected or confirmed infection.

### Secondary Aims

1. To determine the clinical utility of an 'ARC Dose Optimisation Protocol' (Appendix A).
2. To explore the impact of augmented piperacillin-tazobactam dosing on clinical outcomes.

## **HYPOTHESIS**

### Primary Hypothesis:

In critically ill trauma patients receiving piperacillin-tazobactam for suspected or confirmed infection, an augmented dosing strategy optimised by measuring CL<sub>CR</sub> will improve drug exposure (defined by an unbound plasma piperacillin concentration > MIC, at 24-48 and 120-144hrs after randomisation) in a greater proportion of study participants compared to standard therapy.

### Secondary Hypotheses:

Use of augmented piperacillin-tazobactam dosing in such patients will;

- a) be well tolerated, without significant side effects;
- b) result in improved clinical cure; and
- c) trend toward greater ICU-free days to day 28

## **STUDY DESIGN**

The proposed study will be a controlled clinical trial involving two major trauma centers in Australia. Critically ill trauma patients prescribed piperacillin-tazobactam for presumed or confirmed infection will be randomised to either standard prescription, or augmented dosing optimised by CL<sub>CR</sub> measures.

### Outcomes:

Primary:

Unbound piperacillin plasma concentration to MIC ratios determined at 24-48hrs and 120-144hrs after randomisation, and scored as a dichotomous variable (e.g.  $\geq$  MIC or  $<$  MIC).

Secondary:

- a) clinical cure at 14-days post randomisation (scored as a categorical variable)
- b) ICU-free days at day 28 post randomisation (scored as a continuous variable)

Study Population:

Any patient admitted to the ICU post multi-trauma, receiving piperacillin-tazobactam for presumed or confirmed infection.

Sub-groups:

*A priori*, the following sub-groups will be defined on the basis of presumed or confirmed site of infection:

- a. respiratory tract infection
- b. bacteraemia
- c. intra-abdominal infection
- d. skin and soft-tissue infection
- e. urinary tract infection

Inclusion Criteria:

1. Age  $\geq 18$  and  $\leq 50$  years
2. Admission post trauma
3. Informed consent is obtained from the patient or surrogate decision maker
4. The patient is anticipated to require ICU care beyond the next calendar day
5. Plasma creatinine concentration  $< 100 \mu\text{mol/L}$  on the day of randomisation
6. Presence of an indwelling urinary catheter (IDC)

Exclusion criteria:

1. Evidence of acute kidney injury – as per the RIFLE criteria (53)
2. Evidence of acute liver injury – defined as an AST or ALT  $> 5$  x upper limit of normal (ULN), or AST or ALT  $> 3$  x ULN with associated total bilirubin  $> 2$  x ULN
3. Evidence of active haemorrhage – defined by a fall in haemoglobin concentration  $> 20\text{g/L}$  or the need for  $> 2$  units RBC in the preceding 24hrs
4. Increased risk of bleeding – defined by a platelet count  $< 50$ , INR or aPTT  $> 2$  x ULN
5. Extremes of body size – defined as a body mass index (BMI)  $< 16$  or  $\geq 40 \text{ kg/m}^2$
6. Pregnancy
7. Treatment intent is palliative

8. Death is deemed imminent and inevitable
9. Known hypersensitivity to piperacillin-tazobactam
10. Has received piperacillin-tazobactam therapy for > 24hrs prior to randomisation
11. Not eligible for Medicare

## **STUDY PROCEDURES**

### Assessment of Patients for Study Suitability

Trained study personnel including research coordinators, medical staff, pharmacists, and investigators, at each study site, will assess potential study participants. Patients will be eligible for enrolment if they fulfil all of the inclusion criteria, and none of the exclusion criteria.

### Randomisation

Randomisation will be conducted through a password-protected, secure website using a central, computer-based randomisation program. Randomisation will be stratified by participating institution, and patient gender.

### Study treatment

Following randomisation, study participants will receive either standard prescription piperacillin-tazobactam, or augmented dosing, based on an 'ARC Dose Optimisation Protocol' (Appendix A). An 8-hr urinary creatinine clearance measured on Day 1, and then every alternate day post randomisation, will be used to optimise therapy in those patients randomised to the augmented dosing strategy. The total duration of therapy will be at the discretion of the treating clinician, although augmented dosing will cease on Day 7, or discharge from the ICU.

In those randomised to standard prescription, this will utilise the current dosing strategies routinely employed at each participating institution. This typically involves intermittent administration of 4.5g IV piperacillin-tazobactam every 6 to 8 hours. Optimisation of dosing on the basis of CL<sub>CR</sub> measurements is not routinely performed at either site.

### Follow-up Schedule and Data Collection

The primary outcome will be assessed by means of plasma samples, drawn at 24-48hrs and 120-144hrs post randomisation. In those receiving standard dosing, a sample will be drawn at a point halfway through a single dosing interval. In those receiving augmented dosing, a random plasma sample will be drawn during each time period, at least 18-24hrs after the most recent dose alteration. A blinded assessor will assess clinical cure on day 14 post-randomisation. A structured assessment tool (Appendix C) will be used for this purpose. ICU-free days at Day 28 will be determined from the date of randomisation (Day 0). The

number of non-ICU days post ICU discharge, and excluding days of ICU readmission, will be counted for each day a participant is alive up to Day 28. Whilst in the ICU, study participants will have relevant study data extracted from their medical record.

### Microbial Susceptibility

Where available, the local MIC of the cultured pathogen will be used in analysis. Where local MIC data are not available, the population MIC<sub>90</sub> of the infective pathogen, as defined by The European Committee on Antimicrobial Susceptibility Testing (EUCAST); available at: [http://www.eucast.org/clinical\\_breakpoints](http://www.eucast.org/clinical_breakpoints), will be used instead. Where no pathogen is formally identified, the highest MIC for susceptible bacteria (e.g. *Pseudomonas aeruginosa* MIC is 16 mg/L for piperacillin-tazobactam) will be used.

### Bio-analysis

Blood samples will be centrifuged at 3000 rpm for 10 minutes and the plasma stored at -80°C until batched analysis at the Burns, Trauma, and Critical Care Research Center, The University of Queensland. Piperacillin concentrations will be determined by validated high performance liquid chromatography, including within-batch calibrators and quality controls. Samples will be prepared by protein precipitation with a dichloromethane wash, and the extracts separated on a C18 stationary phase and monitored by ultraviolet. To isolate the unbound fraction for analysis, protein-bound piperacillin will be removed from the plasma sample with centrifugal filter devices (Centrifree-30K, Merck Millipore, Tullagreen, Ireland). Accuracy and precision of the assays will be validated at high, medium, and low concentrations of the calibration range.

### Discontinuation of Treatment

Participants will be discontinued from receiving further study treatment on Day 7 or discharge from the ICU. If the patient requires ongoing piperacillin-tazobactam therapy, dosing will be at the discretion of the treating clinician. De-escalation of antibacterial therapy to an agent with more specific cover will be at the discretion of the treating clinician. Any participant experiencing a serious adverse event (SAE) thought directly related to the study medication will be discontinued from further drug administration.

### General ICU Management

All aspects of patient management other than study-related interventions will be at the direction of the treating clinician.

## **ETHICS**

### Guiding Principles

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments and NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007).

### Ethics Committee Approval

The study protocol will be submitted to a Human Research and Ethics Committee constituted according to the NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007) for each participating institution. Approval of the protocol, plans for obtaining consent, and related documents will be obtained prior to the start of the study.

### Confidentiality of patient data

Patients will be randomised by a password-protected, secure website using a central, computer-based randomisation program. All participants will be allocated a unique study number. The research coordinator at each site will compile an enrolment log including the patient's name, date of birth, hospital identification number, unique study number and date and time of randomisation. Subsequent study data will be identified by the unique study number only. The enrolment log and study data will be kept separately. Study data will be entered into a secure electronic data management system. No identifying data will be entered into the website. All study data will be kept in a locked office at the study site.

## **DATA MANAGEMENT**

### Data collection methods

All data will be collected by trained staff at each study site, using a specific paper source document. Data will then be entered into an electronic database. Data queries will be automatically generated based on data verification rules. Data collection will be restricted primarily to those variables necessary to define clinical patient characteristics including: baseline demographics, primary diagnoses, physiological parameters, diagnostic interventions, therapeutic interventions and documentation of deaths and other adverse events. A 'day' in ICU will be defined from midnight.

### Data variables collected

1. Demographic data:
  - a. Identity (initials, date of birth, gender, study number)
  - b. Medical record number
2. Hospital data

- a. Hospital admission and discharge dates
3. ICU data
  - a. ICU admission and discharge dates (including source and readmission)
  - b. Acute physiology and chronic health evaluation (APACHE) III score (over the first 24 hours in ICU)
  - c. Sequential organ failure assessment (SOFA) score (at randomisation)
  - d. Injury severity score (ISS) (on admission)
4. Intervention data
  - a. Date and time piperacillin-tazobactam commenced
  - b. Confirmed or presumed source of infection
  - c. Micro-organism isolated and susceptibility profile
  - d. Date and time of randomisation
  - e. Date and time of first study drug administration
  - f. Date and time piperacillin-tazobactam discontinued
  - g. 8-hr CL<sub>CR</sub> measures (midnight->8am) on Day 1, and then every alternate day in those receiving augmented dosing
  - h. Daily total piperacillin-tazobactam dose
  - i. Use of any additional antibacterial agent
  - j. Unbound plasma piperacillin-tazobactam concentrations 24-48hrs and 120-144hrs post randomisation
  - k. Frequency of potentially toxic piperacillin concentrations (>150mg/L)
  - l. Clinical cure at 14-days post randomisation
  - m. ICU-free days at day 28 post randomisation
  - n. Adverse events (defined below)

## **STATISTICAL CONSIDERTIONS**

### Sample Size

Based on 50%  $f_{T>MIC}$  being achieved in 60% of patients receiving standard dosing, and an improvement in target attainment to 90% in those receiving augmented dosing, with a power of 80%, and alpha error of 0.05, a sample size of 64 patients (32 in each group) is required.

### Analysis

All analyses will be conducted on an intention-to-treat basis without adjustment for baseline variables. Differences in outcome variables will be compared using t-test and Chi-Squared test as appropriate if normally distributed and using non-parametric equivalents if non-normally distributed. No interim analysis is planned. Analysis will primarily be conducted using SPSS version 17 (Chicago, IL, USA).

## **SAFETY**

### Adverse events

Data concerning defined adverse events will be collected. These will include the following:

Anaphylaxis / anaphylactoid reactions  
Major hypersensitivity reactions  
Seizures (not related to existing pathology)  
New onset acute kidney injury (not due to another cause)  
Hepatic encephalopathy (not due to another cause)  
Fluid overload resulting in organ dysfunction (not due to another cause)  
Bleeding (not related to existing pathology)  
Leukopenia (not due to another cause)  
Death (unexpected, and thought not to be related to the underlying process).

Any undefined adverse event will be collected as free text. Given that the participants in this study will all be critically unwell, many abnormalities in signs, symptoms and laboratory values are to be expected and will not necessarily constitute adverse events unless considered to be causally related to the study intervention or otherwise thought to be of concern in the judgement of the investigator.

### Serious adverse events

The baseline morbidity and mortality of patients enrolled into this trial will be high, due to the underlying nature of the disease. As such, events that are part of the natural history of the primary disease process or expected complications of critical illness will not be reported as serious adverse events in this trial unless thought to be causally related to the study intervention or otherwise specified.

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**APPENDIX A – ARC DOSE OPTIMISATION PROTOCOL**

Starting Dose (all patients allocated to intervention arm):		
4.5g IV piperacillin-tazobactam administered when the next scheduled dose is due. Concurrently commence a 24-hr infusion of piperacillin-tazobactam 18g in 250ml 0.9% saline.		
Modify prescription based on CL <sub>CR</sub> results		
Measured 8-hr CL <sub>CR</sub> (ml/min/1.73m <sup>2</sup> ):	Piperacillin-Tazobactam Dose (in 250ml 0.9% saline administered over 24hrs IV):	
	Suspected MIC ≤ 8 mg/L	Suspected MIC > 8 mg/L
≥ 170	24.75g	27g
150 – 169	22.5g	24.75g
120 – 149	20.25g	22.5g
100 – 119	18.0g	20.25g
80 – 99	13.5g	18.0g
60 – 79	11.25g	13.5g
40 – 59	9g	11.25g
20 – 39	4.5 g 8hrly bolus dosing	9 g
≤ 19	4.5 g 12hrly bolus dosing	4.5 g 8hrly bolus dosing
Anuric / RRT	As per clinician	As per clinician



**APPENDIX B – STUDY FLOW**

<b>Day of Study <sup>a</sup>:</b>	<b>Standard Care:</b>	<b>ARC Dose Optimisation:</b>
0	Identify eligible patient Confirm inclusion / exclusion criteria Obtain informed consent Randomize patient	
	Continue dosing as per clinician. Typically 4.5g IV piperacillin-tazobactam every 6 to 8 hours.	Administer 4.5g IV piperacillin-tazobactam when the next scheduled dose is due. Simultaneously commence a 24-hr infusion of piperacillin-tazobactam 18g in 250ml 0.9% saline.
1	Collect all urine between 0000-0800hrs. Send to laboratory for determination of measured CL <sub>CR</sub> .  Continue dosing as per clinician.	Collect all urine between 0000-0800hrs. Send to laboratory for determination of measured CL <sub>CR</sub> .  Determine new 24-hr dose as per ARC Dose Optimisation Protocol. Commence at completion of previous 24-hr infusion.
2	Obtain plasma sample at a point halfway through a single dosing interval <sup>b</sup> .  Continue dosing as per clinician.	Obtain plasma sample 18-24hrs after last change in dose.  No change in dosing.
3	Collect all urine between 0000-0800hrs. Send to laboratory for determination of measured CL <sub>CR</sub> <sup>c</sup> .  Continue dosing as per clinician.	Collect all urine between 0000-0800hrs. Send to laboratory for determination of measured CL <sub>CR</sub> <sup>c</sup> .  Determine new 24-hr dose as per ARC Dose Optimisation Protocol. Commence at completion of previous 24-hr infusion.
4	Continue dosing as per clinician.	No change in dosing.
5	Collect all urine between 0000-0800hrs. Send to laboratory for determination of measured CL <sub>CR</sub> <sup>c</sup> .  Continue dosing as per clinician.	Collect all urine between 0000-0800hrs. Send to laboratory for determination of measured CL <sub>CR</sub> <sup>c</sup> .  Determine new 24-hr dose as per ARC Dose Optimisation Protocol. Commence at completion of previous 24-hr infusion.

6	Obtain plasma sample at a point halfway through a single dosing interval <sup>b,d</sup> .  Continue dosing as per clinician.	Obtain plasma sample 18-24hrs after last change in dose.  No change in dosing <sup>d</sup> .
7	Study cessation. Ongoing dosing as per clinician.	Study cessation at completion of 24-hr infusion. Ongoing dosing as per clinician.

a. Each Study Day begins from midnight (0000hrs)

b. If the frequency of standard dosing has changed in preceding 24hrs, obtain sample after at least 3-doses have been administered.

c. If  $CL_{CR}$  measurements are not available on that study day (e.g. Saturday or Sunday), continue dosing as per previous 24-hr infusion.

d. If unable to obtain plasma sample on that study day (e.g. Saturday or Sunday), collect as soon as possible.

## **APPENDIX C – TEST OF CURE AT DAY 14 POST RANDOMISATION (54)**

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Clinical response will be assessed as follows:

1. Resolution – disappearance of all signs and symptoms related to the infection
2. Improvement – a marked or moderate reduction in the severity and/or number of signs and symptoms of infection
3. Failure – insufficient lessening of the signs and symptoms of infection to qualify as improvement, including death or indeterminate (no evaluation possible, for any reason).

For participants discharged from the ICU prior to the test of cure date, clinical response will be evaluated by review of the patient record for the test of cure date (midnight to midnight) as follows:

1. Resolution – absence of any SIRS criteria attributable to infection
2. Improvement – only 1 SIRS criterion at any one time that is attributable to infection
3. Failure – 2 or more SIRS criteria met concurrently and attributable to infection.

If the subject has a separate episode of infection on the test of cure date, clinical response will be rated for any day (midnight to midnight) in the preceding 7 days. The best clinical response during this period will be recorded. Clinical cure is defined as follows:

1. Resolution – absence of any SIRS criteria attributable to infection
2. All other findings (i.e., sum of 2 and 3 above)

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ICU, intensive care unit; SIRS, systemic inflammatory response syndrome.