AN INVESTIGATION INTO EXTENDED INTERMITTENT INFUSIONS RATHER THAN STANDARD PRACTICE OF ANTIBIOTIC ADMINISTRATION IN CRITICALLY ILL PATIENTS WITH SEPSIS

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Contents

i Glossary of abbreviations

95% CI	95% confidence interval
AE	Adverse event (in main text); adverse events associated with anti-bacterials exhibiting T>MIC kill characteristics (forest plots)
AEa	Adverse events associated with anti-bacterials exhibiting AUC/MIC kill characteristics (forest plots)
AEc	Adverse events associated with anti-bacterials exhibiting C_{max}/MIC kill characteristics (forest plots)
AfC	Agenda for change
APACHE	Acute Physiology and Chronic Health Score
AUC	Area under the curve
AUC_{0-24}:MIC	Area under the curve to minimum inhibitory concentration ratio (used in some reproduced tables)
AUC/MIC	Area under the curve to minimum inhibitory concentration ratio (used throughout the text of the thesis)
B	Bolus intravenous injection usually over 5 mins or less
BOS	Bristol on-line surveys
CCU	Critical care unit
CCN	Critical Care Network
CI	Continuous infusion
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CL	(Drug) Clearance
C_{max}/MIC	Peak serum antibiotic concentration above minimum inhibitory concentration for the microorganism
CONSORT	Consolidated Standards of Reporting Trials
Df (or df)	Degrees of freedom
EII	Extended intermittent infusion, typically given over 3 to 4 hours but not continuously
EU	European Union
FDA	Food and Drug Administration
FICM	Faculty of Intensive Care Medicine
HDU	High Dependency Unit

I^2	Used for quantifying heterogeneity in a meta-analysis, I^2 describes the percentage of variability in point estimates that is due to heterogeneity rather than sampling error
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
MA	Meta-analysis
MH	Mantel-Haenszel test
MIC	Minimum inhibitory concentration
n	Number (e.g. of participants)
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Clinical Excellence
OR	Odds ratio
PAE	Postantibiotic effect
PD (pd)	Pharmacodynamics
PK (pk)	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO	International Prospective Register of Systematic Reviews
QUOROM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
RR	Risk ratio
S/B	Short infusion or bolus injection
S/SPC	Short infusion as described in the summary of product characteristics
SAE	Serious adverse event
SAPS	Simple Acute Physiology Score
SICSAG	Scottish Intensive Care Society Audit Group
SOFA	Sequential Organ Failure Assessment
SPC	Summary of product characteristics
SPSS	Statistical package for the social sciences

T>MIC	Time that antibacterial levels are above the minimum inhibitory concentration
TDM	Therapeutic drug monitoring
UK	United Kingdom
UKCPA	United Kingdom Clinical Pharmacy Association
UKCPA CCG	United Kingdom Clinical Pharmacy Association Critical Care Group
UREC	University Research Ethics Committee
USA	United States of America
Vd	Volume of distribution
WAE	Withdrawal due to adverse event

ii Tables, charts and figures

iii Abstract

Introduction Physiological changes affecting critically ill septic patients may impact on the effectiveness of licensed methods of antibiotic administration. It has been postulated that extending the infusion time over which time-dependent action antibiotics are administered, giving for example a 4-hour infusion rather than an injection over 5 minutes, this may increase efficacy whilst not compromising safety in critically ill septic patients. However, no single study or meta-analysis of similar studies has yet shown any significant benefit in patient orientated outcomes. Even so anecdotal evidence suggests that this practice is becoming established in the critical care environment but the extent of this in the United Kingdom (UK) has never been assessed. **Method** A questionnaire was developed to identify current intravenous antibiotic administration practice and the factors influencing choice in UK critical care units (CCUs). This was circulated to critical care pharmacists via the United Kingdom Clinical Pharmacy Association message board. Along side this a systematic review and meta-analysis were conducted to up date the evidence base. **Results** 17 of the 22 antibiotics surveyed have a single method of administration used on more than 50% of the responding UK CCUs. Piperacillin/tazobactam and meropenem are used on 22.2% and 20.3% respectively of responding CCUs as extended intermittent infusions (EIIs) and vancomycin by continuous infusion (CI) on 49.2%. Respondents most commonly sited both favourable pharmacokinetic/pharmacodynamics and an improvement in patient outcomes as reasons for adopting extended infusions. In addition, continuous infusions of vancomycin are seen to be a safer and a more predictable method of administration than intermittent infusions. Where extended infusions were in use, this practise was associated with a high level of pharmacist input into the multi professional team such as seven-day ward cover. The systematic review identified 40 randomised controlled trials comparing extended infusions to the licensed administration practice of the same antibiotic covering in total 16 different antibiotics. Statistically significant differences in clinical cure and microbiological/bacteriological cure were found in favour of extended infusion methods. A statistically significant difference in mortality was observed when time-dependent antibiotics were analysed separately. No difference in adverse events was identified between the administration methods. **Conclusion** Current UK critical care practice of intravenous antibiotic administration is in

line with the evidence base. This meta-analysis shows that extended infusions are both safe and at least as effective as standard licensed administration methods.

ix **Preface**

I am a specialist critical care and burns pharmacist and have been practising in this role for the last 15 years. I qualified as a pharmacist in 1998 from the University of Manchester and completed my hospital pre-registration training the following year at St Helens and Knowsley Teaching Hospitals NHS Trust. I have since completed a number of postgraduate courses including the clinical pharmacist diploma and supplementary prescribing qualification, both at Liverpool John Moores University, an independent prescribing conversion qualification at Keele University and critical care course at Portsmouth University. In 2012 I embarked part-time on a research qualification at Liverpool John Moores University whilst continuing to work in my specialist clinical pharmacist role. For the last 7 years I have chaired the United Kingdom Clinical Pharmacy Associations Critical Care Group.

I was inspired to investigate the subject of extended infusions of antibiotics for a number of reasons. Antibiotics are one of the only truly curative interventions available for the management of patients with septic shock and currently not enough new antibiotics are coming on to the market and resistance to existing agents is increasingly becoming a problem. Approximately a decade ago I attended a presentation on extended antibiotic infusions at an international conference, I was immediately drawn to the idea finding the logic appealing however the more I subsequently read on the subject the more I realised that the evidence of clear patient benefit wasn't there. At the same time I was aware anecdotally via on line pharmacy and critical care forums that extended infusions of some antibiotics was become usual practise on some critical care units. At the outset of my MPhil a number of large studies were on going but it was as yet unclear how these studies would affect the evidence base.

The factors described above have in turn led on to shaping the elements of the MPhil, I wanted to know what usual intravenous antibiotic administration practices are on United Kingdom critical care units and then if the published up-to-date evidence supported extended infusions. These questions are important to answer as margins can be very fine in the critically ill patient and it is important to understand if current practices are benefiting patients.

I haven't satisfied myself with simply working in my own silo and so since starting this MPhil in 2012 I have collaborated with some of the major names working in this field both in the UK and internationally. I have co-authored an international survey of antibiotic administration and therapeutic drug monitoring practice conducted on behalf of the European Society of Intensive Care Medicine (Tabah et al., 2015) and published a review of antibiotic pharmacokinetics/pharmacodynamics in the critically ill patient (Shah et al., 2015). I have also actively involved myself in the on going research, acting as UK chief investigator and legal representative for an international prospective observational study investigating gentamicin (as yet unpublished AMINO III study). Most excitingly I am on the UK Trial Management Team, and also Principal Investigator at St Helens and Knowsley Teaching Hospital NHS Trust, for the "Beta-lactam infusion group (BLING) III" study. This study will be by far the largest in this area hoping to enrol 7000 critically ill septic patients across 100 intensive care units worldwide. Based on all of this activity I am seen within critical care as a national expert on antibiotic pharmacokinetics/pharmacodynamics and stability and am regularly contacted by colleagues across the UK for advice.

The thesis that follows starts by providing an overview and background to the rationale for using extended infusions of antibiotics in the treatment of critically ill septic patients. This is followed by the overall aim and objectives of this MPhil and then an overview of the methodology used to answer the aim. The next 2 chapters address in detail the two phases of the MPhil which were conducted simultaneously, a survey of UK critical care intravenous antibiotic administration practice and a systematic review/meta-analysis of the published randomised controlled trials. Finally the discussion draws the two phases together followed by my conclusions.

1 Introduction

1.1 Intensive care, critical care and the critically ill patient

Intensive care medicine initially developed largely as a response to developments in medicine and surgery (Departmant of Health, 1999). The most striking example of this was the response to the 1952 poliomyelitis epidemic in Denmark (Lassen, 1953). A shortage of "iron lungs" in hospitals led to the adoption of life support techniques normally used only in operating theatres, with the most critically ill patients being concentrated in designated areas of the hospital. These areas had greater levels of nursing/medical intervention and observation than was standard (Flaattens et al., 2010). Intensive care as a service developed steadily over the ensuing decades: the 1960s saw the nationwide implementation and development of intensive care units (ICUs) across the United Kingdom (UK), and through the 1970s and 1980s medical and nursing staff started to professionalise with the formation of societies, journals, training and associated qualifications (Reynolds and Tansey, 2011). By the end of the 20th century scoring systems specific to ICU, such as the Acute Physiology and Chronic Health Score (APACHE) (Bouch and Thompson, 2008), had been developed to assess severity of illness and associated mortality. This time also saw disciplines such as pharmacy and physiotherapy becoming more directly involved in patient care and high dependency units (HDUs, areas of lower nurse to patient ratios than ICU) had opened (Reynolds and Tansey, 2011).

In 1999, the UK Department of Health launched a review of adult critical care services with the purpose of developing a framework for the future organisation and delivery of critical care (Departmant of Health, 1999). The report suggested a patient- rather than specialty-oriented view and coined the new term Comprehensive Critical Care. As a result, some ICUs, run follow up clinics to review patients post-hospital discharge (Griffiths and Jones, 2007). Currently, critical care is a mixture of a dedicated area of the hospital run by a multidisciplinary team which has all the therapeutic equipment required at their disposal, and an open minded, whole patient approach to care before, during and after the patient's critical care stay. Many hospitals now have critical care units (CCUs, combined ICU/HDUs) with teams of out-reach nurses assessing deteriorating patients on the wards (Faculty of Intensive Care Medicine and Intensive Care Society, 2016).

1.2 Sepsis

Definition: The systemic response to infection has long been termed "sepsis" (Ayres, 1985) but towards the end of the last century is was becoming clear that as this encompassed the whole range of presentations from simple pyrexia through to circulatory collapse it was not adequate to help identify those patients that needed immediate attention. The lack of a more detailed definition also affected the clinicians' ability to interpret the literature; although many studies investigated "sepsis" what they meant by the term could vary greatly.

In 1991 a consensus conference was held with the goal of "agreeing on a set of definitions that could be applied to patients with sepsis and its sequelae" (Bone et al., 1992). Broad definitions of systemic inflammatory response syndrome (SIRS), sepsis (SIRS with presumed or proven infection), severe sepsis (sepsis with end organ dysfunction) and septic shock (severe sepsis with hypotension despite adequate fluid resuscitation with the presence of perfusion abnormalities) were agreed upon. In 2001 a large body of experts convened to revisit the definitions published in 1992, believing the advent of new tests for biomarkers such as procalcitonin or interleukin 6 would lead to change but the group expanded on the signs and symptoms and left the definitions themselves untouched (Levy et al., 2003). 2016 however saw a major change with the advent of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (Singer et al., 2016). There were two main outcomes, firstly "SIRS" was deemed to lack sensitivity and specificity and was replaced with the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score and secondly the new consensus task force thought that there were too many terms currently in use and as "severe sepsis" was seen as redundant it was dropped.

The changes described above mean that care needs to be taken when interpreting statistics quoted in the published literature over time but regardless of the definition used it is clear to see that sepsis kills.

Prevalence: 1 in 20 deaths in England in 2010 was associated with sepsis (McPherson et al., 2013). The now defunct patient group term "severe sepsis" accounted for approximately 25% of all admissions to ICU in England, Wales and Northern Ireland between 1996 and 2004 (Harrison et al., 2006) and at that time it was the leading cause of non-cardiac mortality in ICU (Angus et al., 2001). More recently, under the newest definitions, sepsis and septic shock amongst ICU patients have been shown to have a hospital mortality of 35.1% and 55.5% respectively (Shankar-Hari et al., 2017).

In 2007 the Extended Prevalence of infection in Intensive Care (EPIC II) study (Vincent et al., 2009) investigated the source of sepsis on ICU and identified the most common causative microorganisms. This 1-day point prevalence study captured data on 13,796 patients in 1,265 ICUs across 75 countries. The lung was the most common site of infection (63.5%), with the abdomen accounting for 19.6%, blood 15.1% and urinary tract at 14.3% (patients may have more than one source, hence a total > 100%). 46.8% of patients had Gram-positive infections (of which greater that 2/3 were *Staphylococcus spp*.), 62.2% had Gram-negative infections and 17% were fungi. This remains the largest and most comprehensive prospective study providing in depth details of the nature of infection on the ICU to date.

Treatment: But sepsis needn't mean death. When initiated within an hour of diagnosis, antibiotic therapy along with appropriate fluid and vasopressor support has been shown to reduce mortality (Kumar et al., 2006; Rhodes et al., 2017). Once a diagnosis has been made, sepsis is treated empirically with broad-spectrum antibiotics that reflect the target site and cover suspected organisms (Rhodes et al., 2017). If the causative microorganism is later identified, then the antibiotic therapy can be tailored to target that specific microorganism. Over time a combination of complacency, a lack of interest from the pharmaceutical industry and indiscriminate usage in both humans and animals but particularly in livestock to promote growth have put the "magic bullet" at real risk of becoming a blank.

Very few new classes of antibiotics have appeared on the market in the last five decades (see table 1) and although some have novel actions only one of these, Linezolid (an oxazolidinone), has a

completely new mechanism of action. There has also been a steady decline over time in the total number of individual antibiotics being approved for human use. In the five year period 1983 - 1987 the US Food and Drug Administration (FDA) approved 16 new antibiotics in comparison to 10 in the period 1993-97 and only 2 between 2008-12 (Boucher et al., 2013). In the face of a potential humanitarian crisis associated with very common micro-organisms becoming resistant to all existing antibiotics, independent researchers and pharmaceutical companies are being incentivised to focus their effort on bringing new antibiotics to the market (Hampton, 2015). This may slowly be taking effect, in 2015, 2016 and 2017 the FDA approved 1, 2 and 3 new antibiotics in each of the years respectively (Andrei et al., 2018).

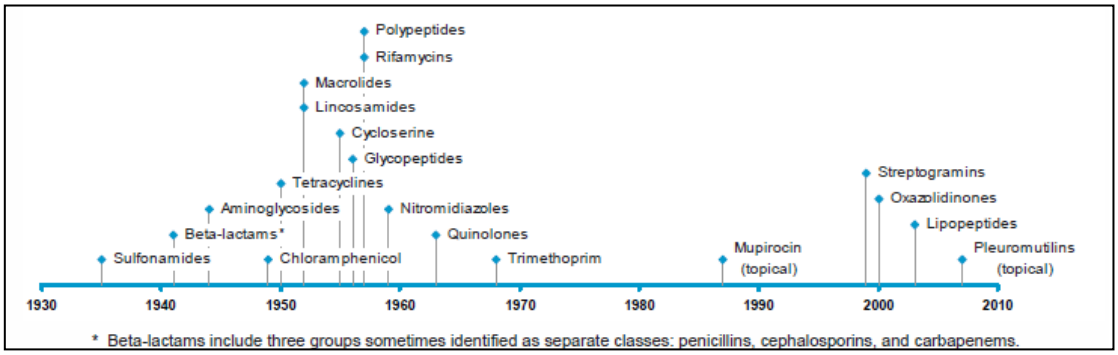


Figure 1.1: New classes of antibiotic arriving on the market (adapted from (Song, 2012))

The lack of new antibiotics coupled with ever-increasing resistance to existing agents (Spellberg, 2014) is making the management of infection more difficult, which is especially problematic in the critically ill patient. Antibiotics are the only truly curative intervention that exists for the septic patient, all other therapies such as vasopressors, intravenous fluids and mechanical ventilation are merely supportive, buying time for the antibiotics to have their affect (Rhodes et al., 2017).

One possibility for increasing the chances of antibiotic therapy being successful is to give antibiotics that would normally be administered as a bolus injection or a short infusion (over 30 minutes) as extended intermittent infusions (e.g. over three or four hours) or continuously (Shah et al., 2015). There may be a number of advantages to using one of the extended administration methods, which are discussed in the next section, but any change in patient oriented outcomes (e.g. survival,

decreased hospital stay, etc.) have not been previously shown and this requires attention. The suitability of antibiotics to be given by extended administration methods is determined by their pharmacokinetic and pharmacodynamic properties.

1.3 Factors affecting antibiotic therapy in critically ill patients – Pharmacokinetics and pharmacodynamics

Pharmacokinetics is the effect the body has on a drug and is generally split into four phases: absorption, distribution, metabolism and elimination. Below is a brief summary of each process and an explanation of any affect environment (critical care) or disease (e.g. septic shock) has on it.

Absorption: this generally refers to absorption from the gastrointestinal tract. In the critical care setting absorption often plays a minor role, as many antibiotics, are given intravenously. The assumption being that the patient has "absorbed" 100% of the administered dose.

Distribution: this phase describes where a drug goes in the different parts of the body and how long it takes the drug to get there and equilibrate between the various tissues and organs of the body. Volume of distribution (Vd) can be greatly increased in the critically ill patient (Gonçalves-Pereira and Póvoa, 2011) mainly due to the vasodilation associated with shock whereby fluid and protein (albumin) leak out of the circulating blood volume into the tissues carrying both water soluble drugs and highly protein bound drugs with them. The increased volume of distribution in critically ill patients may impact on the standard dosing regimens leading to sub-therapeutic blood levels of drug. This may have little consequence for drugs that are titrated to effect (for example, noradrenaline to a target blood pressure) but for antibiotics where it is not possible to titrate to effect this may negatively affect efficacy.

Metabolism: this is the process of enzymic degradation of the drug to products or metabolites that are eventually cleared from the body. Metabolites can be active (that is, have an action like that of the parent drug) or inactive (be inert and have no further action on the body). Drug metabolism is generally carried out in the liver but can also take place in other organs for example the kidneys or in the tissues/blood. Metabolism can be affected if hepatic blood flow is compromised or if the liver is

impaired (for example, ischemia secondary to hypo-perfusion). If renal dysfunction is also present then the potential for accumulation of active renally excreted metabolites must also be taken into account when assessing the dosing of a hepatically metabolised drug.

Elimination: this final phase general takes place via the kidneys (though some can occur via the faecal route). Critically ill patients often have an increased cardiac output due to fluid loading and the administration of drugs that increase the force and/or rate of cardiac contraction and this leads to increased kidney perfusion, an increased creatinine clearance and a subsequent increase in drug/antibiotic clearance. This phenomenon, which has been termed "augmented renal clearance" (Carrie et al., 2017), increases the clearance rates of drugs and antibiotics effectively reducing antibiotic levels and therefore efficacy. Conversely, some critically ill patients may have pre-existing chronic kidney disease, develop a sepsis/perfusion related kidney injury (for example, acute tubular necrosis) or have a combination of the two (an acute on chronic kidney injury). This is a very different issue as the resulting affect is reduced renal perfusion (titled "end organ dysfunction" in figure 2 over leaf) and therefore reduced clearance of renally cleared drugs/antibiotics leading to supra-therapeutic levels. If the kidneys stop working altogether then their function can be replicated artificially using a method known generically as renal replacement therapy. This involves pumping blood from the body, past a semi-permeable membrane and back into the body, the membrane acts in a similar way to the kidney and molecules ordinarily cleared renally will either travel across the membrane down a concentration gradient, referred to as dialysis, or down a pressure gradient, referred to as filtration. Renal replacement therapy can potentially have any of a number of effects on the pharmacokinetics of a drug including increasing the Vd, influencing the clearance and in some cases drugs may even bind to the plastic tubing, known as an extracorporeal circuit (see figure 2), used throughout the therapy.

The flow-chart over leaf (figure 2) summaries the pathophysiological affects that sepsis can have on the body, how they affect pharmacokinetics and the pharmacodynamic outcomes.

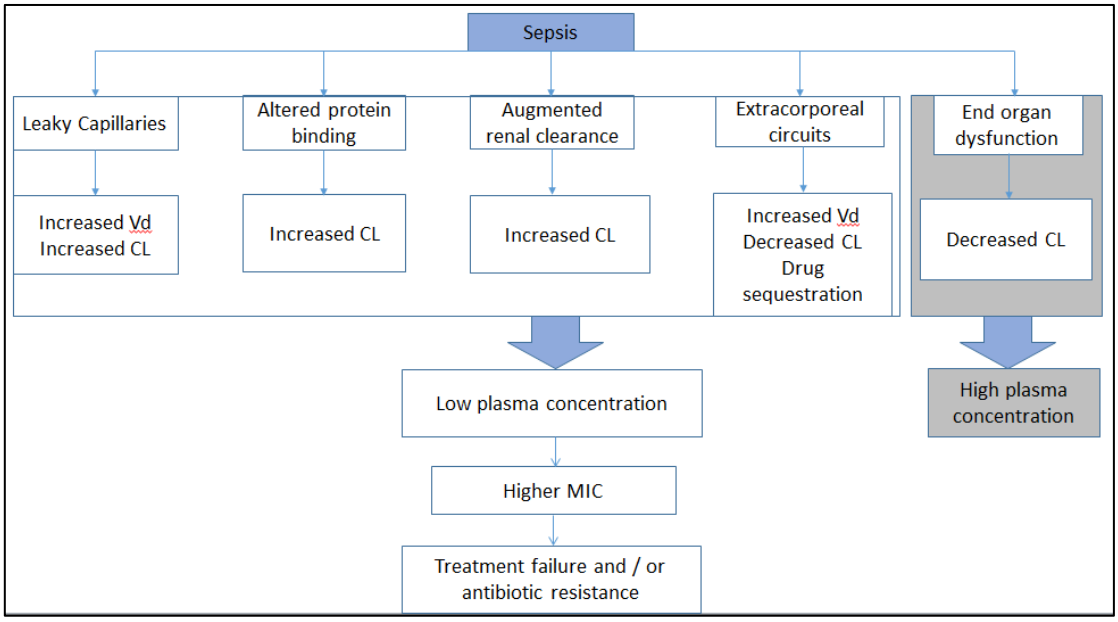


Figure 1.2. Pathophysiological changes that occur during sepsis and their effects on pharmacokinetics. Vd: volume of distribution; CL: clearance; MIC: minimum inhibitory concentration. (Shah et al., 2015)

Pharmacodynamics is the action the drug has on the body (or micro-organism). This includes desired and adverse effects. Pharmacodynamic studies (known as pd-studies) have categorised antibiotics into two main groups; concentration-dependent and time-dependent action (Ambrose et al., 2007). The effectiveness of the concentration-dependent antibiotics is determined by the peak serum antibiotic concentration above minimum inhibitory concentration (MIC) for the microorganism, often abbreviated to C_{max}/MIC. These antibiotics often also exhibit a significant post-antibiotic effect (PAE) meaning that even after the plasma level has dropped below the MIC there will be a period of time before the micro-organism recovers and starts to proliferate again (Craig, 1998). Large infrequent (e.g. daily) doses of these antibiotics provides best efficacy. Aminoglycosides, such as gentamicin, fit into this group. Time-dependent action antibiotics, the second group, have been shown to have greatest efficacy when the serum antibiotic concentration is maintained above the MIC for prolonged periods of the dosing interval (described as time greater than the MIC or T>MIC). It follows therefore that a method of delivery that maintains the concentration consistently above the MIC (more frequent dosing or extended/continuous infusions) should achieve effective treatment more predictably than bolus intermittent dosing. One study (Mouton and den Hollander, 1994) has shown that bacterial killing is maximised when a certain concentration of antibiotic above the MIC has been

reached. Extended infusion administration over 3 or 4 hours may help attain these targets and has been shown to achieve higher trough (i.e. between dose) concentrations (Roberts and Lipman, 2006). Penicillins, carbapenems and cephalosporins (together known as β-lactams) fit into this group.

Although all antibiotics are described as having either time- or concentration-dependent action not all of them can have their action neatly described by the two parameters described previously, C_{max}/MIC or T>MIC. A final parameter exists, the ratio of the area under the concentration time-curve at 24 hours (AUC) to the MIC (abbreviated to AUC_{0-24}:MIC or AUC/MIC), where neither the peak concentration nor the time spent above the MIC alone matter but the total concentration over the MIC over 24 hours predicts efficacy (Moise et al., 2000; Abdul-Aziz et al., 2015). Somewhat confusingly antibiotics described as both time-dependent, such as vancomycin and linezolid, and concentration-dependent, such as fluroquinolones, are best described by this parameter. Figure 3 below shows a graphical representation of these parameters over a single dosing interval.

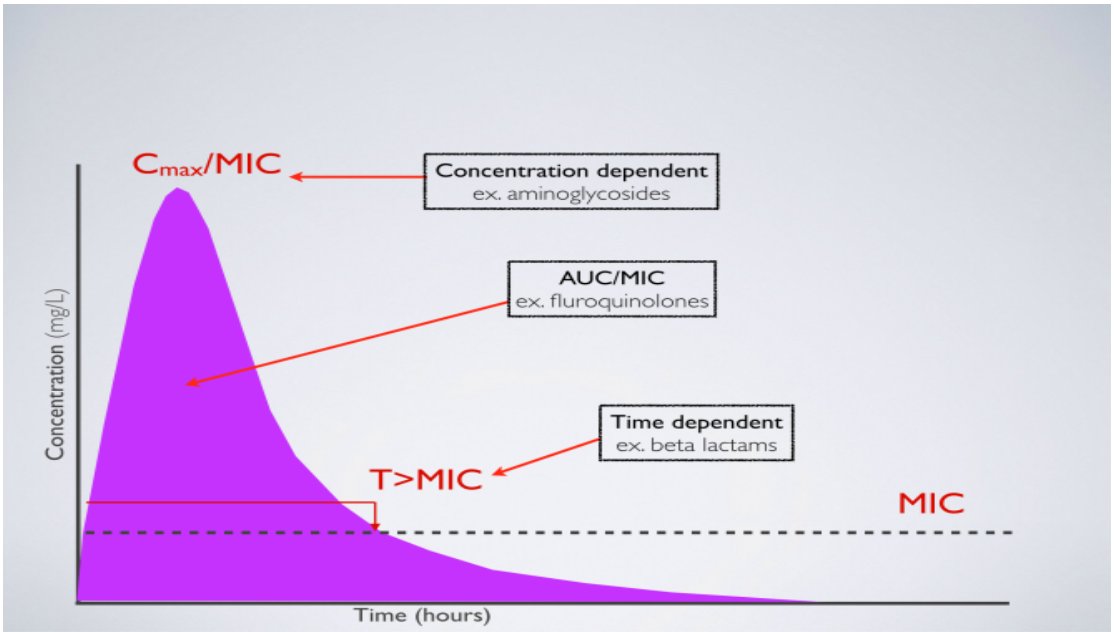


Figure 1.3. PK/PD parameters of antibiotics on a concentration vs time curve. AUC, area under the concentration–time curve; Cmax, maximum drug concentration; MIC, minimum inhibitory concentration; T>MIC, duration of time that drug concentration remains above MIC. Adapted from Roberts and Lipman 2009 (Roberts and Lipman, 2009)

1.4 Extended dose administration

The concept of giving extended or continuous infusions has been regularly investigated since at least the 1970s (Feld et al., 1977; Bodey et al., 1979; Wright et al., 1979) and for many different antibiotics in various different patient groups but interest from the critical care community as a whole has arisen relatively recently (Roberts et al., 2009c). Using this approach is rational for antibiotics with time-dependent action, in particular for those antibiotics in which T>MIC is the parameter best correlating with efficacy (Shah et al., 2015). Researchers have taken two methodological approaches to investigating the effects of extended administration method, either focusing on the pk/pd interaction between the antibiotics and the human subjects (both healthy and infected) or by investigating efficacy and safety in clinical practice.

There are three potential alternative administration-time methods of antibiotic dosing that may increase the length of time spent at target serum antibiotic levels above the MIC.

1.4.1 Frequent small doses: This is not an extended administration method, as it would involve bolus injection or short infusions, but worth considering nonetheless as it would potentially achieve the desired outcome of maintaining the antibiotic level in the serum above the MIC for prolonged periods of time. In theory, giving a small dose of antibiotic more frequently may avoid unnecessary high concentration peaks and keep between-dose troughs above the MIC. However, in practice there are many reasons why this would not be practical or effective. Firstly, without a loading dose being given, the small single doses may never achieve a concentration high enough above the MIC for the drug to be effective. This might not just lead to treatment failure but also promote antibiotic resistance by maintaining levels in the "mutant selection window", an antibiotic concentration at the target site that is above the MIC so will kill sensitive organisms but at a concentration that is too low to kill the less susceptible organisms effectively promoting their growth (Abdul-Aziz et al., 2015). Even with a loading dose there are major drawbacks predominately relating to cost effectiveness, for example excess waste due to vial size, nursing time required to prepare, double-check and administer each dose and the infection risks associated with frequent manipulations of intravenous access devices all make this approach undesirable.

1.4.2 Continuous infusions: Antibiotics may be administered as a continuous infusion over the duration of treatment. The administration of vancomycin by this method is both logical and well described (James et al., 1996; Wysocki et al., 2001) as is the pharmacokinetics in different patient groups (Rybak et al., 1990; Grace, 2012) but there are no prospective studies showing patient-orientated benefits (Roberts et al., 2008b; Gonçalves-Pereira and Póvoa, 2011) and the use of continuous infusion is still generally not well studied in the critically ill population with just one randomised controlled trial investigating its efficacy (Wysocki et al., 2001). More recently β-lactams (the broad group including penicillins, carbapenems and cephalosporins), for which T>MIC exclusively correlates with efficacy, have become the main focus of researchers' attention (Dulhunty et al., 2015; Abdul-Aziz et al., 2016; Roberts et al., 2016; Zhao et al., 2017). Continuous infusions however have their disadvantages: these include vascular access, unknown stability when mixed with other drugs, and restricted patient mobility.

1.4.3 Extended intermittent infusions: Three- or four-hour infusions of antibiotics may have the same potential benefits as continuous infusions and overcome some/all of the disadvantages. A number of studies have been conducted over the last decade in this area (Lü et al., 2013; Bao et al., 2017; Fan et al., 2017; Yang et al., 2017; Ram et al., 2018) but as of yet no single study has been adequately powered to show any mortality benefit.

A recent meta-analysis of individual patient data from RCTs using continuous infusions has called for a large, definitive study to be conducted (Roberts et al., 2016) and there is yet to be a published RCT conducted in the UK critical care population.

Although the concept of extended administration methods has been around for a long time a number of large studies (Dulhunty et al., 2015; Abdul-Aziz et al., 2016; Fan et al., 2017) have been published since the last major systematic review of the literature (Shiu et al., 2013) and antibiotic administration practices in UK CCUs have never been investigated. It is important to understand the current UK position in relation to the evidence base to ensure that patients are receiving optimal care. The following studies address this and form the thesis.

1.5 MPhil aim and objectives

1.5.1 Aim

To investigate whether UK critical care practice of antibiotic administration is supported by the current evidence base to maximise clinical efficacy and safety.

1.5.2 Objectives

i. To ascertain current usual local methods of intravenous antibiotic administration across UK critical care units to define if a common practice exists

ii. To ascertain the factors influencing the adoption of extended or continuous infusions of antibiotics.

iii. To conduct an up-to-date evaluation of the evidence base for extended infusions of antibiotics in adult patients with sepsis

iv. To ascertain if the literature supports the adoption of any particular practices in UK CCUs

2 Study design and methodology

2.1 Methodological considerations

In order to meet the overall aim of this study, two main questions needed addressing. Firstly, what antibiotic administration practices are common on UK critical care units (CCUs) and to ascertain the factors influencing the adoption of novel or extended methods of infusions of antibiotics. Secondly, does the published literature support the use of extended infusions of antibiotics in the critically ill patient population? This thesis will bring these elements together and reflect in the discussion whether UK CCU practice is supported by the published, peer-reviewed evidence base.

2.1.1 Phase 1: Assessing intravenous antibiotic administration practice

There are numerous approaches that could be taken to collecting data on current practice but two key elements of the study needed to be taken into consideration when making this choice, namely the geographical population to be sampled and who is going to be providing the data. Once these factors had been decided upon a decision was made about the most suitable method of data collection and an appropriate approach to statistical analysis of these data.

2.1.1.1 Choice of geographical population

The most influential guidance on the management of sepsis is the surviving sepsis campaign, now in its third update (Rhodes et al., 2017), which is international in both its authorship and assessment of the evidence base and so a potential approach would be to investigate practice on a wider, global level. An international or Europe-wide study of practice would have had wide reaching interest but would not have provided any meaningful results beyond simply stating what practices exist. Globally there are many differences in healthcare systems leading to different definitions of critical care, antibiotic availability and antibiotic resistance patterns between different countries. Another factor to consider is the logistics of gathering data across such a huge area and the fact that a response rate as such would have been impossible to calculate. Data would have been further biases by the response being largely restricted to English speaking participants.

Conversely, a much smaller geographical population could have been investigated, for example the focus could have been on Merseyside or the North West of England. These data would have been of

interest to local policy makers and a high response rate would have been likely as following up non-responders would have been relatively simple due to the small sample size. But as a UK wide survey would still have been missing from the published literature, the impact of such a small study on a wider audience, UK or international, would have been limited.

Choosing to study the UK as a whole rather than just one country e.g. England was influenced by the structure of UK healthcare as the National Health Service (NHS) covers all four countries in the UK so therefore systems, structure and governance are largely the same throughout so there is a common language describing what critical care is, how it functions and the grades of doctors, pharmacists, etc. The common microorganisms, resistance patterns and antibiotic availability are also relatively uniform across the UK. The number of critical care units across the UK is known and so an accurate response rate could be calculated and although response was likely to be lower and the practicalities of chasing individual CCUs more challenging than focusing on a smaller region the benefits of the quality of data outweigh the negatives of a smaller proportional response.

2.1.1.2 Choice of target respondents

Critical care pharmacists were chosen as the target recipients of the questionnaire based on a number of factors. Specialist pharmacists in general have day-to-day involvement in patient care and as part of their role will be involved in the development and implementation of local guidance pertaining to drug administration. A fundamental part of the pharmacists role is to check the accuracy of prescriptions in line with licensed or local practice and advise staff of all grades and disciplines involved in direct patient care on how to prescribe, prepare and administer medicines safely. Because of these factors pharmacists will be aware of what actually happens as usual practice in their specialist area, in this instance critical care and are therefore the ideal respondents. A final aspect is the fact that the United Kingdom Clinical Pharmacy Association (UKCPA) critical care message board provides a simple way of contacting the target population; not all critical care pharmacists are members but at the time approximately 500 pharmacists were registered to receive messages and there are only approximately 240 CCUs in the UK.

2.1.1.3 Choice of data collection method

Following the decision on geographical population and group of target participants, a method of data collection was required. The core element was engaging with the pharmacists who are involved in the process under investigation, in this instance intravenous antibiotic administration. This interaction can range from face-to-face meetings with small groups of participants through to sending questionnaires out to very large numbers of participants and hoping the majority of them will respond.

Focus groups are the most personal option and involve gathering small groups of participants with a moderator guiding the discussion. These groups lend themselves to open discussion where the investigator may not need or want clear-cut binary yes/no answers and exploring and clarifying perspectives is actively encouraged (Tong et al., 2007). They are however a very time consuming and, if the participants are spread over a large geographical area, a potentially expensive way to gather data if that form of discussion is not required. In healthcare, focus groups are usually used in studies that collect predominantly qualitative data to contribute new perspectives (Tong et al., 2007).

A more structured approach can be taken in the form of a list of questions or questionnaire. This can be delivered in a number of ways ranging from one to one interviews with the participants through to sending the questions out to a target group of potential participants. Questionnaires are widely used in epidemiological studies as a practical and structured method of data collection (Edwards et al., 2010). A questionnaire consists of a list of questions in either an “open” (free text) or “closed” (set options) style and are designed to answer the over all question being posed. The investigator tailors the questionnaire to suit his or her own needs; using predominantly closed type questions restricts the respondents options and ability to express themselves but therefore reduces variability of response making the results much more amenable to statistical analysis (Boynton and Greenhalgh, 2004).

Face-to-face or telephone interviews of individual participants would likely be the most comprehensive way to collect the data; achieving a high response rate and ensuring the participant understood and answered each of the questions (Bowling, 2005). For this study the advantage of an interview style over focus groups would be that the questions could be closed and focused, as the aim was to investigate what practice was in a particular critical care unit and what had directly affected

that participants choice of practice. This method also has major drawbacks which include the potential for the researcher to create bias in the responses and the fact that this approach could be prohibitively time consuming, expensive and simply not practical for a survey of practice covering potentially hundreds of participants over a large geographical area (Boynton, 2004; Edwards et al., 2010).

Rather than the investigator contacting participants individually a more practical solution would be to present the questions in the form of a questionnaire to all potential participants electronically or via post. The postal method has shown repeatedly over time to deliver better response rates than online questionnaires (Mavis and Brocato, 1998; Grava-Gubins and Scott, 2008; Hohwü et al., 2013) however it was unsuitable for this study. As described above critical care pharmacists were chosen to be the sole target participants for this study but as a list of critical care pharmacists for UK CCUs is not available the only means of contacting potential participants was either a generic letter sent to "the pharmacist" on each UK CCU or to post the link to the questionnaire on the United Kingdom Clinical Pharmacy Association Critical Care Group message board, the later option was chosen for practical reasons.

A systematic review and meta-analysis performed for the Cochrane collaboration in 2009 examined factors influencing the response rate to both postal and electronic questionnaires (Edwards et al., 2010). Of the 513 eligible trials examined 32 investigated electronic questionnaires reporting 27 different interventions. The positive outcomes associated with statements about response rate to date, use of a white background and offering to report results back to respondents were all taken into account in the design of this questionnaire and supporting information sent to the potential participants.

2.1.1.4 Choice of statistical methods

Where possible the questionnaire used closed questions restricting the respondent to a number of options and no free text. In the first instance all data, demographic and outcome, was analysed using simple frequency analysis. The data was assessed for trends and potential confounding factors and reported descriptively or as simple percentages.

In general, data can be split in to three main types – interval scale (continuous measurement), ordinal scale (categorical data with a logical order e.g. highest to lowest) and nominal scale (categorical data with no assumption of order e.g. yes/no or male/female) (Rowe, 2007). The vast majority of the data collected through the questionnaire was nominal in nature. To further analyse certain aspects of the data, whether one answer provided influences the answers to another question, a chi-test was used. The Chi-square test is intended to test how likely it is that an observed distribution is due to chance. Also known as a "goodness of fit test", it measures how well the observed distribution of two categorical variables fits with the distribution that is expected if the variables are independent and as such was deemed the most suitable test to identify any relationships between different demographics and the usual intravenous method of administration of each antibiotic.

2.1.1.5 Summary of final approach to assessing practice

The decision was made to focus the investigation on administration practice in UK critical care units and collect the data via survey of the critical care pharmacists, with each element contributing to the choice of the others.

The full questionnaire is available in appendix 2. Details of the literature review that guided the development of the questionnaire, design, the platform used and piloting of the questionnaire are in Chapter 3.

2.1.2 Phase 2: Assessing the evidence base

2.1.2.1 Choice of method of data collection

'Usual' practice, whether at an individual CCU level or a UK level, will follow guidelines and protocols. These documents will be built using the evidence base available at the time of development, which can potentially range from expert opinion or best practice through to one or more large well-conducted randomised controlled trials (RCTs). Many common conditions such as myocardial infarction or diabetes management will have large influential RCTs that will guide therapy and one would expect management to be consistent between hospitals. In the critical care setting however the pool of patients available to be enrolled in studies is relatively small, there is a high mortality rate and the patients presenting are often clinically heterogeneous. A study enrolling critically ill patients

with sepsis is likely to have a very variable cohort of patients with different infection sites/sources, causative organisms, pre-existing co-morbidities (e.g. chronic obstructive pulmonary disease, diabetes mellitus, etc.) and new clinical conditions (acute kidney injury, atrial fibrillation, etc.). All of these confounders potentially hide any important results. Considering these factors, studies in the critically ill patient tend to target the enrolment of relatively small numbers and so the choice of primary outcomes tends to reflect this with studies frequently now focusing on length of stay on critical care and morbidity rather than mortality. Even the biggest critical care studies rarely show outstanding differences between therapies. Searching for and finding all publications addressing a specific clinical question then analysing the pooled results can potentially identify benefits of therapies that would otherwise be missed; the first part of this process is known as a systematic review of the literature and the second part is a meta-analysis.

The key to both processes is rigor and therefore thoroughness and openness make this means of generating evidence very powerful. For example, one main element of the systematic review process is to assess for bias within each study and potential publishing bias, and these assessments are completed to a set format and published in the final article for the clinician to pore over and reach their own conclusions. For a number of decades this process has been seen as generating the highest grade of evidence allowing data to be pooled from multiple similar studies so that conclusions can be drawn that the original studies were not designed or powered to assess (Canadian Task Force on the Periodic Health Examination, 1979; Burns et al., 2011; Howick et al., 2011).

However the success of the systematic review and meta-analysis is not a given and over a number of years many elements have been developed to minimise the risk of poorly thought out reviews. The process of increasing the consistency in quality of systematic reviews and meta-analyses started with the Quality of Reporting of Meta-Analysis (QUOROM) statement (Moher et al., 1999), this was then expanded to include the systematic review process – the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009) and finally the PRISMA-P statement focussing specifically on the initial protocol writing (Moher et al., 2015). The later of thse strongly recommends that the preparation and registration of systematic review and meta-analysis protocols occur to reduce publication bias of systematic reviews and to reduce the risk of duplication

of effort. An example of such a register is the International Prospective Register of On-going Systematic Reviews called PROSPERO http://www.crd.york.ac.uk/prospero

For the systematic review process to realise its full potential the data being pooled needs to be available in the articles being analyses and this is another area where over the years attempts have been made to standardise the information presented in the published articles. In 1996 the CONSORT (Consolidated Standards of Reporting Trials) statement (Begg et al., 1996) was published in an effort to encourage researchers to include in their articles "complete, clear and transparent information on its methodology and findings" to allow the reader to accurately assess the impact of the study on their practice. The CONSORT statement is now on its third revision (Schulz et al., 2010).

The process of systematically reviewing the literature provides a structured means of identifying and capturing the evidence base, meta-analysis then appraises the articles as a whole and if the process is conducted properly it provides the highest grade of evidence and thus is the logical choice for addressing this phase of work.

A protocol was developed in line with the PRISMA-P statement (Moher et al., 2015) and based around the PICOS (population, intervention, control, outcomes, study design) method of formulating a question. This protocol was registered on the PROSPERO database (PROSPERO ID CRD42017067213) at the outset of the study. The systematic review included only randomised controlled trials (RCT) (blinded or open label) comparing two different administration method of the same antibiotic in adult patients with presumed or proven sepsis. The choice to focus on RCTs was made as these studies represent the highest level and quality of individual pieces of evidence.

It was also decided from the outset to apply no geographical, publication date or language restrictions on the search as it was felt that although the focus of the over all study is on UK practice this would be based on the global evidence base.

The major limitation of the process of systematic review is that one could argue that the overall quality of the data it produces is only as good as the weakest study included, but if the processes described above are followed then the reader can for themselves judge what if any weaknesses exist for themselves and draw their own conclusion.

2.1.2.2 Choice of method of statistical analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Moher et al., 2009) clearly sets out high level details of what the international group of expert authors consider to be the minimum standards for all aspects of the statistical analysis of the data extracted from a systematic review of the literature. A partner article (Liberati et al., 2009) further expands on and explains the statements. Items 12 – 16 in the suggested checklist relate directly to the statistical analysis and are reproduced below, as 1-5, with an explanation as to how these elements are approached in this study.

1. Risk of bias in individual studies – "Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis" (Moher et al., 2009). The Cochrane risk of bias tool (Higgins et al., 2011) was adopted for this study, it consists of 5 items for which there is evidence for their biasing influence on the estimates of an intervention's effectiveness in RCTs (sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting) and a catch-all item called ''other sources of bias'' which included funding sources, declarations of interest, use of open label antibiotics and any mismatch between treatment and control groups. All aspects were assessed for each individual paper and reported as absolute numbers of each risk (high, low or unclear) within each item and presented pictographically in table 4.1 "Methodological quality summary" in the results section of chapter 4.
2. Summary measures – "State the principal summary measures (e.g., risk ratio, difference in means)" (Moher et al., 2009). All outcomes in this study were dichotomous and the treatment effect was measured using the risk ratio (RR) with its associated 95% confidence interval (95% CI) and using a random-effects model. A random-effects model was deemed most appropriate due to the large amount of perceived clinical heterogeneity between the studies and to balance the weighting applied to the studies so as not to reduce the effect of the many smaller studies. The Cochrane handbook (http://handbook-5-1.cochrane.org;

section 9.2.2.1) suggests that interpretation of odds is more complicated than risk hence the choice of RR in this meta-analysis.

3. Synthesis of results – "Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis" (Moher et al., 2009). The I^2 statistic has been used as the main measure of statistical heterogeneity. Overall heterogeneity should be assessed in the wider context of the studies included but as a general rule I^2 greater than 50% was considered as important heterogeneity, an I^2 of less than 30% was considered lower risk (Higgins and Thompson, 2002; Higgins et al., 2003).
4. Risk of bias across studies – "Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias,….)" (Moher et al., 2009). Evidence of publication bias was assessed both visually using funnel plots (Egger et al., 1997) and statistically. Duval and Tweedie's Trim and Fill (Duval and Tweedie, 2000) method was used to impute the number of studies that might exist but that were missing from the literature search and estimate what effect these studies might have had on the outcome. Both the observed and imputed studies were viewed visually in funnel plots. Asymmetry and/or a large number of imputed studies and their effect was noted and attempts made to ascertain the reasons.
5. Additional analysis – "Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified" (Moher et al., 2009). The only subgroup defined for separate analysis *a priori* was individual antibiotics that featured in 5 or more articles. In view of the results of the questionnaire reported in chapter 3, antibiotics with significant UK-wide usage as extended infusions were also analysed individually. Subgroups were analysed using the same statistical methods as described for the main results. Specifics of the sensitivity analysis were not defined *a priori* but were performed on primary outcomes and any outcomes yielding a significant result. Sensitivity analysis was conducted to assess the impact of decisions made in the design phase of the meta-analysis on the significance of the results. For example, replacing RR with odds ratio (OR) and in another instance using a fixed-effects model rather than random-effects as part of the overall analysis to investigate what effect, if any, the choice of statistical test had had.

2.2 Summary of overall methodological approach

To summarise, the final approach taken to address the aim of the study was as follows. A questionnaire was circulated to UK critical care pharmacists electronically via the UKCPA CCG message board to assess current methods of intravenous antibiotic administration practice on UK critical care units. Along side this, a systematic review and meta-analysis of published RCTs comparing methods of intravenous antibiotic administration was conducted to assess the evidence base. The findings of the review were used to examine UK practice and assess its appropriateness.

3 Phase 1: An investigation to define the current practices of intravenous antibiotic administration in septic patients in United Kingdom Critical Care Units (UK CCUs)

3.1 Introduction

Choice of antibiotic in the hospital setting is largely guided by local policy and antibiotic guidelines that have been developed with common organisms/infection sites and resistance/susceptibility patterns in mind. Antibiotic policies will generally state the antibiotic to be prescribed, its dose, frequency and route of administration but it rarely states a method of administration e.g. how quickly a bolus should be given or the time over which an infusion should run.

At the time of conception of this study there was nothing in the published literature investigating current practice. Conducted at a similar time to this questionnaire and published in 2015 was an international survey led by Alexis Tabah (Tabah et al., 2015), it investigated what current practices of antimicrobial dosing and monitoring exist in Intensive Care Units (ICU) around the world. 402 health care professionals from 53 countries responded. Respondents were predominantly specialist ICU medical staff (78%) with 12% being pharmacists. The survey was based around a clinical scenario with a questionnaire devised to gather information on the dosing, administration and monitoring practices for 5 antibacterial agents/groups commonly used in critically ill patients, namely glycopeptides (e.g. vancomycin), piperacillin/tazobactam, carbopenems, aminoglycosides and colistin. The study showed very diverse practices in the dosing and monitoring of the antibiotics studied and suggested that further research to develop best practice guidelines is required.

Guidance is important and is often issued nationally to standardise practice in line with gold standards. This is particularly important in common conditions that are often managed in non-specialist environments. For instance a ruptured aortic aneurism would be managed in a specialist cardiothoracic centre but a myocardial infarction would be dealt with in any hospital and there is an

expectation that care would be the same wherever the patient presented. Infection and more specifically sepsis are major causes of mortality globally with lower respiratory tract infection ranked 2nd in 2010 behind ischaemic heart disease (Lozano et al., 2012). In the general intensive care setting infection and related sepsis is the leading cause of death with a mortality rate of up to 60% (Vincent et al., 2009). In the modern era of evidenced based medicine many causes of significant morbidity/mortality have nationally recommended therapies that are consistently applied unless the patient has a contra-indication. For example NICE have issued many guidelines on the prevention and management of cardiac disease even down to documents for specific therapies such as lipid modification (NICE, 2014). Regardless of where one presents in the UK with a cardiovascular event they should receive atorvastatin 80mg once daily unless contraindicated and if they don't this would be very hard to justify. Although guidance exists around certain aspects of antibacterial therapy such as timing (i.e. how soon after a patient presents with sepsis antibiotics need to be administered) and which classes of antibacterial should be used (Dellinger et al., 2013) there is very little to guide clinicians around methods of intravenous antibacterial administration. In light of the plethora of favourable pk/pd evidence for extended infusions of certain antibiotic classes some clinicians may be adopting these methods first line whilst as yet they are off-label and there is no compelling evidence of mortality/morbidity benefit. Guidance in this area may aid the clinician to make a balanced decision on whether they adopt this practice or not.

A survey of UK practice would provide insight into current approaches and any deviations from the methods of administration detailed in the marketing authorisation. It would also allow us to examine whether any of the novel methods, such as EIIs and CIs, are commonplace or usual practice. CCUs would be able to gauge their practice relative to a UK-wide database of practice and this in turn may lead some outliers to modify practice accordingly to standardise care.

3.2 Aim and objectives

3.2.1 Aim

To ascertain current usual local methods of intravenous antibiotic administration across UK critical care units to determine if a common practice exists and the factors influencing the adoption of extended or continuous infusions of antibiotics.

3.2.2 Objectives

i. To collect demographic data about the responding pharmacist/critical care unit
ii. To identify how antibiotic prescribing is managed in the critical care setting
iii. To identify if any antibiotics in a given class are used in preference to others of the same class nationally e.g. carbopenems
iv. To identify whether any usual practice exists
v. To identify whether extended or continuous infusion administration is used in preference to licensed administration practices in any critical care units
vi. To examine the driving forces e.g. grade of pharmacist for adoption of uncommon practices in outlying units
vii. To examine what patient orientated factors influence choice of method of intravenous administration e.g. renal function

3.3 Methods

3.3.1 Literature Search

A title and abstract search was conducted through Medline, Embase and CINAHL electronically from launch (1950, 1980 and 1982 respectively) to 31st May 2013. Searches were restricted to human studies but performed without any other limits such as language or age of subject. Searches used combinations of the following terms matched in each database thesaurus: critical care, intensive care, antibiotic, anti-bacterial and health care survey (see appendix 6 for full search strategy). Titles and

abstracts were retrieved and reviewed. Duplicates were removed and articles were filtered at this stage to exclude those without an English abstract, whose subject was the paediatric population, and any that did not contain information about antibiotic administration. Articles including patients managed outside of the critical care environment were included as access to critical care as defined in the UK may not be the same worldwide. Where necessary full articles were retrieved and reviewed for the remaining articles.

3.3.2 Questionnaire development and design

3.3.2.1 Participants

The participant group for this study was critical care pharmacists who are members of the United Kingdom Clinical Pharmacy Association Critical Care Group (UKCPA CCG). Only pharmacists currently working in UK CCUs with an up to date knowledge of their CCU antibiotic administration practice were invited to participate.

Critical care pharmacists practicing outside of the UK were excluded as their practice may differ due to differences in licensing, drug availability, causative organisms and resistance patterns. No Non-UK critical care pharmacists (i.e. Non-UK members of the UKCPA CCG) responded, only pharmacists registered with the UKCPA CCG message board received the invite to participate and they were asked to provide details of the hospital trust in which they worked. Other exclusion criteria were not being a critical care pharmacist and/or not being a member of the UKCPA CCG. Non-critical care pharmacists were asked to exit the questionnaire at the first question. Critical care pharmacists that are not members of the UKCPA CCG were excluded by the fact that they did not receive the email alerts with the hyperlink attached.

3.2.2.2 Questionnaire design

The questionnaire was designed using a web-based provider, Bristol Online Surveys, and is attached in full as appendix 2.

Choice of the topics and questions for inclusion/exclusion in the questionnaire was guided by personal experience of the subject matter and by taking into account published literature to identify common themes and relevant antibiotics (Craig, 1998; Roberts et al., 2011a; Drusano and Lodise, 2012; Carlier et al., 2013; Dulhunty et al., 2013a).

The questionnaire begins with conformation that the respondent is a currently practicing UK-based critical care pharmacist. If they weren't they were asked to stop at this point. The remainder of the questionnaire comprises questions that capture the following:

1. Pertinent demographic information.
2. The usual/common method of intravenous administration of each antibiotic
3. Alternative methods being used to administer intravenous antibiotics
4. The driving forces for selection of certain intravenous administration practices

The questions in full are available in appendix 2.

Where possible the questionnaire used closed questions and radio buttons restricting the respondent to set answers. The perceived benefit of this style of question was that it would categorise the information received. Where this approach wasn't possible a semi-closed style was used with drop-down options with an option for free-type responses. Open questions were limited to instances were there were too many options to practically list e.g. Hospital Trust, the answer couldn't easily be predicted or a description of practice was required.

An area where there was potential for confusion and which could affect the reliability of the result was in the choice of administration method, e.g. an infusion over 1 or 2 hours would usually be

described as a short infusion but respondents may also describe this as an extended intermittent infusion. To manage this risk five methods of administration were described with a help option for participant to hover over for further description of the method in question. Four main methods of administration were described. It was also necessary to describe a fifth that is a combination of 2. These methods and their explanations are reproduced in table 3.1 below.

Table 3.1 An explanation of the different methods of administration, and the abbreviation used in the text

Method of administration (abbreviation used in the text)	Description
Bolus (B)	Bolus injection i.e. over 5 minutes or less, also called a "slow push" in clinical practice.
Short infusion (S/SPC)	Short infusion as per the SPC.
Short infusion/Bolus (S/B)	Short infusion as per the Summary of Product Characteristics (SPC) or Bolus injection dependent on dose. For some antibiotics the SPC suggests different methods of administration dependent upon the size of the dose being administered. For example, Flucloxacillin 1g as a bolus or short infusion but 2g as a short infusion only.
Extended intermittent infusion (EII)	The drug is infused over a period that is longer than that suggested in the SPC, usually over 3 or 4 hours but not continuously
Continuous infusion (CI)	The drug is infused continuously, usually at a set rate, for the duration of the treatment course

3.3.2.3 Ethics and consent

Ethical approval for the study was obtained from Liverpool John Moores University Research Ethics Committee (UREC) (13/SPS/044).

Three questions were included that could potentially allow identification of the pharmacist who completed the questionnaire; NHS Trust, grade and level of experience. These details were required

to allow identification and removal of duplicate responses from the same Trust but no details identifying Trusts will be published, as the aim of the study is to look at UK trends not individual Trust practice.

By completing the questionnaire it was assumed that the participant was consenting to be involved in the study, as informed in the participant information (see appendix 2) at the start of the questionnaire.

3.3.2.4 Piloting

Following UREC approval, the questionnaire underwent a pilot phase on four purposively sampled critical care pharmacists in other UK NHS Trusts to assess validity and reliability and to test practical issues such as ease of use, unforeseen question ambiguity, etc. The questionnaire was then further piloted on a small group of intended recipients to test reliability of response. Comments received were considered but no changes to the questionnaire were deemed necessary.

3.3.2.5 Recruitment

Participants were invited to complete the questionnaire via the UKCPA CCG message board. After the first posting there were two follow-up messages with the link as reminders at 2 weeks and 6 weeks after the initial posting (see appendix 3 for the participant information sheet and appendix 4 for copies of the messages posted). There are approximately 240 CCUs in the UK and, at the time of posting the link, 600 pharmacists registered with the CCG message board. As there were more pharmacists registered with the message board than there are CCUs in the UK (and it is the practice on the CCUs that the research is focused on) there was a risk of duplicate responses (from the same hospital by different pharmacists). The approach to duplicates was standardised for the study; they were screened by CCU and the response from the most experienced pharmacist selected. This method was selected on the basis that they would potentially be more knowledgeable about the practices than more junior pharmacists. Agenda for Change band (AfC) (Jones et al., 2005) was used

as the marker of experience (8b-9 being the most experienced and 6 being the least), if there was more than one pharmacist on the same band the years experience was taken into account next. A list of all Critical Care Units was obtained from the Intensive Care National Audit & Research Centre (ICNARC, England, Wales and Northern Ireland) and the Scottish Intensive Care Societies Audit Group (SICSAG, Scotland) and all units listed with a pharmacist who is a member of the UKCPA CCG were invited to participate. This information also enabled an accurate response rate to be calculated during final data analysis.

3.3.2.6 Data analysis

Before the questionnaire was launched, a plan of statistical analysis was developed and included in the university ethics application. Data were exported from Bristol Online Surveys® into Excel® (Microsoft® Excel® of Mac® 2011, version 14.6.2) and SPSS® (IBM SPSS statistics version 21) as comma separated values (.csv). Demographic data (questions 2-10) were presented using Excel as distribution frequencies and percentages as were data comparing antibiotics, the method of administration, the stated factors influencing practice and the rate of TDM (questions 12-17). Usual practice was identified as existing when an antibiotic was administered by the same method on greater than 50% of responding CCUs. SPSS® was used to perform a Chi squared test to assess differences between groups, specifically antibiotic administration practice and certain demographics (questions 2-5 and 7-10). A two-sided P-value <0.05 was considered statistically significant.

3.4 Results

3.4.1 Literature search

A structured search of the literature found no articles reporting surveys of antibacterial administration practices in the adult critical care setting in UK or elsewhere in the world. For full search strategy see appendix 1.

3.4.2 Questionnaire pilot

The questionnaire was piloted on a total of 6 UK critical care pharmacists. They fed back verbally or via email. Only one suggested change was made, that a respondent should fill out one form per Trust rather than per unit but this was rejected on the basis that it would affect the ability to analyse data on different units in the same Trust if practice on the units was different. The pilot data were not included in the study as the pharmacists were unable to use the live online survey, once launched the survey could not then be altered in any way.

3.4.3 Response rate

At the time of the questionnaire there were 244 CCUs in the UK. The questionnaire asked for the pharmacist responding to do so for all the CCUs that they worked on, some may cover multiple CCUs within the same Trust. In total, 54 pharmacists responded on behalf of 64 CCUs, a response rate of 26.2%.

3.4.4 Pharmacist Demographics

90.6% (58/64) of responding CCUs were from England, one CCU was in Northern Ireland and the remaining 5 in Scotland (Table 3.2). At least one unit responded from the majority of Critical Care Networks (CCNs)/regions in the UK as defined by ICNARC/SICSAG (23/29, Chart 3.1). The specialty of 93.7% (60/64) of the CCUs was described as General/Mixed (as apposed to specifically Medical, Surgical or Neurosciences for example) by the responding pharmacist (Table 3.2).

Of the 54 pharmacists 92.6% (50/54) were “senior” pharmacists, AfC banding 8a or greater (Table 3.3) and 44.4% (24/54) have greater than 10 years experience in Critical Care (Table 3.3). The pharmacist attended the ward to review patients only on weekdays on 84.3% of units (54/64), everyday on 14.1% (9/64) and rarely on 1.6% (1/64) (Table 3.3). On 75% (48/64) of units the pharmacist regularly attends the consultant-led ward round (Table 3.3). 81.3% (52/64) of units had a ward round with the

microbiologist at least on weekdays, the remaining units (18.7%, 12/64) had weekly ward rounds (Table 3.3).

3.4.5 Administration practices

The usual method of administration of 22 antibacterials was ascertained on each CCU (Table 3.4). Frequency analysis shows that 17 of the 22 antibiotics have a single method of administration used on more than 50% of the responding CCUs (Table 3.5).

Four antibiotics are administered on at least 20% of CCUs by EII or CI: Piperacillin/tazobactam, doripenem, meropenem and vancomycin. Doripenem is only used on 3 of the responding CCUs so was not included in further analysis. Piperacillin/tazobactam and meropenem are used on 22.2% and 20.3% respectively of responding CCUs as EIIs and vancomycin by CI on 49.2% (Table 3.4). Different factors significantly affected the adoption of EII/CI for each drug. Higher pharmacist AfC banding ($p=0.028$), greater pharmacist cover ($p<0.001$) but not pharmacist attendance on the ward round ($p=0.82$) and greater microbiologist input ($p=0.031$) all significantly influenced the adoption of EIIs as the usual method of administration of piperacillin/tazobactam in preference to the method stated in the SPC. Practice also varied significantly between CCNs/Regions (Table 3.6) with some regions adopting predominantly EII usage and others using either bolus or short infusion. The only factor significantly driving EII administration of meropenem was greater pharmacist cover ($p<0.001$, see Table 3.7). Adoption of a policy of vancomycin administration by CI was significantly affected by the presence of the pharmacist on the consultant-led ward round ($p=0.03$, see Table 3.8). 7.8% (5/64) of CCUs altered the method of administration in patients on renal replacement therapy (Table 3.9). 15.6% (10/64) of CCUs altered the method of administration for other patient factors (Table 3.10). The most commonly stated rationale for using EII/CI was "Evidence Based – pharmacokinetic/pharmacodynamics properties" with 48.4% (31/64) of CCUs, cost was the least popular with only 3.7% (2/64) (Table 3.11). 9.4% (6/64) thought that the total daily dose of drug differed when using EII/CI, in all cases the drug in question was vancomycin, on 2 CCUs they thought they would use a lower over all dose but on 4 they thought they would use a bigger dose. No CCU used EII with the specific aim of reducing the total daily dose of antibacterial required. Therapeutic

drug monitoring (TDM) is done on 100% of responding CCUs but only on the antibacterials that traditionally require it i.e. aminoglycosides (e.g. gentamicin) and glycopeptides (e.g. vancomycin).

Table 3.2: Characteristics of participating critical care units (CCUs). Frequencies (%)

Variable		No. of CCUs (n=64)	
Country			
	England	58	(90.6)
	Wales	0	(0)
	Scotland	5	(7.8)
	Northern Ireland	1	(1.6)
Geographical location (according to Critical Care Network	See Chart 1		
Type of CCU			
	Medical	0	(0)
	Surgical	1	(1.6)
	General/mixed	60	(93.7)
	Cardiothoracic	1	(1.6)
	Neurosciences	0	(0)
	Other*	2	(3.1)
	Not known		
Size of CCU			
	<10 beds	14	(21.9)
	10-20 beds	31	(48.4)
	>20 beds	12	(18.8)
	Not known	7	(10.9)

*Burns/trauma x 1, complex respiratory x1

Chart 3.1: Number of responding Critical Care Units (CCUs) by Critical Care Network (CCN)/Region

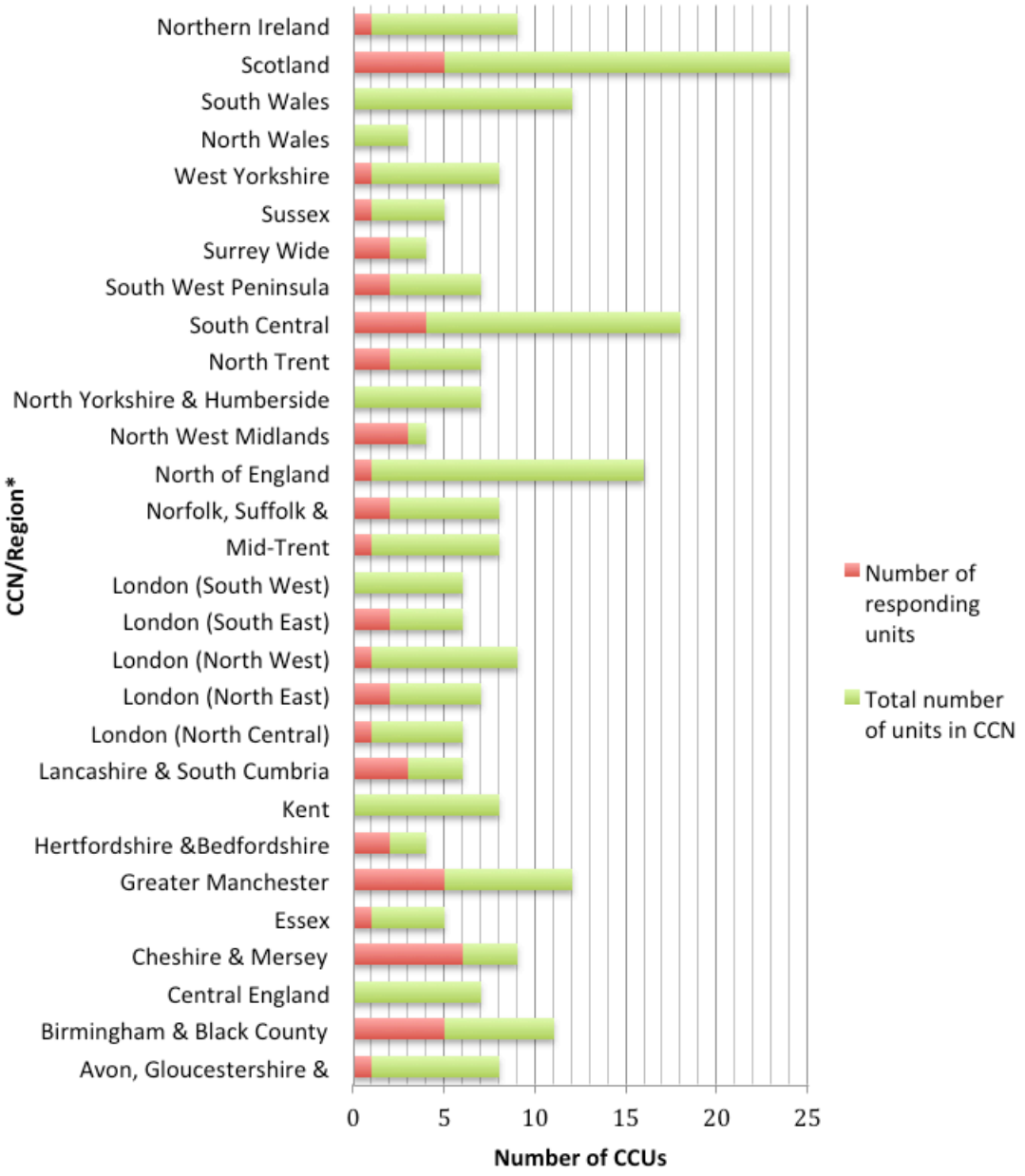


Table 3.3: Characteristics of pharmacist and microbiologist input on the CCU. Frequencies (%)

Variable		No. of CCUs (n=64)	
Agenda for Change band			
	6	0	(0)
	7	6	(9.4)
	8a	31	(48.4)
	8b-9	27	(42.2)
Number of years working in critical care			
	<1	2	(3.1)
	1-5	11	(17.2)
	6-10	19	(29.7)
	>10	32	(50.0)
Does the CCU have pharmacist cover			
	Never	0	(0)
	Rarely/ad hoc	1	(1.6)
	Weekdays	52	(81.3)
	Weekdays and Saturdays	0	(0)
	Everyday	11	(17.2)
Does the pharmacist generally attend the consultant-led ward round	Yes	47	(73.4)
	No	17	(26.6)
Does the medical microbiologist do regular ward rounds on the CCU	No	0	(0)
	Weekly	13	(20.3)
	Weekdays	41	(64.1)
	Everyday	10	(15.6)
	Not sure	0	(0)

Table 3.4: Comparison of antibiotic with its usual method of administration on each CCU. Frequency (% of total CCUs using the antibiotic)

Antibiotic	Usual method of administration*												Number of CCUs
	B		S/B		S/SPC		EII		CI		N/A		
Benzylpenicillin	30	(48.4)	6	(9.7)	22	(35.5)			4	(6.4)	2		62
Flucloxacillin	30	(46.9)	8	(12.5)	22	(34.4)			4	(6.2)			64
Amoxicillin	38	(65.5)	8	(13.8)	12	(20.7)					6		58
Ampicillin	1	(50)			1	(50)					62		2
Co-amoxiclav	40	(67.8)			13	(22)	6	(10.2)			5		59
Piperacillin/ Tazobactam	17	(27)			32	(50.8)	14	(22.2)			1		63
Ticarcillin/ Clavulanic acid					10	(100)					54		10
Cefotaxime	20	(60.6)	2	(6.1)	11	(33.3)					31		33
Ceftazidime	20	(40.8)	1	(2)	20	(40.8)	8	(16.4)			15		49
Ceftriaxone	22	(36.7)	1	(1.7)	33	(55)	4	(6.6)			4		60
Cefuroxime	24	(61.5)			11	(28.2)	4	(10.3)			25		39
Doripenem					2	(66.7)	1	(33.3)			61		3
Ertapenem	5	(13.2)			33	(86.8)					26		38
Imipenem/ Cilastatin					5	(100)					59		5
Meropenem	29	(45.3)	4	(6.3)	18	(28.1)	13	(20.3)					64
Tigecycline					38	(100)					26		38
Clarithromycin					63	(98.4)	1	(1.6)					64
Clindamycin					62	(96.8)	2	(3.2)					64
Vancomycin					32	(50.8)			31	(49.2)	1		63
Teicoplanin	34	(57.6)			25	(42.4)					5		59
Linezolid					60	(96.7)	2	(1.7)			2		62
Ciprofloxacin					64	(100)							64

*Key to heading abbreviations

B = Bolus injection i.e. over 5 minutes or less, also called a “slow push” in clinical practice.

S/B = Short infusion as per the Summary of Product Characteristics (SPC) or Bolus injection dependent on dose. For some antibiotics the SPC suggests different methods of administration dependent up the size of the dose being administered. For example, Flucloxacillin 1g as a bolus or short infusion but 2g as a short infusion only.

S/SPC = Short infusion as per the SPC.

EII = Extended intermittent infusion i.e. the drug is infused over a period that is longer than that suggested in the SPC

CI = Continuous infusion i.e. the drug is infused continuously for the duration of the treatment course

N/A = not used on a given CCU

Table 3.5: Antibiotic, its usual method of administration and the percentage of CCU administering this way

Antibiotic	Method of Administration*	Frequency/CCUs using (%)
Amoxicillin	B	38/58 (65.5)
Co-amoxiclav	B	40/59 (67.8)
Piperacillin/Tazobactam	S/SPC	32/63 (50.8)
Ticarcillin/Clavulanic acid	S/SPC	10/10 (100)
Cefotaxime	B	20/33 (60.6)
Ceftriaxone	S/SPC	33/60 (55)
Cefuroxime	B	24/39 (61.5)
Doripenem	S/SPC	2/3 (66.7)
Ertapenem	S/SPC	33/38 (86.8)
Imipenem/Cilastatin	S/SPC	5/5 (100)
Tigecycline	S/SPC	38/38 (100)
Clarithromycin	S/SPC	63/64 (98.4)
Clindamycin	S/SPC	62/64 (96.8)
Vancomycin	S/SPC	32/63 (50.8)
Teicoplanin	B	34/59 (57.6)
Linezolid	S/SPC	60/62 (96.7)
Ciprofloxacin	S/SPC	64/64 (100)

*Key to heading abbreviations

B = Bolus injection i.e. over 5 minutes or less, also called a "slow push" in clinical practice.
S/SPC = Short infusion (e.g. over 20 minutes) as per Summary of Product Characteristics (SPC).

Table 3.6: Factors affecting method of administration of piperacillin/tazobactam

Variable	Method of administration*						
	B	S/B	S/SPC	EII	CI	N/A	P-value[§]
Country							
England	16		27	14		1	0.129
Scotland			5				
Wales							
Northern Ireland	1						
CCN/Region							
			For details see table 7a				0.017
Size of CCU (no. beds)							
<10	5		6	3			0.177
10 – 20	6		17	8			
>20	5		3	3		1	
Not known	1		6				
AfC band							
6							0.028
7			6				
8a	12		13	5		1	
>8b	5		13	9			
How long have you been working in Critical Care (years)							
<1			2				0.604
1-5	5		5	1			
6-10	5		10	4			
>10	7		15	9		1	
Does the CCU have pharmacist cover							
Never							<0.001
Rarely/ad hoc	1						
Weekdays	15		31	5		1	
Weekdays & Saturdays							
Everyday	1		1	9			
Does the pharmacist generally attend the ward round							
Yes	12		23	11		1	0.820
No	5		9	3			
Does the CCU have regular ward rounds with the microbiologist							
7 days a week	2		3	4		1	0.031
Monday to Friday	9		22	10			
Weekly	6		7				
No							
Not sure							

[§]Chi-squared test

*Key to heading abbreviations

B = Bolus injection i.e. over 5 minutes or less, also called a "slow push" in clinical practice.
S/B = Short infusion as per the Summary of Product Characteristics (SPC) or Bolus injection dependent on dose.
S/SPC = Short infusion as per the SPC.
EII = Extended intermittent infusion i.e. the drug is infused over a period that is longer than that suggested in the SPC
CI = Continuous infusion i.e. the drug is infused continuously for the duration of the treatment course
N/A = not used on a given CCU

Table 3.7: factors affecting method of administration of meropenem

Variable	Method of administration*						
	B	S/B	S/SPC	EII	CI	N/A	P-value[§]
Which country							
England	25	4	16	13			0.556
Scotland	3		2				
Wales							
Northern Ireland	1						
CCN/Region							
			For details see table 7a				0.089
Size of CCU (no. beds)							
<10	6		5	3			0.424
10 – 20	14	1	8	8			
>20	6	2	2	2			
Not known	3	1	3				
AfC band							
6							0.056
7	2		4				
8a	18	1	8	4			
>8b	9	3	6	9			
How long have you been working in Critical Care (years)							
<1			2				0.521
1-5	5	1	4	1			
6-10	10	1	5	3			
>10	14	2	7	9			
Does the CCU have pharmacist cover							
Never							<0.001
Rarely/ad hoc			1				
Weekdays	28	4	16	4			
Weekdays & Saturdays							
Everyday	1		1	9			
Does the pharmacist generally attend the ward round							
Yes	23	1	13	10			0.194
No	6	3	5	3			
Does the CCU have regular ward rounds with the microbiologist							
7 days a week	5		1	4			0.087
Monday to Friday	16	3	13	9			
Weekly	8	1	4				
No							
Not sure							

[§]Chi-squared test

*Key to heading abbreviations

B = Bolus injection i.e. over 5 minutes or less, also called a "slow push" in clinical practice.
S/B = Short infusion as per the Summary of Product Characteristics (SPC) or Bolus injection dependent on dose.
S/SPC = Short infusion as per the SPC.
EII = Extended intermittent infusion i.e. the drug is infused over a period that is longer than that suggested in the SPC
CI = Continuous infusion i.e. the drug is infused continuously for the duration of the treatment course
N/A = not used on a given CCU

Table 3.8: Factors affecting method of administration of vancomycin

Variable	Method of administration*						
	B	S/B	S/SPC	EII	CI	N/A	P-value[§]
Which country							
England			30		27	1	0.455
Scotland			1		4		
Wales							
Northern Ireland			1				
CCN/Region							
			For details see table 7a				0.154
Size of CCU (no. beds)							
<10			10		4		0.580
10 – 20			14		16	1	
>20			5		7		
Not known			3		4		
AfC band?							
6							0.142
7			3		3		
8a			20		11		
>8b			9		17	1	
How long have you been working in Critical Care (years)							
<1			1		1		0.291
1-5			7		4		
6-10			12		6	1	
>10			12		20		
Does the CCU have pharmacist cover							
Never							0.109
Rarely/ad hoc			1				
Weekdays			29		22	1	
Weekdays & Saturdays							
Everyday			2		9		
Does the pharmacist generally attend the ward round							
Yes			19		27	1	0.030
No			13		4		
Does the CCU have regular ward rounds with the microbiologist							
7 days a week			3		7		0.342
Monday to Friday			20		20	1	
Weekly			9		4		
No							
Not sure							

[§]Chi-squared test

*Key to heading abbreviations

B = Bolus injection i.e. over 5 minutes or less, also called a "slow push" in clinical practice.
S/B = Short infusion as per the Summary of Product Characteristics (SPC) or Bolus injection dependent on dose.
S/SPC = Short infusion as per the SPC.
EII = Extended intermittent infusion i.e. the drug is infused over a period that is longer than that suggested in the SPC
CI = Continuous infusion i.e. the drug is infused continuously for the duration of the treatment course
N/A = not used on a given CCU

Table 3.9: Administration practices in patients receiving renal replacement therapy where different from usual practice

Change in practice	Frequency
Reduce volume	2
CI of Piperacillin/Tazobactam as 9g over 24hrs	1
Piperacillin/Tazobactam as short infusion rather than bolus	1
Vancomycin as per SPC rather than CI	1

Table 3.10: Other factors influencing deviation from usual administration practices in CCU patients

Factor	Frequency
Reduce volume if fluid restricted	2
Divide dose of vancomycin if endocarditis	1
EII/CI if pt "septic shock"	4
EII/CI in major burns	1
EII for Pseudamonas *spp*	2

Table 3.11: Reasons for choosing EIIs or CIs over conventional administration strategies

Factor	Frequency
Cost	2
Reduced toxicity	13
Evidence based – improved outcomes	26
Evidence based – pk/pd properties	31
Never used	22
Other*	9

*Other

*Ease of administration and/or monitoring

3.5 Discussion

3.5.1 Overview

This is the first UK-wide survey of critical care units conducted to examine methods of intravenous antibiotic administration, establish what usual practice exists and the extent of novel methods of administration. It was found that usual administration practice existed for the majority of intravenous antibiotics surveyed and in all instances this usual practice followed the licensed method stated in the SPC. Three antibiotics are frequently administered by EII or CI; meropenem and piperacillin/tazobactam by EII and vancomycin by CI. The significant demographic and patient-orientated driving forces varied. The most commonly stated rationale for adoption of EII or CI was the PK/PD profile of the drug but TDM was only routinely done for glycopeptides and aminoglycosides.

3.5.2 Questionnaire design

For a questionnaire to be successful in collecting accurate information every effort must be made to make sure the results yielded are both valid and reliable. Validity refers to the accuracy of the measurement i.e. does the questionnaire ask the right questions to meet the aims of the study. Are any key subjects missed/excluded. Can the results be generalised to the wider UK CCU population. Reliability refers to the consistency of the measurement i.e. the degree to which the questions used elicit the same type response. Reliability and validity were both addressed extensively at the questionnaire design and development phase.

3.5.3 Response rate

26.2% of UK CCUs responded to this questionnaire. What constitutes a “good” or “adequate” response rate is much debated and there does not appear to be a clear answer. The annual Faculty of Intensive Care Medicine (FICM) survey of the critical care consultant workforce over a 4 year period between 2010 and 2014 has had a response rate varying between 40 and 50% (The Faculty of Intensive Care Medicine, 2015). Response rates in general to questionnaires circulated by the UKCPA are generally between 10 and 20% (Carter, 2015). This rate is however lower than other published

surveys involving specifically critical care pharmacist members of the UKCPA (Yassin et al., 2014; Bourne, 2015), both of which had response rates of approximately 60%. These surveys investigated UK practice via the UKCPA CCG message board but had active follow up of non-responders by telephone call and direct email. Another study (Tabah et al., 2015), an international survey of antibiotic administration practices on CCUs carried out at a similar time to this study, did not measure response rate but documented responses from 328 hospitals in 53 different countries.

Several factors may have influenced the response rate. The general level of interest in the subject at the time the questionnaire was posted and the time required to complete the questionnaire, the participant information sheet gave a guide time of 15 minutes, may have adversely influenced this overall response rate. Another potential problem associated with all questionnaires conducted in this manner is the risk of convenience sampling and its associated bias. Convenience sampling involves selecting subjects because of their convenient accessibility and risks missing those that don't have access to the questionnaire, in this case critical care pharmacists that were not members of the UKCPA CCG. Hopefully this will have had little biasing effects on the overall results, as there are many more pharmacists registered with the message board than there are CCUs in the UK. There is currently no way of determining if the pharmacist on any given CCU is also a member of the UKCPA CCG but a recent workforce survey showed that only 2% of CCUs where without pharmacist cover (Borthwick et al., 2018). A final potential limitation is that there was no way of checking that the pharmacist completing the questionnaire was who they said they were or worked in that Trust.

3.5.4 Demographics

Most (90.6%) of the responses were from pharmacists practicing in England and English CCUs account for 80.3% (196/244) of the UK total as listed by ICNARC and SICSAG. This geographical split is consistent with that reported in the previously mentioned UK studies with higher total response rates, in a survey of pharmacist independent prescribers 86% of respondents were from England (Bourne, 2015). 5 of the 24 Scottish CCUs responded (20%) but only 1 CCU in Northern Ireland out of

a possible 9 and none of the 15 Welsh CCUs responded. This bias towards English CCUs may be due to the demographics of the membership of the UKCPA CCG, i.e. it may be that the members are predominantly based in England. Alternatively, as previously discussed, it may reflect the level of interest in the subject matter; it may be that critical care pharmacists working in England are more interested in antibiotic administration or pk/pd aspects of drug administration. The pattern of regions responding (see chart 3.1) may give us more insight into the reason for the bias. England and Wales have been divided into Critical Care Networks (CCNs, organization networks that oversee the delivery of critical care services across a geographical area), review the geography of the responses and although most regions/CCNs are represented in the responses some areas have a higher response rate than others, namely my own CCN and those neighbouring in the North West of England. Again this may reflect the level of interest locally in the subject rather than people responding because they know the investigator. Another possible reason for variation is that some CCUs may not have CCU pharmacists and this may be not just an individual hospital problem but also a regional/CCN one. Although a recent workforce survey showed that only 2% of UK CCUs are currently without a critical care pharmacist, many pharmacists do not class themselves as specialists and may not have felt confident responding.

93.7% of respondents described their CCU as a general/mixed unit; this is consistent with other published surveys of CCUs, for example 91.7% in Yassin et al (Yassin et al., 2014), and implies that the CCU admits both medical and surgical emergency and elective patients. Different administration practices between specialties e.g. medicine and surgery, was not investigated further because of the lack of specialist units responding. Approaching half (48.4%) of CCUs were stated to have between 10 and 20 beds with the remainder being evenly split either side of this i.e. <10 and >20.

3.5.5 The pharmacist

There was only one duplicate response recorded and one pharmacist had both a higher grade and more years critical care experience so the junior respondent was excluded from the data analysis.

90.6% of responding pharmacists were AfC band 8a or above, and again this is in keeping with other studies involving critical care pharmacists, e.g. Yassin et al reported >85% (Yassin et al., 2014), and seems to show, along with previously mentioned points, that the respondents are a cohort representative of the current critical care pharmacist workforce..

50% of responding pharmacists had greater than 10 years experience working in critical care, approximately 80% had more than 5 years and only 3.1% had less than a years experience. Any underrepresentation of the less experienced pharmacists is likely to have happened where those pharmacists were part of a team with more experienced leads and so therefore unlikely to have any impact on the overall trends/patterns.

The respondent was asked if the CCU had "pharmacist cover": this was intended to mean that the pharmacist visit involved reviewing the patients and their medication charts but as it was not defined as this it is not possible to say whether this was the case in all instances. It is unlikely but possible that in some instances the pharmacist fulfils an ordering and stock management role rather than a clinical role. Approximately 4/5th (81.3%) of CCUs had weekday pharmacist visits, 1/5th (17.2%) had a visit everyday and 1 CCU had only an ad-hoc service. No responding pharmacists suggested that their CCU had no cover although it is thought that about 2% of UK CCUs still have no pharmacist input (Borthwick et al., 2018). It is proposed that the reason this later point is not reflected in the questionnaire responses is two-fold. Firstly the target audience was pharmacists who were members of the UKCPA CCG who would tend to be working in critical care but this isn't necessarily true (e.g. some UKCPA members sign up to all of the message boards). The second reason is that the first question asked if the respondent was currently working in critical care; if they answered "no" the questionnaire stopped at that point. A limitation to be considered when analysing practice compared with frequency of pharmacist visit is that two hospital trusts accounted for 8 of the 11 CCUs with everyday visits (both Trusts have 4 CCUs) and so it could be argued that the practices of the these two Trusts will exaggerate the effect of differences in these data. The questionnaire could have avoided this by asking for responses by hospital trust not CCU but this would run the risk of missing variances in practice between different units with different specialties e.g. surgical, cardiothoracic etc and may

have left respondent unable to complete the questionnaire if there where differences. In addition to this, different pharmacists with different practices/levels of input may cover each CCU independently.

Approximately 75% of responding pharmacists stated that they generally attend the consultant led ward round. Ward round attendance in this study has been used as a further marker of pharmacist involvement in the "Critical Care Team". It is an indication that the pharmacist who attends the ward potentially has more input and a deeper professional relationship with the team than a pharmacist who just visits, which may mean a quick look at the medicine charts without necessarily having any meaningful input into the decision making around patient care.

To analyse whether the presence of a pharmacist on the CCU affected administration practices a survey targeting the multi disciplinary team as a whole would be required.

3.5.6 Antibiotic choice

This study identifies national trends towards prescribing specific antibiotics within certain classes. Of the broad-spectrum penicillins, amoxicillin alone and in combination with clavulanic acid (co-amoxiclav) were used by most units whereas ampicillin was rarely used. Piperacillin/tazobactam was the clear favourite out of the anti-pseudomonal penicillins and meropenem was the most commonly prescribed carbopenem. The reason for choice of an antibacterial within a given class was not asked as it was beyond the aims and objectives of the study but it is likely to be influenced by many factors such efficacy, resistance, cost and side-effect profile. For example, locally meropenem is the favoured carbopenem as it has a broader spectrum of activity than ertapenem and lower risk of CNS toxicity than imipenem.

These observations confirm that pursuing the study of meropenem or piperacillin/tazobactam will be relevant to clinical practice.

3.5.7 Existence of "usual" practice

To date, methods of administration which are being commonly used on UK CCUs have not been adequately evaluated. As previously discussed, a literature review at the time of inception of the study found no UK or international studies of current practice in CCUs. In the intervening time one international study has been published (Tabah et al., 2015). This study, an international survey published in 2015 but conducted in 2013 at a similar time to my own survey, investigated practices of antimicrobial dosing and monitoring in existence in Intensive Care Units (ICU) around the world with respondents being predominantly from 3 regions (UK, Australia/New Zealand and USA/Canada). Where overlap with my questionnaire exists results are similar.

The method by which an intravenous antibiotic is administered forms part of the product license and is therefore stated in the Summary of Product Characteristics (SPC). In line with this, where a given antibiotic was used, 90.1% of all administration across the 22 antibiotics investigated and 64 responding CCUs was in line with the SPC. Of these 22 antibiotics, 17 (Table 4) had an identified usual method of administration as defined by more than 50% of responding units usually administering the drug by the same method - no definition of a standard value for usual practice could be found in the literature. In all instances this usual practice reflected a licensed method of administration as stated in the SPC. For the remaining 5 antibiotics practice was largely split across 2 licensed methods of administration leading to neither one coming out as a clear favourite. For example the SPC for benzylpenicillin states that it can be administered either as a bolus injection or as a short infusion. 40.8% of respondents usually gave as a bolus, 35.5% as a short infusion and 9.7% a combination of both dependent on the dose being administered. This factor can also be seen even where usual practice was seen. Amoxicillin is licensed as either a bolus or a short infusion but in this instance rather than a close split, approximately two thirds of respondents gave as a bolus. Three antibiotics have very low usage amongst the responding units. Only 5 CCUs use imipenem/cilastatin but they all administer by short infusion. 3 units use doripenem (2 giving via short infusion and one by EII) and only 2 units use ampicillin (1 by each of bolus and short infusion). Usual practice for these later 2 antibiotics is therefore hard to define.

In general, where only one method of administration was stated in the SPC nearly all CCUs adopted that one practice. Ciprofloxacin, linezolid, tigecycline, tiracillin/clavulanic acid and clarithromycin all have very specific methods of administration stipulated and little or no evidence in the literature to suggest or support deviation from the license so unsurprisingly all have standard practice reflecting this (100%, 96.7%, 100%, 100% and 98.4% of respondents for a sole method for each antibiotic respectively, see tables 3.4 and 3.5).

3.5.8 Are extended intermittent (EII) or continuous infusions (CI) of any antibiotics used in preference to licensed administration practices in any critical care units?

There are logical reasons for extending the length of time over which certain antibiotics are infused in the light of pk/pd studies but with no proven improvement in morbidity/mortality outcomes the question remains why one would deviate from the product licence.

Of the 22 antibiotics investigated in the questionnaire, 13 were given on at least one CCU by either EII or CI (table 3.4).

Most of this deviation (10/13 antibiotics) was restricted to a small number of CCUs (4 or less) for each antibiotic and limited to only 5 hospital trusts. Some of these responses may have been erroneous, one CCU suggested they used EIIs of Clarithromycin (the only CCU to do so), clindamycin and linezolid for which evidence is lacking in the literature, but do not use EIIs for any of the antibiotics for which there is at least pk/pd related evidence, such as meropenem and piperacillin/tazobactam.

One Trust with 4 CCUs accounted for 66.6% (4 out of 6 CCUs) of co-amoxiclav EII practice and all EII practice of ceftriaxone and ceftazidime. Another Trust with 4 CCUs accounted for all of the CI practice of benzylpenicillin and flucloxacillin. These two Trusts combined accounted for all EII practice of ceftazidime (see table 3.4). Counting CCUs separately rather than analysing the results by Trust has led to an inflated appearance in some of the values, for example 16% (8/49) of CCUs give ceftazidime as an EII but this equates to only 5% of Trusts (2/37). CCUs were counted separately to identify differences between specialties e.g medical units versus surgical or cardiothoracic, as well as between

Trusts, through 93.7% (60/64) of responding units described themselves as "General/mixed" so deeper analysis by specialty is not practical or worthwhile.

Three antibiotics stand out where >20% of CCUs administer these by EII or CI as the standard method of administration. Piperacillin/tazobactam and meropenem are both commonly given by EII, on 22.2% and 20.3% of CCUs respectively and vancomycin is given by CI on 49.2% of units.

3.5.9 Where EIIs/CIs are usual practice what at are the driving forces for adoption of these practices and do any patient orientated factors influence choice of practice?

3.5.9.1 Vancomycin

Vancomycin pk/pd remains only partially understood (Vandecasteele et al., 2012); in vitro, like the β-lactam antibiotics, it exhibits slow time dependent kill (Löwdin et al., 1998) however it has a moderately long post-antibiotic effect, unlike β-lactams and more like an aminoglycoside, meaning the time spent above the MIC becomes less relevant (Moise-Broder et al., 2004). More recently it has been suggested that the most important parameter is actually MIC/AUC (Holmes et al., 2013). This uncertainty didn't stop investigators as early as the 1980s looking into the efficacy of continuous infusions (Barois et al., 1986; Brinquin et al., 1993); these early studies, although small, showed consistent achievement of target levels, clinical cure and, in one study, no increase in renal toxicity. Possibly the best and most referenced study conducted to date was published in 2001. Marc Wysocki conducted the first prospective multicentre randomised study which compared efficacy, safety and cost effectiveness of CIs compared with standard therapy (Wysocki et al., 2001). This was a relatively large study with approximately 60 patients in each arm and even though it showed a shorter time to target concentrations in the CI arm it failed to demonstrate any microbiological or clinical superiority of CIs. Toxicity was similar in both groups and CIs were 23% cheaper for a 10 day course than standard dosing. The controversy continues with a recent study showing that nephrotoxicity increases as trough levels increase in patients receiving standard dosing, 5% incidence when initial trough <10 mg/L compared with 33% if trough >20 mg/L (Lodise et al., 2009). It is not discussed in the paper but this effect may be due to higher peak concentrations associated with high troughs rather than the trough itself but it is none the less of concern as published CI protocols target levels of 15 – 25mg/L

In light of the lack of definitive evidence to support the use of CIs over licensed methods of administration it is possibly surprising to see that approximately half of responding CCUs (49.2%) have adopted CIs as their standard practice. Of all the factors investigated, only pharmacist attendance on the ward round seemed to significantly influence the choice of method of administration of vancomycin (see table 3.8, p=0.03). Simply attending the ward to review patient charts had no influence on choice (p=0.109). This potentially implies that the level of involvement of the pharmacist in the wider team may influence administration choice but other factors such as grade and years experience that may similarly but more weakly correlate to input did not show this (p=0.142 and 0.291 respectively). With vancomycin the significance is possibly more clear-cut than in the cases of piperacillin/tazobactam and meropenem. It involved comparing the usage of just two methods of administration rather than three or four i.e. short infusion to that of CIs and so is likely to be a truly significant factor. With the exception of microbiologist input and CCN/region, these data suggest that where EIIs/CIs are used as usual practice the pharmacist is experienced and an integral member of the CCU team. In only a small group of instances did a patient orientated factor affect choice of administration practice. One respondent switched from CI to standard therapy if the patient was receiving renal replacement therapy and another similarly switched in patients with endocarditis. This may be through fear of treatment failure or in the case of endocarditis to conform with national and international guidance which generally advise to dose at 30mg/kg/day in 2 divided doses (Habib et al., 2015). Therapeutic drug monitoring (TDM) was used to guide therapy in all CCUs using vancomycin regardless of method of administration. In the UK TDM is standard practice with intravenous vancomycin therapy historically to avoid toxicity but latterly to ensure therapeutic levels so this is not surprising (Llopis-Salvia and Jiménez-Torres, 2006). CIs potentially make TDM easier (discussed below) and this is potentially another driving force for CI selection with vancomycin, although this question was not specifically asked in the survey.

3.5.9.2 Piperacillin/tazobactam and meropenem

Both piperacillin and meropenem fit into a wider class of antibiotics referred to β-lactams that includes all penicillins, cephalosporins and carbopenems. Both the pharmacokinetics and pharmacodynamics have been well described for the β-lactams as a whole (Craig, 1998; Lodise et al.,

2006) and when piperacillin/tazobactam and meropenem (Nicolau, 2008) have been investigated they have fitted with previous finding for the class as a whole. The β-lactams all exhibit a slow continuous kill that is related almost entirely to the time spent above the minimum inhibitor concentration (T>MIC). Once concentrations of drug fall below the MIC bacteria start to multiply almost immediately.

Both antibiotics are generally administered every eight hours and have half-lives of approximately 1 hour in patients with normal renal function. These factors combined show that for a period in each dosing interval not only will drug level be below the MIC for approximately 3 hours there may be no detectable drug level at all. This is not only going to lead to treatment failure but also potentially to increased resistance to these agents (Roberts et al., 2008a). Both bigger and/or more frequent doses or the use of EIIs/CIs have been suggested as ways of improving clinical outcome and reducing resistance (Felton et al., 2013; Abdul-Aziz et al., 2015).

The popularity of these two agents in particular has lead to their methods of administration being much studied. They are both currently licensed to be administered as short infusions with a suggested duration of 30 minutes. Meropenem is also licensed to be administered as a bolus injection over 5 minutes. Advice to bolus piperacillin/tazobactam was removed from the UK SPC in 2011 to bring it in line with the rest of the EU where it is only licensed to be given by short infusion, the reason stated was harmonisation (european medicines agency, 2011). There are now many papers and review articles suggesting the pk/pd benefits of CIs and EIIs of these two agents (Roberts et al., 2008b; Abdul-Aziz et al., 2012) and more recently studies suggesting there may be improved clinical and bacteriological efficacy (Chytra et al., 2012; Abdul-Aziz et al., 2016).

22.2% and 20.3% of responding CCUs give piperacillin/tazobactam and meropenem respectively as an EII, and none of the respondents currently use continuous infusions of either drug. This pattern of usage reflects the literature; whilst there are plenty of papers touting the potential benefits of extended infusion periods, until recently (post the questionnaire), these all report use of 3- or 4-hour EIIs rather than CIs. CIs have the disadvantage of tying up an intravenous line 24 hours a day for a

single drug and also restrict the movement of patients if they are otherwise mobile. With the exception of the beta-lactam study group (BLING) in Australia, most antibiotic studies are of EIIs with the exception of vancomycin where a CI has the advantage of making TDM easier – the sample can be taken at anytime in a 24 hour period rather than having to wait for a trough (i.e. the lowest level in the dosing period) immediately before a dose. In my practice where CIs of vancomycin are used, each patient has a TDM level with the routine 6 am blood test so necessary adjustments can be made on the ward round after 9 am. Not all infections are necessarily in the blood though and so a postulated advantage of β-lactam CIs is that tissue levels are consistently maintained. The lower uptake of CCUs using EIIs of piperacillin/tazobactam and meropenem than CIs of vancomycin may well be due to the fact that the practice has appeared much more recently in the literature and/or because of the added benefit with regards to vancomycin TDM.

Of the factors investigated, one showed a significant correlation with the choice of EIIs over licensed practice and this was the frequency of pharmacists reviewing the patients on the CCU ($p < 0.001$, see tables 3.6 and 3.7). With both piperacillin/tazobactam and meropenem on CCUs where the pharmacist reviewed patients on weekdays only they were more likely to use either bolus or short infusions (92% and 90% respectively) whereas on the CCUs with a daily visit EIIs were more common (both 82%). Although this result was highly significant and 11 of the 62 responding CCUs have a pharmacist visit every day this actually only accounts for 4 of the 52 responding Trusts (2 Trusts with everyday visits had 4 responding CCUs each). There were other factors seeming to affect choice of administration method for both piperacillin/tazobactam and meropenem. The higher the pharmacist AfC banding (piperacillin/tazobactam $p=0.028$, meropenem $p=0.056$) and more frequent the microbiology input (piperacillin/tazobactam $p=0.031$, meropenem $p=0.087$) the more likely they were to use EIIs. The former, combined with level of pharmacy cover, may imply that the larger and better staffed CCUs are more likely to adopt unusual practice but against this is the fact that there was no correlation with size of CCU or pharmacist ward round attendance. A factor that may have contributed to these important variations in practice with piperacillin/tazobactam and meropenem is the fact that, at launch, both drugs had two licensed methods of administration either as a bolus or as a short infusion. CCUs may have picked which method suited their needs best at that time and then

just stuck with it. It may therefore have made more sense to combine the 2 originally licensed methods and compare them to EIIs, in doing this the significance may well have then disappeared.

3.5.10 Where EIIs/CIs are not usual practice what factors, if any, influence deviation to use these methods?

Where EIIs or CIs where not the usual method of administration, some respondents stated that under certain circumstances they would use them (see tables 3.9 and 3.10). The reasons stated could be split into two categories. The first would be classed as patients with conditions that are perceived to have significantly altered the pk/pd parameters such as septic shock and major burn injury. Both of these conditions cause an increase in volume of distribution and an increase in renal clearance of water soluble, low protein bound drugs such as the β-lactams being discussed (Shah et al., 2015). Multiple studies have shown drug levels to be altered in these patient groups (Weinbren, 1999; Roberts et al., 2011a; Udy et al., 2015) and some have shown that EIIs or CIs lead to a more favourable pk/pd profile (De Waele et al., 2014). It is therefore logical that prescribers may target the patients who are likely to gain the most from these practices. The second category is in targeting organisms that have the highest MICs and therefore require high concentrations of antimicrobial at the target site; 2 CCUs used EIIs of piperacillin/tazobactam and meropenem solely for the treatment of *Pseudomonas spp.* which have a high MIC and are noted for high treatment failure rates and development of resistance (McCarthy, 2015). Many studies investigating EIIs of β-lactams exploit their ability to maintain levels 4 times greater than the MIC of *Pseudomonas spp.* as the target (Mouton and den Hollander, 1994; Lodise et al., 2007b).

3.5.11 Factors influencing choice of administration method

Participants were asked to state their reasons for choosing EIIs/CIs over conventional administration strategies, and could select as many options as applied to them and also suggest reasons not listed.
31 out of 62 respondents stated that the driving force was the published evidence on the pk/pd benefits of EIIs and CIs, with 26 stating that they considered the evidence showed improved outcomes - however, currently it is difficult to fully agree with this and perhaps indicates some

pharmacists may have only a superficial grasp of the evidence. 13 respondents reported reduced toxicity, specifically of vancomycin, as a driving force. Here the general opinion was that CIs of vancomycin are more convenient – easier for the nursing staff to manage, easier to adjust, with timings of TDM less important, simpler interpretation and therefore under/over dosing easier to avoid. Interestingly only 2 respondents stated cost saving as a driving force. Cost improvement plans and means of efficiencies in drug budgets are at the forefront of most pharmacists' decision making at some point during every working day and given that there are many papers, particularly from the USA, reporting lower total daily doses being required were EIIs/CIs are used it is perhaps surprising more respondents didn't mention this as a consideration. One study explored using a loading dose of 4.5g piperacillin/tazobactam followed by a CI of 9g per day rather than the licensed dose of 4.5g three or four times daily; this study (Grant et al., 2002) showed similar clinical efficacy but a treatment course cost of $399.38 for CIs vs $523.49 for licensed practices (p=0.028).

3.5.12 The role of therapeutic drug monitoring

TDM is universally carried out for aminoglycosides (such as gentamicin) and glycopeptides (such as vancomycin). This is no surprise as in the UK as TDM is a part of standard care when using these antibiotics due to their nephrotoxic and ototoxic nature and narrow therapeutic drug index (the window of serum level where the drug is effective but not toxic) and more recently with vancomycin to make sure the serum level is consistently above the MIC. A recent international survey (Tabah et al., 2015) asked a similar question but found that many centres outside the UK don't do any TDM, 20% of respondents did no gentamicin levels and a further 19% only did levels if the patient was in renal failure. Where there does seem to be some disconnect within UK practice though is in the fact that although 75% of those using EIIs/CIs profess to be doing so for pk/pd reasons no one is measuring serum levels of the other commonly use drug, piperacillin/tazobactam or meropenem. This doesn't give the whole picture though many of the respondents will only have been doing CIs of vancomycin and no EIIs and will be doing TDM to guide their dosing. Another factor to consider is that although CCUs aren't doing levels, that doesn't mean they wouldn't do them if they had the ability to. Most TDM was developed for drugs with narrow therapeutic indexes to avoid toxicity were as the aim

with antibiotics such as piperacillin/tazobactam and meropenem would be to check the patient is therapeutic. Currently very few institutions have the ability to do levels for these drugs and even less are able to take samples from NHS patients. Where this facility is available it invariably takes to long for the results to come back for them to be useful clinically. I do however envisage this changing in the future as preserving the existing antibiotics we have available to use becomes more and more important, TDM of common antibiotics will not only allow the clinician to tailor the dose to the patient and microorganism but to also potentially avoid the development of antimicrobial resistance.

3.6 Conclusion

In conclusion, common intravenous administration practices exist for most antibiotics used in UK CCUs. CCUs tended to follow licensed methods of administration and where there was no usual practice this was because there was a split in responses across multiple licensed methods of administration.

The most common deviation from usual (mainly licensed) practice was the adoption of either extended intermittent or continuous infusion. Piperacillin/tazobactam, meropenem and vancomycin are commonly prescribed on UK CCUs and their pk/pd profiles lend themselves to extended methods of infusion. Respondents sited these properties and a perceived improvement in patient outcomes as reasons for adopting extended infusions. In addition, due to its narrow therapeutic index and high risk of serious toxicity, continuous infusions of vancomycin are seen to be a safer and more predictable method of administration than intermittent infusions. Where extended infusions were in use this practice was associated with a high level of pharmacist input into the multi professional team such as seven-day ward cover. Although these unlicensed methods are widespread there is still limited evidence showing any patient benefit, such as reduced length of CCU stay, and none showing improved mortality. This, combined with a lack of access to therapeutic drug monitoring for all but one or two antibiotics, makes it hard to justify using these unlicensed methods as common practice in all CCU patients.

4 Phase 2: A systematic review and meta-analysis comparing the efficacy and safety of extended versus intermittent infusions of antibiotics in adult patients with sepsis

4.1 Introduction

Previous systematic reviews have approached this subject in two ways, by either focusing on the pk/pd interaction between the antibiotics and the human subjects (both health and/or infected) or by investigating efficacy and safety in clinical practice focusing on critically ill patients with a proven or suspected infection.

4.1.1 Published reviews

4.1.1.1 Pharmacokinetics and pharmacodynamics (pk/pd) studies

Many studies focus on modelling the pharmacokinetics and pharmacodynamics of individual antibiotics in animal and human models using biological samples and simulations such as Monte Carlo modelling. Monte Carlo simulations use computer software to virtually expand the sample size of a study and in doing so provide predictions of the likely outcomes of a range of therapeutic responses (Roberts et al., 2011b). This approach is useful to maximise knowledge of drug pharmacokinetics in areas such as critical care and paediatrics where there is an absence of large scale studies (Bradley et al., 2010; Roberts et al., 2011b).

In 2005, Kasiakou and colleagues conducted a systematic review focussing specifically on randomised controlled trials in humans exploring the pharmacokinetic and pharmacodynamics parameters associated with continuous and intermittent infusions of time-dependent kill antibiotics (Kasiakou et al., 2005a). As might be expected, where reported, the maximum serum concentration (Cmax) in the intermittent infusion groups was higher than the steady state concentration in the continuous infusion group. As previously discussed, for time dependent kill antibiotics Cmax is less important than the total time spent above the MIC for that antibacterial/micro-organism combination (T>MIC). Six trials looked at infected patients and reported T>MIC. No difference was reported in 3 trials and T>MIC was higher for patients receiving continuous infusions in the remaining 3 of which two looked at critically ill patients (Benko et al., 1996; Hanes et al., 2000).

4.1.1.2 Trials in patients with presumed or proven infections

Since 2005 a number of systematic reviews and meta-analyses of trials in patients with presumed or proven infections have been published. These reviews have approached this broad subject in a number of ways. Firstly they have either investigated all antibiotics (Kasiakou et al., 2005b; Chant et al., 2013; Shiu et al., 2013), specifically focused on β-lactams (Roberts et al., 2009c, 2016; Tamma et al., 2011; Falagas et al., 2013; Lal et al., 2016) or some of the most recent reviews have even focused on individual agents such as meropenem (Yu et al., 2018). Many of these reviews selected randomised controlled trials only but a number have also included cohort studies (Chant et al., 2013; Falagas et al., 2013; Lal et al., 2016). Reviewers have tended to focus on studies investigating septic patients as a whole, but some have chosen specific patient groups such as those with nosocomial pneumonia (Lal et al., 2016). A 2016 review (Roberts et al., 2016) had very specific inclusion criteria analysing only available individual patient data from randomised controlled trials, leading to the inclusion of only 3 papers all published in the preceding 5 years and all by the same authors as of the review.

Another difference is in the approach to the presentation of the data with a split between reviewers favouring to report clinical success (Roberts et al., 2008b; Tamma et al., 2011; Shiu et al., 2013) and clinical failure (Kasiakou et al., 2005b; Chant et al., 2013). However, "mortality" is fairly consistently reported across reviews.

On the whole, many of these reviews have found improved clinical cure or reduced clinical failure rates, sometimes statistically significant, but by and large have not shown any improvement in mortality associated with this.

The most comprehensive review currently available (Shiu et al., 2013) is still widely quoted but this predates some of the most important and robust studies now published in this area (Dulhunty et al., 2015; Abdul-Aziz et al., 2016) and so a new review is urgently needed. Other reviews have been of varying quality and have generally extended beyond RCTs or been very specific to individual classes of antibiotic e.g. β-lactams, or groups of patients e.g. those on critical care. Another factor to consider is that many papers in earlier reviews are 3 or 4 decades old, have small patient numbers and use

antibiotics that are rarely, if ever, used today. Whilst these studies are still of value in a meta-analysis, the last decade has seen a number of much larger and perhaps more relevant studies. Most of the more recent publications follow the internationally accepted guidance on the preparation and publication of systematic reviews and meta-analyses (Moher et al., 2015) and therefore there is clarity around the quality of the studies included and it is easier to assess where any bias may lie.

4.2 Aim and objectives

4.2.1 Aim

The aim of this phase was to conduct an up-to-date evaluation of the evidence base for extended infusions of antibiotics in adult patients with sepsis.

4.2.2 Objectives

i. Perform a systematic review of relevant published randomised controlled trials (RCTs)

ii. Perform a meta-analysis of suitable RCTs to compare the clinical efficacy and safety of extended and intermittent intravenous administration of antibiotics in adult patients with a severe acute bacterial (presumed or proven) infection.

iii. Perform sub-group analysis of individual antibiotics

iv. Perform sensitivity analysis on primary and significant outcomes

4.3 Method

4.3.1 Study selection

4.3.1.1 Types of studies

Open label or blinded parallel group randomised controlled trials (RCTs) comparing extended and intermittent intravenous administration of the same antibiotic were selected for review. Studies were excluded from the systematic review based on the following conditions: studies not involving humans, all studies in humans under the age of 18, RCTs involving cross-over of participants, and non-RCTs (e.g. retrospective studies, commentaries, meeting abstracts, editorials, review articles and book chapters).

4.3.1.2 Types of participants

Male or non-pregnant females aged 18 years or over with a presumed or proven bacterial infection requiring intravenous antibiotics.

4.3.1.3 Types of interventions

Extended intravenous administration includes extended (for example over 3 or 4 hours) and continuous infusions. Standard intravenous administration includes licensed intermittent infusions and boluses.

4.3.1.4 Outcome measures and definitions

The following outcomes were defined *a priori:*

Primary outcomes

i. Clinical cure (any pre-defined criteria specific to the infection being studied that addresses signs and symptoms of infection)
ii. Number of patients who experienced at least one serious adverse event (SAE) (defined as resulting in death, is life threatening, involved or prolonged hospitalisation, involved persistent or significant disability or incapacity, is another condition that investigators judge to represent significant harm/hazard)

Secondary outcomes

i. Mortality (any time frame, where multiple time points were reported the longest was selected for data analysis)
ii. Infection recurrence (same organism) within 14 days of resolution of primary infection
iii. Microbiological cure (any pre-defined criteria that assessed microbiological outcomes)
iv. Secondary/super infection (a new infection with different organisms from those observed in the primary infection)
v. Number of patients withdrawing as a result of an adverse event (WAE)
vi. Number of patients with at least one adverse event (AE)

4.3.2 Protocol development

The protocol for this systematic review was developed in line with the PRISMA-P guidelines (Moher et al., 2015) and registered on the PROSPERO website (www.crd.york.ac.uk/PROSPERO/). These two processes dovetail together to support the development of reproducible and robust systematic reviews and meta-analyses.

Many published studies recorded a measure of positive clinical response, for example a combination of clinical cure and clinical improvement. This was reported either alone or with clinical cure. This outcome measure was added during data extraction. In some instances authors reported a composite of cure and improvement as "clinical cure" for the purpose of the meta-analysis this was recorded and analysed as "clinical response" in line with the definition of this in other articles. Some articles reported "clinical failure" i.e. a lack of cure or improvement, where the data was unambiguous and the patients who had responded positively could be accurately assessed, then these data were included as "clinical response". The raw data as extracted from each study are presented in appendix 9.

4.3.3 Search strategy

The following databases were utilised:

- Cochrane Central Register of Controlled Trials (The Cochrane Library), accessed June 2016
- Medline (ProQuest), 1946 to Week 1 June 2016
- Embase (Ovid), 1974 to Week 1 June 2016

The searches were built around three core elements (for full search strategy see appendix 6)

i. **The drug**, combining broad terms such as "antibiotic" through to narrower terms such as individual drug names e.g. "meropenem"
ii. **The severity of illness**, incorporating terms for critical illness and sepsis
iii. **Method of administration** including pharmacokinetics

The terms were searched in each database as they were and also matched to the thesaurus. Where appropriate the terms were exploded and/or asterisked to find all possibilities with the same root (for

example antibiotic*) and/or hyphenated (for example anti-bacterial). Initial searches were not restricted by any limits, for example, to participant age, date or language.

The searches were further refined by applying the search strategy suggested in "The Cochrane Highly Sensitive Search Strategies for identifying randomised trials" (Higgins and Green, 2011a). This was developed to identify randomised trials in Medline but has also been adapted for use with Embase (Higgins and Green, 2011b). The Cochrane handbook offers two versions: a sensitivity-maximising version and a sensitivity- and precision-maximising version; the sensitivity-maximising version was used in these searches.

Following this, restrictions were applied to remove animal studies and focus the results on human adults. References from relevant papers were also be reviewed, as was the investigator's own library. Expert opinion was sought to identify other papers including those in press or RCTs likely to be published in the very near future.

In April 2018 the search was updated by re-running the database searches as described above. Some terms and abbreviations within Athens had changed since the original search so this search was modified to take this into account. A final step was added to restrict the results at this stage to 2015 to present day. Again references and the investigators own library were examined for relevant articles. Details of the complete searches including numbers of titles retrieved at each stage can be found in appendix 6.

4.3.4 Data collection and analysis

4.3.4.1 Study selection

Titles, and where necessary the abstracts, of the search results were screened by the investigator (GB). A second independent researcher (ML) reviewed a 20% sample of the search results in the spirit of good practice to enhance the robustness and the investigator's confidence in the outcome of the screening process. GB generated this 20% sample by listing the results alphabetically in their entirety and selecting every 5th title/abstract for review by ML. Any discrepancies between reviewers were resolved by re-review of those studies until agreement was reached. Studies not meeting the inclusion criteria as defined *a priori* were excluded. Studies meeting the inclusion criteria were further

examined, full texts were retrieved and where possible English translations obtained. GB reviewed these studies and the reason for rejection at this point was recorded. If data from a study had been published on more than one occasion then care was taken to ensure that outcomes were only included once and that all publications were referenced for the study.

4.3.4.2 Data extraction

Data extraction was performed by GB using two pre-formed Excel datasheets (Microsoft Excel for Mac 2011, version 14.7.2); one form for bias assessments and one for outcome data (see appendices 8 and 9). If only an English abstract was available then as much information as possible was included from the information available. Where clarification of results or further information was required the corresponding author was emailed. The following data were extracted:

1. For Bias assessments
    a. Method (e.g. prospective, blinded, etc)
    b. Participants (e.g. number, gender, age, inclusion/exclusion criteria)
    c. Interventions (e.g. antibiotic, dose and method of administration)
    d. Outcomes (overview of the relevant outcomes)
    e. Areas of bias (selection, performance, detection, attrition, reporting and other bias as described by Higgins et al (Higgins et al., 2011))
2. For meta-analysis
    a. Antibiotic(s) studied
    b. Intervention (continuous or extended infusion)
    c. Details of outcome measures
    d. Sample tested (intention to treat, per protocol, etc.)
    e. Events for each outcome

4.3.4.3 Assessment of risk of bias in included studies

The quality of the randomised controlled trials included in the systematic review was assessed using the following criteria as laid out in "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials" (Higgins et al., 2011)

- Selection bias (random sequence generation)
- Selection bias (allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective reporting)
- Other bias (anything else, ideally pre-specified)

Definitions of low, high and unclear risk for each of the domains were set out prior to the start of data collection and are available in appendix 7. The detailed results for each paper are shown in appendix 8.

4.3.4.4 Measure of treatment effect

All outcomes were dichotomous and the treatment effect was measured using the risk ratio (RR) with its associated 95% confidence interval (95% CI) and using a random-effects model. The justification of the choice of these measures is described in detail in chapter 2 "*2.1.2.2 Choice of method of statistical analysis".*

4.3.4.5 Unit of analysis

The unit of analysis used was the patient participant and data from each randomized patient were included in the analysis. Where results were presented as a total number of events but it was not clear how many individual patients had been affected then the results were excluded from the final analysis. For example, if adverse events were tallied by the type of event and therefore an individual patient may have had more than one type of event, or had the same event more than once, then the total number of patients affected in the study was unknown and these data were excluded.

4.3.4.6 Missing/ambiguous data

Efforts were made to contact authors for clarification if any data in published studies were considered to be missing or the published data were ambiguous, for example if data in the text and tables appeared not to correspond.

4.3.4.7 Assessment of heterogeneity

The I^2 statistic has been used as the main measure of heterogeneity. Heterogeneity should be assessed in the wider context of the studies included but as a general rule I^2 greater than 50% was considered as important heterogeneity, an I^2 of less than 30% was considered lower risk (Higgins and Thompson, 2002; Higgins et al., 2003).

A random-effects model was used to assess if there was a statistically significant difference between the intervention and control groups in the studies. This model was chosen due to the large number of small studies and inter-study differences in class of antibiotic and type of infection being treated.

4.3.4.8 Assessment of reporting bias

Evidence of publication bias was assessed both visually using funnel plots (Egger et al., 1997) and statistically using Duval and Tweedie's Trim and Fill (Duval and Tweedie, 2000) method as described in chapter 2 "*2.1.2.2 Choice of method of statistical analysis".*

4.3.4.9 Data synthesis

Data from the retrieved studies were exported from Excel into Comprehensive Meta Analysis (Comprehensive Meta Analysis, version 3.3.070, November 20, 2014), which was used to perform all data synthesis and analysis, including funnel plots and high-resolution forest plots.

4.3.4.10 Subgroup analysis

The only subgroup defined for separate analysis *a priori* was individual antibiotics that featured in 5 or more studies. In view of the results of the questionnaire conducted for chapter 3 of this programme of work, antibiotics with significant UK-wide usage as extended infusions were also analysed individually. In articles that reported investigating antibiotics by general class, e.g. β-lactams, and data for individual antibiotics were not published, then attempts were made to contact the authors to provide a breakdown of the published data by antibiotic if that information was available.

4.3.4.11 Sensitivity analysis

Specifics of the sensitivity analysis were not defined *a priori* but were performed on primary outcomes and any outcomes yielding a significant result. Sensitivity analysis was conducted to assess the impact of arbitrary decisions made in the design phase of the systematic review on the significance of the results.

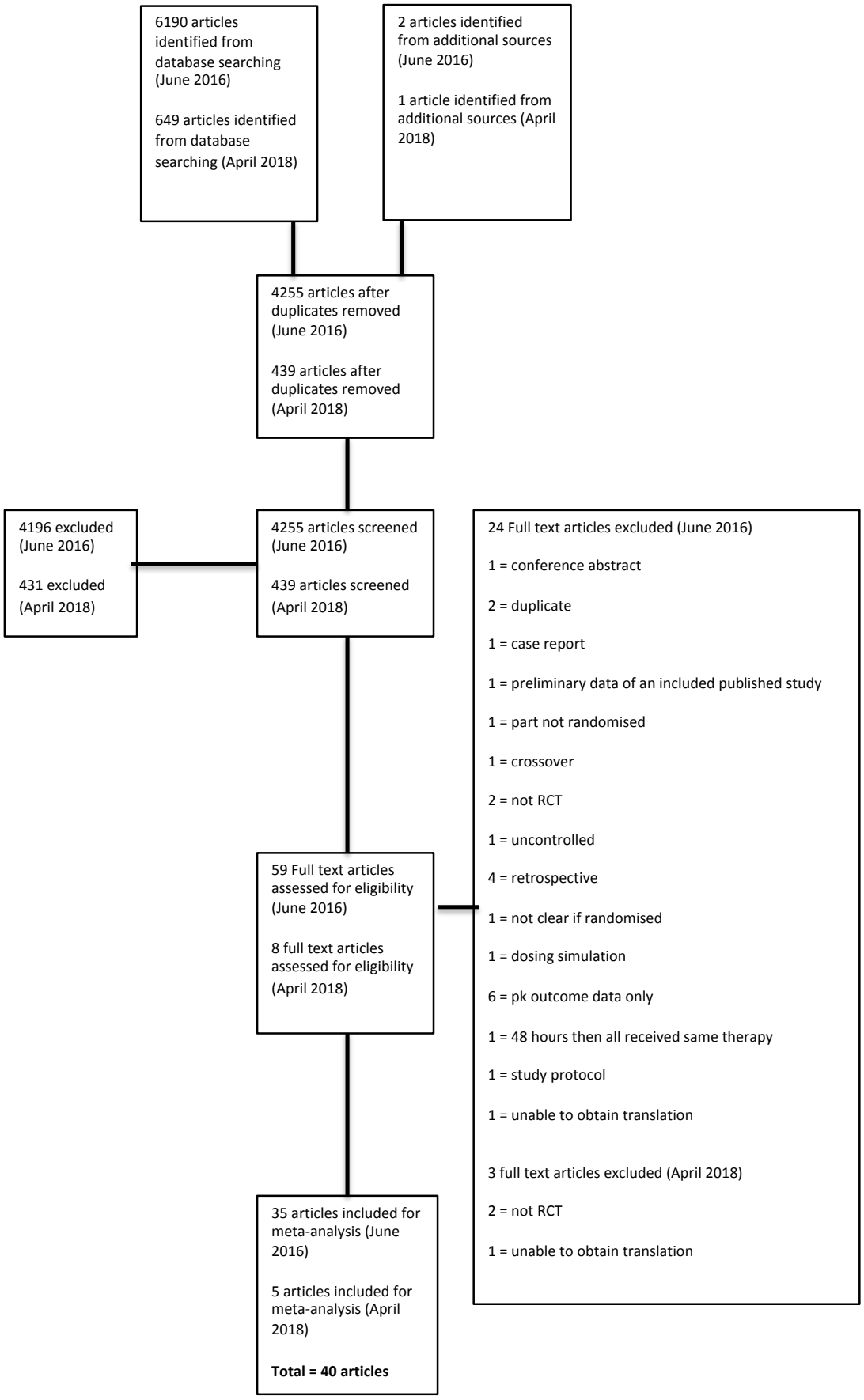
4.4 Results

4.4.1 Literature search

The initial database search conducted in June 2016 identified 6190 articles with an additional 2 articles being identified from other sources. After removal of duplicates 4255 articles remained. Titles, and where appropriate abstracts, of these articles were screened and 4196 articles were excluded for not meeting the pre-defined inclusion criteria. 59 potentially eligible full text articles were reviewed and 24 excluded for not meeting the pre-defined inclusion criteria (see figure 4.1) and the remaining 35 articles were included in the systematic review. Of the 35 articles included, 2 were only available as English abstracts (one full text article in Japanese and one in Chinese) (Okimoto et al., 2009; Lü et al., 2013) but sufficient information was available within the abstract to deem them suitable for inclusion in the review. Two articles included patients from the same study (McNabb et al., 2001; Nicolau et al., 2001) but both presented different outcomes, one clinical success (Nicolau et al., 2001) and the other adverse events (McNabb et al., 2001), therefore both studies were included in the systematic review.

In April 2018 the database search was rerun and an additional 649 articles identified with 1 further article coming from other sources. After removal of duplicates 439 articles remained and after screening of titles and abstracts 7 articles potentially met the pre-defined inclusion criteria and required full text review. Two articles were excluded and the remaining 5 included in the systematic review (see figure 4.1).

Figure 4.1: PRISMA Flow diagram showing selection process study selection process



4.4.1.1 Included studies

Forty articles were included in the meta-analysis, 34 investigating continuous infusions and 6 extended infusions. The studies ranged in size from 10 to 422 patients, with a mean size of 85 patients (median 50) and 10 articles reported on studies containing at least 100 patients. The systematic review contained a combined total of more than 3300 patients. All included articles investigated adults over the age of 18 exclusively with the exception of two (Feld et al., 1977; Wright et al., 1979). The age range across the studies was 11 to 102 years old. One article (Feld et al., 1977) stated no age range within their inclusion/exclusion criteria but included patients of 15 and over, however as the median age was 43 to 46 years old, the study was included as it was deemed that the number of patients under 18 would have been small. One article (Wright et al., 1979) again did not specify within the inclusion/exclusion criteria that patients must be over 18 years old but the documented age ranges in both the pneumonia and shock lung groups are 11-69 (mean 44) and 11-55 (mean 33) years old respectively. The article by Bao et al stated in their inclusion criteria an upper age limit of 70 years old but had a median age in both groups of 71 and a maximum age of 82 in the extended infusion group and 80 in the intermittent infusion group (Bao et al., 2017). Two articles did not comment on the age range of the patients included (Lagast et al., 1983; Lipman et al., 1999).

Males accounted for between 42% and 89% of the patients in the included articles; in only 3 articles were there more females than male participants. Two articles did not state the male/female split (Wright et al., 1979; Lipman et al., 1999).

Antibiotics studied included piperacillin (+/- tazobactam) (number of articles = 14), ceftazidime (9), meropenem (7), cefepime (2), temocillin (2), ticarcillin-clavulanate (2), tobramycin (2), vancomycin (2), cefamandole (1), cefoperazone (1), cefotaxime (1), ceftriaxone (1), gentamicin (1), imipenem-cilastatin (1), linezolid (1), sisomicin (1). A number of studies investigated more than one antibiotic, these were multi-centre studies and allowed for the choice of β-lactam antibiotic to reflect local practice.

In 24 articles the use of non-study antibiotics was not documented nor was it clear whether concomitant use of non-study antibiotics was allowed. Two studies stated the use of non-study antibiotics in the exclusion criteria (Lubasch et al., 2003; Lau et al., 2006). The remaining 14 articles all allowed the use of additional open label antibiotics during the study but with varying levels of restrictions. Bao et al (Bao et al., 2017) allowed their use but counted their use as a sign of clinical failure when assessing clinical outcome. Fan et al. (Fan et al., 2017) excluded concomitant β-lactam use but allowed all other antibiotics. Most articles stated they were allowed but did not allude to which antibiotics had been used and in how many patients. Two studies listed the antibiotics prescribed and assessed for statistically significant differences between treatment and control groups (Chytra et al., 2012; Abdul-Aziz et al., 2016).

Seven articles included in the systematic review contributed no data to the meta-analysis. Three of these articles did not present any outcomes relevant to the meta-analysis (Lipman et al., 1999; Pedeboscq et al., 2001; Yang et al., 2017). One article reported adverse events but only for the treatment group and no other relevant outcomes (Nicolau et al., 1999b). For two articles only English abstracts were available and it was not possible to align the outcomes described within these with the outcomes predetermined for the meta-analysis (Okimoto et al., 2009; Lü et al., 2013) (see appendix 9 for raw outcome data). Finally, Bodey and colleagues reported outcomes as events rather than per patient (Bodey et al., 1979).

Reported clinical cure and response rates varied within one article and as the true values could not be ascertained these outcomes from the study were excluded from the meta-analysis (Cotrina-Luque et al., 2016)

As described earlier, two articles included patients from the same study (McNabb et al., 2001; Nicolau et al., 2001) but both presented different outcomes, one clinical success (Nicolau et al., 2001) and the other adverse events (McNabb et al., 2001), the relevant data was extracted for the meta-analysis with care taken to avoid any duplication of patients.

4.4.1.2 Excluded studies

Twenty-seven of the 67 articles identified for full text review were excluded for the following reasons: not RCT (8), pk outcome data only (6), duplicate (3), conference abstract (1), case report (1), preliminary data of an included published study (1), part not randomised (1), crossover (1), uncontrolled (1), not clear if randomised (1), dosing simulation (1), 48 hours then all received same therapy (1), study protocol (1).

4.4.2 Assessment of risk of bias in the included studies

On the whole the articles generally showed a high or unclear risk of bias. This was particularly apparent with performance bias, as only three studies out of the 40 assessed were double blinded. Attrition and reporting bias faired much better in general with 62% and 45% of articles respectively being assessed as low risk. No article was low risk for all methodological quality markers assessed although one study was judged to be at low risk for all fields except for an unclear risk in "other bias" due to pharmaceutical industry sponsorship (Dulhunty et al., 2015). For an overview of the risk of bias assessments see table 4.1 "Methodological quality summary". For full details of the assessment of each article see appendix 8 – "Risk of bias" tables.

Table 4.1: Methodological quality summary – review author's judgement of the risk of bias associated with each methodological quality item for that of each of the included studies

Key – risk of bias

+	Low
?	Unclear
-	High

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdul-Aziz 2016	+	+	-	-	+	+	+
Adembri 2008	?	?	-	-	+	+	?
Angus 2000	?	?	?	?	-	-	-
Bao 2017	?	?	-	-	?	+	+
Bodey 1979	+	?	?	?	-	-	?
Buck 2005	?	?	-	-	+	?	?
Chytra 2012	?	+	-	-	+	+	+
Contrina-Luque 2015	+	?	?	?	?	?	?
De Jongh 2007	?	?	-	-	-	?	?
Dulhunty 2013	+	?	+	+	+	+	?
Dulhunty 2015	+	+	+	+	+	+	?
Fan 2017	+	-	-	-	+	?	?
Feld 1977	?	?	?	?	-	+	?
Feld 1984	?	?	?	?	+	?	?
Georges 2005	?	?	-	-	?	-	?
Hanes 2000	?	?	?	?	?	-	?
Lagast 1983	?	?	?	?	+	-	?
Laterre 2015	?	?	?	?	?	-	?
Lau 2006	?	?	-	-	-	-	-
Lipman 1999	+	?	?	?	?	?	-
Lu 2013	?	?	-	-	+	?	?
Lubasch 2003	?	?	-	-	+	+	?
McNabb 2001	?	?	-	-	-	+	?
Nicolau 1999a	?	?	?	?	+	-	?
Nicolau 1999b	?	?	-	-	-	-	?
Nicolau 2001	?	?	-	-	-	+	?
Okimoto 2009	?	?	-	-	?	?	?
Rafati 2006	?	?	?	?	+	+	?
Ram 2018	+	+	-	+	+	+	?
Roberts 2007	+	+	-	+	+	+	-
Roberts 2009a	?	+	?	?	+	?	?
Roberts 2009b	?	+	-	-	+	+	-
Roberts 2010	?	+	-	-	+	?	-
Sakka 2007	?	?	-	-	+	?	?
Schmelzer 2013	+	?	-	-	?	?	-
Van Zanten 2006	?	?	-	-	-	?	?
Wright 1979	?	?	-	-	?	?	?
Wysocki 2001	+	+	-	?	-	-	-
Yang 2017	?	?	-	?	+	+	+
Zhao 2017	?	+	-	?	+	+	?

4.4.2.1 Selection bias - Random sequence generation

Eleven articles (Bodey et al., 1979; Lipman et al., 1999; Wysocki et al., 2001; Roberts et al., 2007; Dulhunty et al., 2013a, 2015; Schmelzer et al., 2013; Abdul-Aziz et al., 2016; Cotrina-Luque et al., 2016; Fan et al., 2017; Ram et al., 2018) adequately described the generation of randomisation sequences to be deemed at low risk of bias. The remaining 29 articles were judged to have an unclear risk of bias as although they all stated that the patients were randomised they did not describe the method of random sequence generation or the information was not available in the English translations of the abstracts (Okimoto et al., 2009; Lü et al., 2013).

4.4.2.2 Selection bias - Allocation concealment

Ten articles (Wysocki et al., 2001; Roberts et al., 2007, 2009a, 2009b, 2010; Chytra et al., 2012; Dulhunty et al., 2015; Abdul-Aziz et al., 2016; Zhao et al., 2017; Ram et al., 2018) stated that randomisation occurred using sealed opaque envelopes and so were deemed to be low risk. Seven articles (Bodey et al., 1979; Feld et al., 1984; Buck et al., 2005; Sakka et al., 2007; Adembri et al., 2008; Dulhunty et al., 2013a; Bao et al., 2017) stated that randomisation occurred using sealed envelopes but opacity was not stated so were deemed to be of unclear risk. One article (Fan et al., 2017) randomised patients by hospital number therefore the enrolling physician would be able to predict which treatment arm the patient would enter so was deemed to be high risk. Allocation concealment was unclear in one article (Cotrina-Luque et al., 2016) were it was not stated whether un-blinded pharmacy staff involved in supply of the randomised therapy were involved in the clinical care of the patients so was deemed to be of unclear risk. The remaining 21 articles were judged to have an unclear risk of bias as the method of allocation concealment was not stated, in two cases only the abstract was available in English (Okimoto et al., 2009; Lü et al., 2013).

4.4.2.3 Performance bias - Blinding of participant and researchers

Nineteen articles (Georges et al., 1999; Nicolau et al., 2001; Wysocki et al., 2001; McNabb et al., 2001; Lubasch et al., 2003; Buck et al., 2005; Lau et al., 2006; Roberts et al., 2007, 2009b, 2010; van Zanten et al., 2007; Adembri et al., 2008; De Jongh et al., 2008; Okimoto et al., 2009; Chytra et al., 2012; Abdul-Aziz et al., 2016; Yang et al., 2017; Fan et al., 2017; Ram et al., 2018) described studies that

were open label/un-blinded at the point of administration so deemed to be at high risk of bias. Two articles (Dulhunty et al., 2013a, 2015) describe studies that were double blinded and so deemed to be at low risk of bias. One article (Nicolau et al., 1999b) described the study as single blinded but did not state which part of the process was blinded so was deemed to be at unclear risk of bias. One article (Lü et al., 2013) was only available as an English abstract and did not describe the blinding process so was deemed to be at unclear risk of bias. The remaining seventeen articles did not comment on blinded as so were deemed to be at unclear risk of bias.

4.4.2.4 Detection bias - Blinding of outcome assessment

Fifteen articles (Georges et al., 1999; Nicolau et al., 2001; McNabb et al., 2001; Lubasch et al., 2003; Buck et al., 2005; Lau et al., 2006; van Zanten et al., 2007; Adembri et al., 2008; De Jongh et al., 2008; Okimoto et al., 2009; Roberts et al., 2009b, 2010; Chytra et al., 2012; Abdul-Aziz et al., 2016; Fan et al., 2017) described studies that were open label/un-blinded at the point of outcome assessment so deemed to be at high risk of bias. Two articles (Dulhunty et al., 2013a, 2015) were double blinded and so assessed as being at a low risk of bias. Three more articles were single blinded; two articles (Roberts et al., 2007; Ram et al., 2018) were un-blinded at the point of administration to the patient but the investigators assessing outcomes were blinded so these were deemed to be at low risk of bias, one article (Nicolau et al., 1999b) described the study as single blinded but did not state which part of the process was blinded so was deemed to be at unclear risk of bias. One article (Wysocki et al., 2001) appeared to be blinded at the point of outcome assessment but did not explicitly state this so was deemed to be at unclear risk of bias. One article (Lü et al., 2013) was only available as an English abstract and did not describe the blinding process so was deemed to be at unclear risk of bias. The remaining eighteen articles did not comment on blinding so were deemed to be at unclear risk of bias.

4.4.2.5 Attrition bias - Incomplete outcome data

All enrolled patients were accounted for in the results of twenty-one articles (Lagast et al., 1983; Feld et al., 1984; Nicolau et al., 1999a; Lubasch et al., 2003; Buck et al., 2005; Rafati et al., 2006; Roberts et al., 2007, 2009a, 2009b, 2010; Sakka et al., 2007; Adembri et al., 2008; Chytra et al., 2012; Dulhunty et

al., 2013a, 2015; Abdul-Aziz et al., 2016; Cotrina-Luque et al., 2016; Yang et al., 2017; Zhao et al., 2017; Fan et al., 2017; Ram et al., 2018) and twenty of these studies were deemed to be at low risk of bias, one (Cotrina-Luque et al., 2016) was deemed to be at unclear risk of bias as although it was a multi-centre study the majority of patients came from a single centre and the study fell very short of the target number of patients. One article (Lü et al., 2013) only available as an English abstract was deemed to be at low risk of bias as all patients randomised were accounted for. One article (Okimoto et al., 2009) also only available as an English abstract did not comment on patient numbers so was deemed to be at unclear risk of bias. One article (Lipman et al., 1999) did not discuss the number of patients screened or enrolled in the study and so was deemed to have an unclear risk of bias. The remaining sixteen articles had one or more issues relating to data completeness such as excluded patients, patients lost to follow up, additional outcomes included not stated *a priori*. These articles were deemed to be at unclear or high risk of bias.

4.4.2.6 Reporting bias - Selective reporting

Fifteen articles (Feld et al., 1977; McNabb et al., 2001; Nicolau et al., 2001; Lubasch et al., 2003; Roberts et al., 2007, 2009b; Adembri et al., 2008; Chytra et al., 2012; Dulhunty et al., 2013a, 2015; Abdul-Aziz et al., 2016; Yang et al., 2017; Zhao et al., 2017; Bao et al., 2017; Ram et al., 2018) reported on all pre-specified outcomes so were deemed to be at a low risk of bias. One article (Cotrina-Luque et al., 2016) reported on all pre-stated outcomes but states in the article the outcomes changed during the study due to low enrolment and was deemed to be at an unclear risk of bias. Thirteen articles (Wright et al., 1979; Georges et al., 1999; Nicolau et al., 1999b; Angus et al., 2000; Hanes et al., 2000; Rafati et al., 2006; Sakka et al., 2007; van Zanten et al., 2007; De Jongh et al., 2008; Roberts et al., 2009a, 2010; Laterre et al., 2015; Fan et al., 2017) reported on one or more outcome not stated *a priori* and were deemed to be at unclear or high risk of bias. One article (Schmelzer et al., 2013) collected data on clinical outcome but did not report the results in the article so was deemed at unclear risk of bias. Selective reporting was un-evaluable and therefore deemed unclear in two articles (Okimoto et al., 2009; Lü et al., 2013) which were only available as English abstracts. The remaining eight articles did not report results for all individual patients, they reported “events” or did not state absolute numbers and were deemed to be at unclear or high risk of bias.

4.4.2.7 Other bias

No other potential sources of bias were identified in four articles (Chytra et al., 2012; Abdul-Aziz et al., 2016; Bao et al., 2017; Yang et al., 2017) and these were deemed at low risk of bias. Other potential sources of bias were unclear in two articles (Okimoto et al., 2009; Lü et al., 2013) as only English abstracts were available and so these studies were deemed to have unclear risk of bias. The remaining thirty-four articles contained one or more of the following potential sources of other bias; conflicts of interest not stated or potentially influential; industry funding or supply of antibiotics; unclear or unstated use of open label antibiotics; demographics of treatment groups not evenly matched; antibiotic dosing not evenly matched between treatment groups; severely underpowered, these articles were deemed to be at unclear or high risk of bias.

4.4.3 Outcomes

No single study reported on all of the meta-analyses pre-stated outcomes. The table below describes the number of articles reporting each outcome.

Table 4.2: Number of articles reporting meta-analysis primary and secondary outcomes

Outcome	Number of articles (out of a possible 40)
Clinical cure	11
Clinical response	12
Serious adverse event (SAE)	2
All-cause mortality	23
Infection recurrence within 14 days of resolution of primary infection	3
Microbiological/bacteriological cure	5
Secondary/super-infection	9
Withdrawal secondary to adverse event (WAE)	4
Adverse event (AE)	14

4.4.3.1 Primary and secondary outcomes

Primary outcomes

Clinical cure: Eleven articles reported clinical cure (Nicolau et al., 2001; Georges et al., 2005; Roberts et al., 2009a, 2007; Adembri et al., 2008; De Jongh et al., 2008; Chytra et al., 2012; Dulhunty et al., 2013a, 2015; Laterre et al., 2015; Abdul-Aziz et al., 2016). Two articles (De Jongh et al., 2008; Roberts et al., 2009a) reported clinical cure in all patients assessed therefore a risk ratio is not estimable and these articles are not represented visually in the forest plot. All of these articles reported studies investigating time-dependent antibiotics. A statistically significant difference in clinical cure was observed (n = 1083, risk ratio (RR) 1.231, 95% CI 1.081 to 1.403, P = 0.002). No evidence of statistical heterogeneity was found (degrees of freedom (df) = 8, P = 0.357, I^2 = 9.4%).

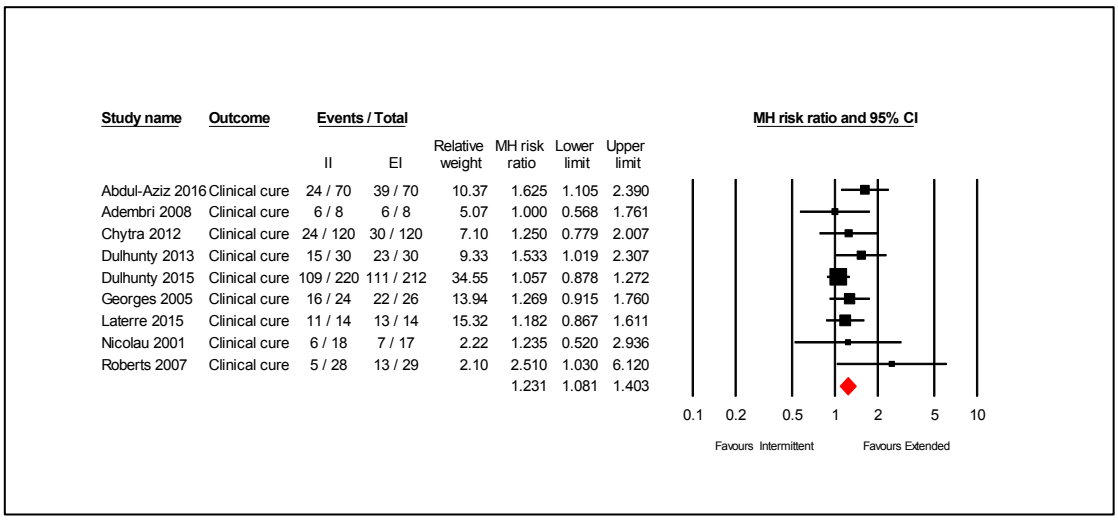


Figure 4.1a: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of clinical cure of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test.

Analysis of the funnel plot showing observed (white) and imputed (black) articles suggests that publication bias exists favouring articles showing a positive effect from extended infusions.

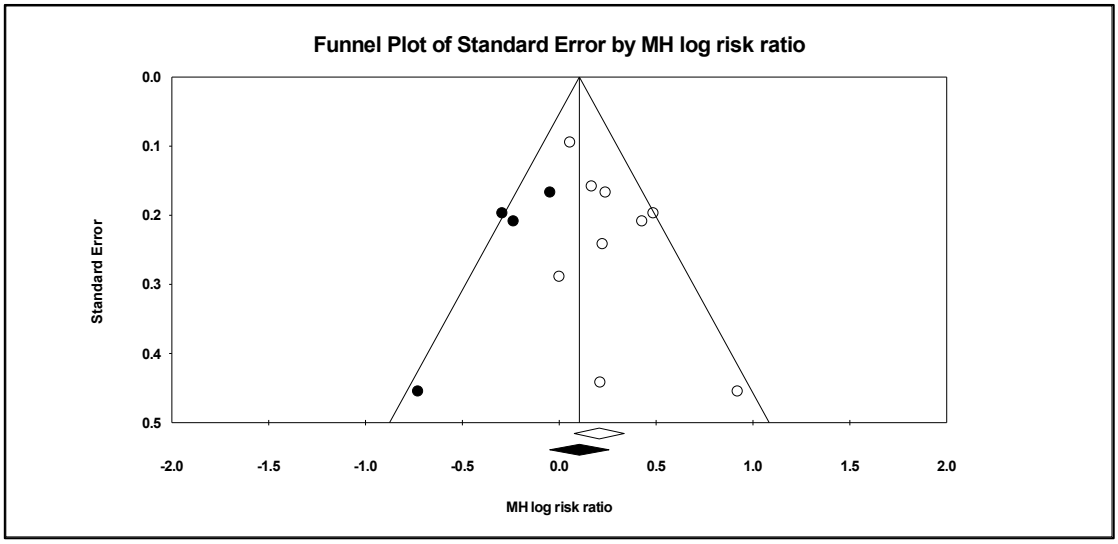


Figure 4.1b: Funnel plot comparison showing existing (o) and imputed (•) studies: clinical cure

Trim and Fill (Duval and Tweedie, 2000) identifies 4 potentially missing studies and renders the result no longer significant (random effects model, point estimate 1.109, 95% CI 0.952 to 1.293).

Number of patients who experienced at least one serious adverse event (SAE): Two articles reported the number of patients who had experienced at least one SAE (Dulhunty et al., 2015; Bao et al., 2017). Both of these articles reported studies investigating time-dependent antibiotics. No statistically significant difference in SAE was observed (n = 482, RR 0.858, 95% CI 0.515 to 1.431, P = 0.558). No evidence of statistical heterogeneity was found (df = 1, P = 0.468, I^2 = 0.0%)

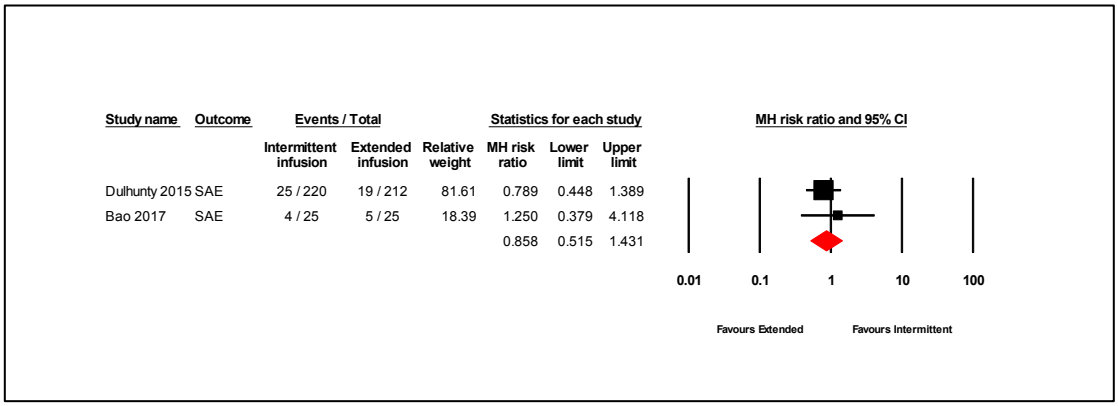


Figure 4.2: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of serious adverse events (SAE) of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test

The number of articles reporting SAE was insufficient to assess for publication bias.

Secondary outcomes

Clinical response: Twelve articles reported clinical response (Hanes et al., 2000; Wysocki et al., 2001; Nicolau et al., 2001; Lubasch et al., 2003; Buck et al., 2005; Lau et al., 2006; Roberts et al., 2007; van Zanten et al., 2007; Chytra et al., 2012; Bao et al., 2017; Zhao et al., 2017; Ram et al., 2018). Eleven of these articles reported studies investigating time-dependent antibiotics and one article (Wysocki et al., 2001) MIC:AUC ratio. No statistically significant difference in clinical response was observed (n = 1132, RR 1.027, 95% CI 0.974 to 1.083, P = 0.319). No evidence of statistical heterogeneity was found (df = 11, P = 0.743, I^2 = 0.0%).

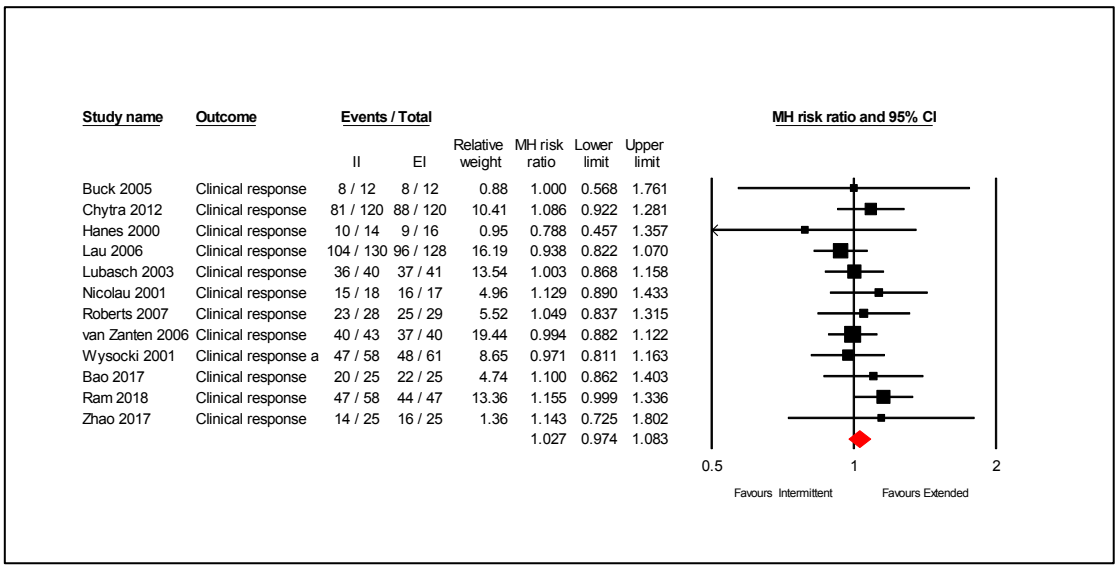


Figure 4.3a: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of clinical response of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test.

Analysis of the funnel plot showing both observed (white) and imputed (black) studies suggests that publication bias exists favouring publication of articles showing a positive effect from extended infusions. Trim and Fill (Duval and Tweedie, 2000) identifies 2 potentially missing studies but doesn't alter the statistical significance of the result (random effects model, point estimate 1.007, 95% CI 0.958 to 1.058).

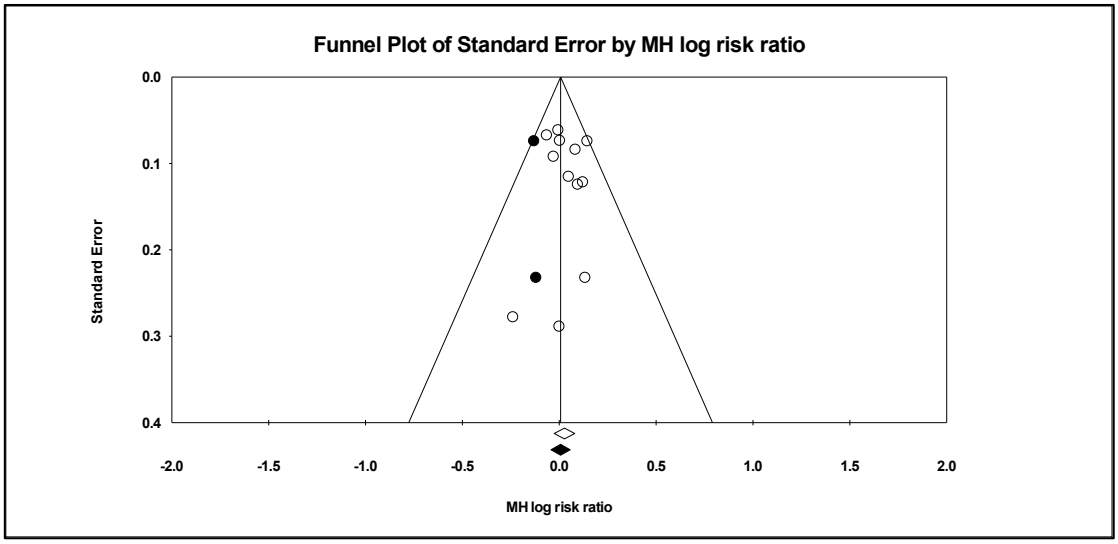


Figure 4.3b: Funnel plot comparison showing existing (o) and imputed (•) studies: clinical response

Analysis of the eleven articles reporting clinical response for time-dependent antibiotics only also showed no statistically significant difference between the treatment groups (n = 1013, RR 1.033, 95% CI 0.977 to 1.092, P = 0.254). No evidence of statistical heterogeneity was found (df = 10, P = 0.702, I^2 = 0.0%).

Analysis of the funnel plot with imputed studies using the Trim and Fill method (Duval and Tweedie, 2000) identifies 3 potentially missing studies but doesn't alter the statistical significance of the result (random effects model, point estimate 1.015, 95% CI 0.952 to 1.08364).

All cause mortality: Twenty three articles reported all-cause mortality (Feld et al., 1977, 1984; Wright et al., 1979; Angus et al., 2000; Hanes et al., 2000; Wysocki et al., 2001; Georges et al., 2005; Rafati et al., 2006; Roberts et al., 2007, 2009a, 2010; Sakka et al., 2007; van Zanten et al., 2007; De Jongh et al., 2008; Chytra et al., 2012; Dulhunty et al., 2013a, 2015; Laterre et al., 2015; Abdul-Aziz et al., 2016; Cotrina-Luque et al., 2016; Zhao et al., 2017; Fan et al., 2017; Ram et al., 2018). Two articles (De Jongh et al., 2008; Roberts et al., 2010) reported no deaths in all patients assessed and are not represented visually in the forest plot. Nineteen of these articles reported studies investigating time-dependent antibiotics, 3 (Feld et al., 1977, 1984; Wright et al., 1979) concentration dependent and one MIC:AUC ratio (Wysocki et al., 2001). No statistically significant difference in mortality was observed (n = 2165,

RR 0.868, 95% CI 0.743 to 1.014, P = 0.075). No evidence of statistical heterogeneity was found (df = 20, P = 0.82, I^2 = 0.0%).

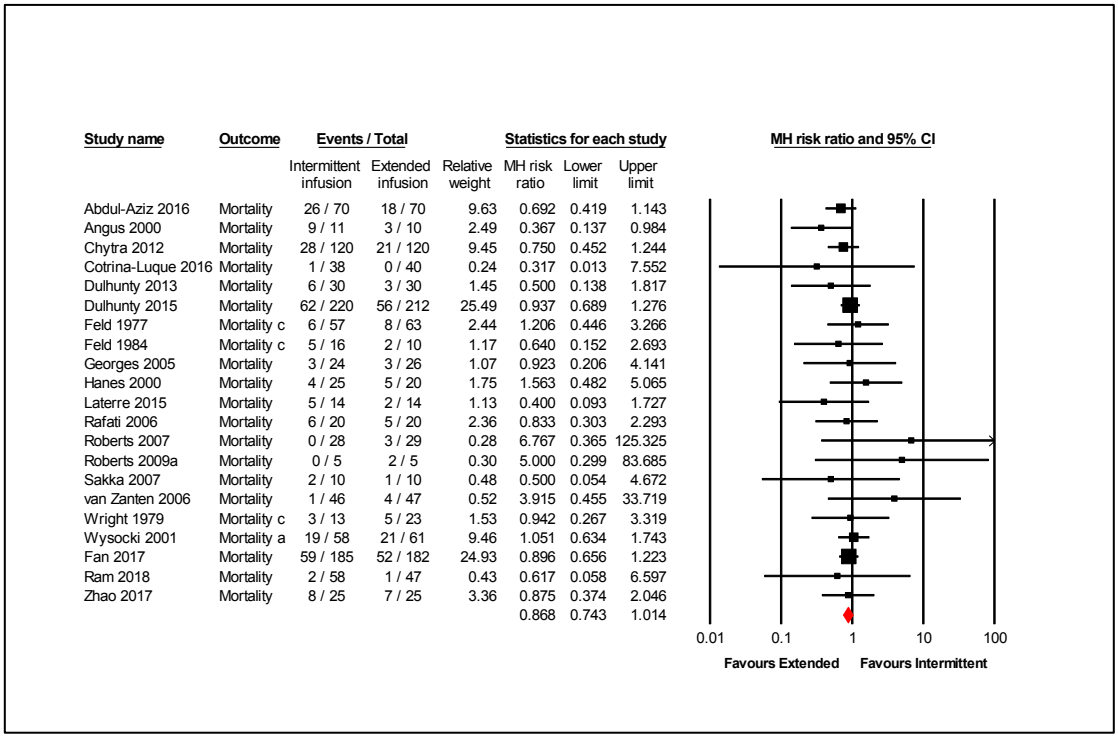


Figure 4.4a: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of mortality of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test

Analysis of the funnel plot showing both observed (white) and imputed studies suggests that there are no missing studies and that no publication bias exists.

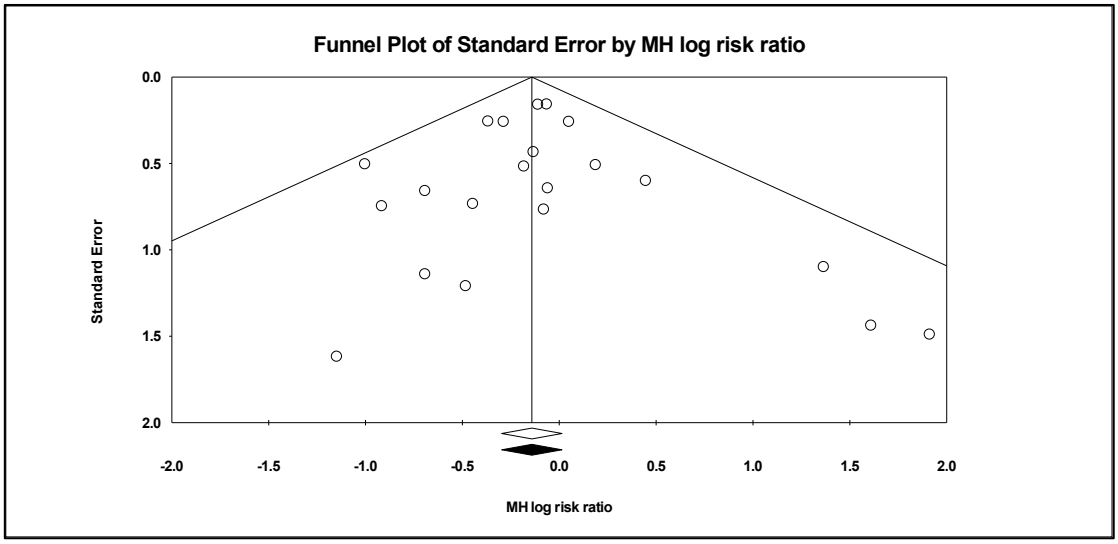


Figure 4.4b: Funnel plot comparison showing existing (o) and imputed (•) studies: mortality

Nineteen articles compared time-dependent antibiotics (Angus et al., 2000; Hanes et al., 2000; Georges et al., 2005; Rafati et al., 2006; Roberts et al., 2007, 2009a, 2010; Sakka et al., 2007; van Zanten et al., 2007; De Jongh et al., 2008; Chytra et al., 2012; Dulhunty et al., 2013a, 2015; Laterre et al., 2015; Abdul-Aziz et al., 2016; Cotrina-Luque et al., 2016; Zhao et al., 2017; Fan et al., 2017; Ram et al., 2018). Two articles (De Jongh et al., 2008; Roberts et al., 2010) reported no deaths in all patients assessed and are not represented visually in the forest plot. A statistically significant difference in mortality was observed (n = 1861, RR 0.844, 95% CI 0.713 to 0.999, p = 0.049). No evidence of statistical heterogeneity was found (df = 16, P = 0.676, I^2 = 0.0%).

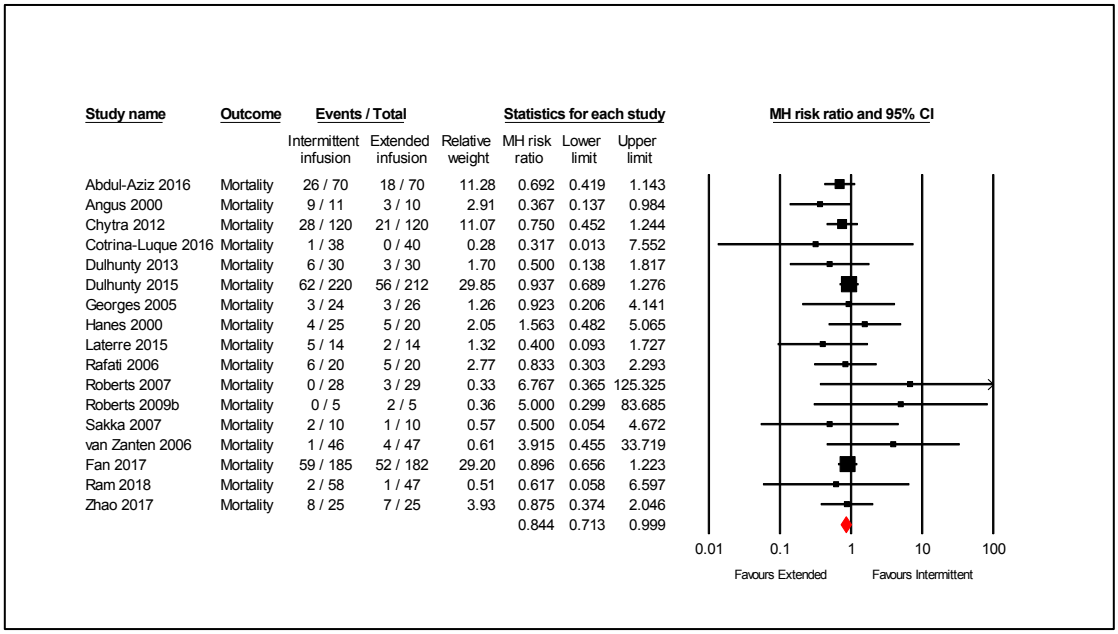


Figure 4.5a: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of mortality of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various time-dependent antibiotics. MH = Mantel-Haenszel test

Analysis of the funnel plot showing both observed (white) and imputed studies suggests that there are no missing studies and that no publication bias exists.

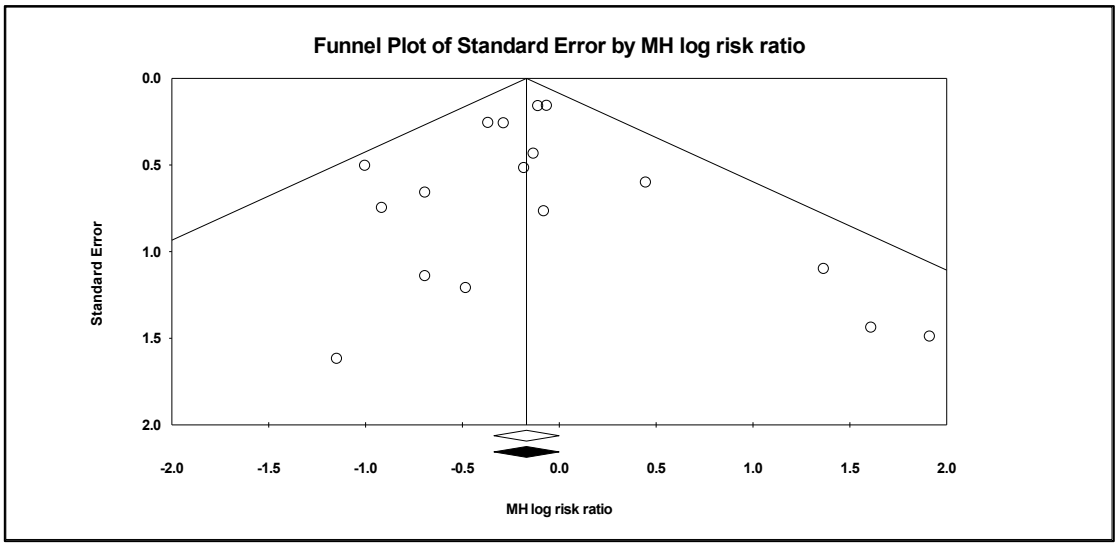


Figure 4.5b: Funnel plot comparison showing existing (o) and imputed (•) studies: mortality (time-dependent only)

Infection recurrence within 14 days of resolution of primary infection: Three articles (Lagast et al., 1983; Roberts et al., 2007; Lü et al., 2013) reported on recurrence of the primary infection within 14 days of stopping the antibiotic therapy. No statistical significant difference was observed (n = 152, RR 1.024, 95% CI 0.219 to 4.793, p = 0.976). No evidence of statistical heterogeneity was found (df = 2, P = 0.670, I^2 = 0.0%).

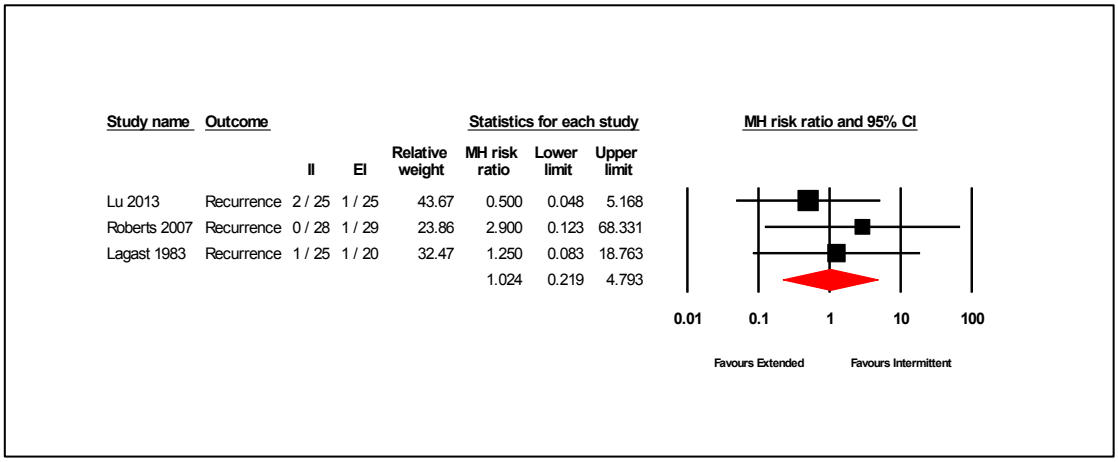


Figure 4.6a: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of infection recurrence of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test

Analysis of the funnel plot showing both observed (white) and imputed (black) studies suggests that some publication bias may exist favouring publication of articles showing a positive effect from extended infusions. Trim and Fill (Duval and Tweedie, 2000) identifies 2 potentially missing studies which do not alter the statistical significance of the result (random effects model, point estimate 0.500, 95% CI 0.145 to 1.718).

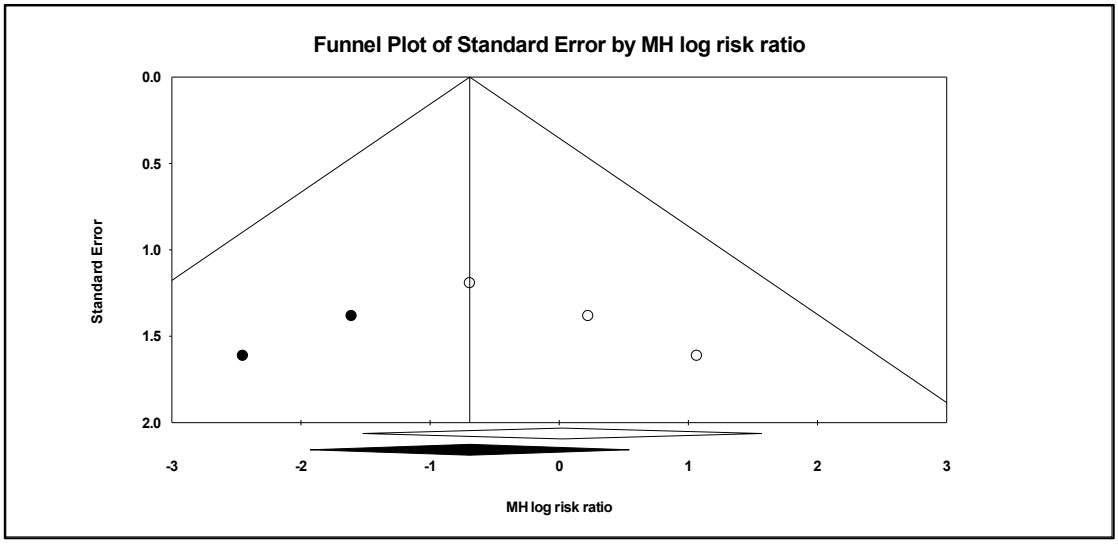


Figure 4.6b: Funnel plot comparison showing existing (o) and imputed (•) studies: infection recurrence

Microbiological/bacteriological cure: Five articles (Georges et al., 2005; Roberts et al., 2007; Adembri et al., 2008; Chytra et al., 2012; Cotrina-Luque et al., 2016) reported microbiological or bacteriological cure.

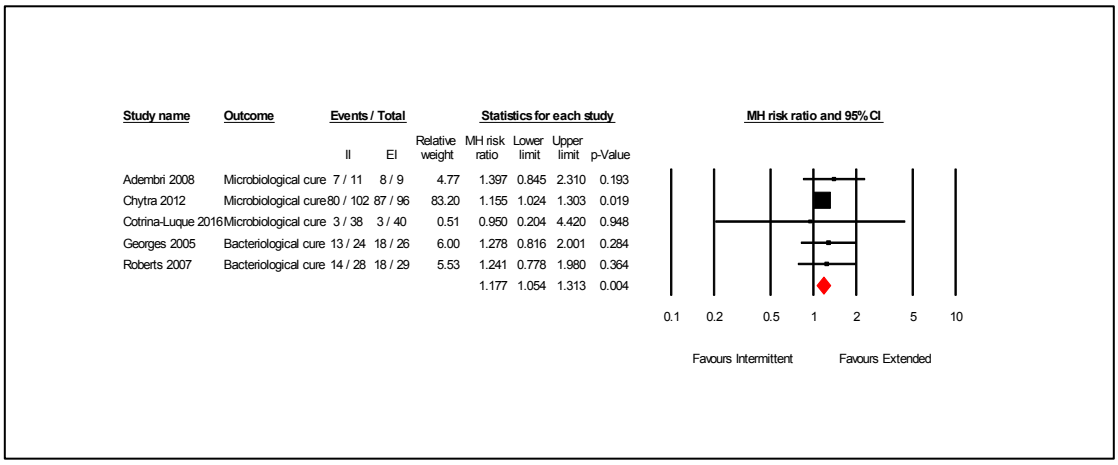


Figure 4.7a: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of microbiological/bacteriological cure of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test

All of these articles reported studies investigating time-dependent antibiotics. A statistically significant difference in microbiological cure was observed (n = 403, RR 1.177, 95% CI 1.054 to 1.313, p = 0.004). No evidence of statistical heterogeneity was found (df = 4, P = 0.936, I^2 = 0.0%).

Analysis of the funnel plot showing both observed (white) and imputed (black) studies suggests that some publication bias may exist favouring publication of articles showing a positive effect from extended infusions. Trim and Fill (Duval and Tweedie, 2000) only identifies 1 potentially missing study which doesn't alter the statistical significance of the result (random effects model, point estimate 1.166, 95% CI 1.048 to 1.299).

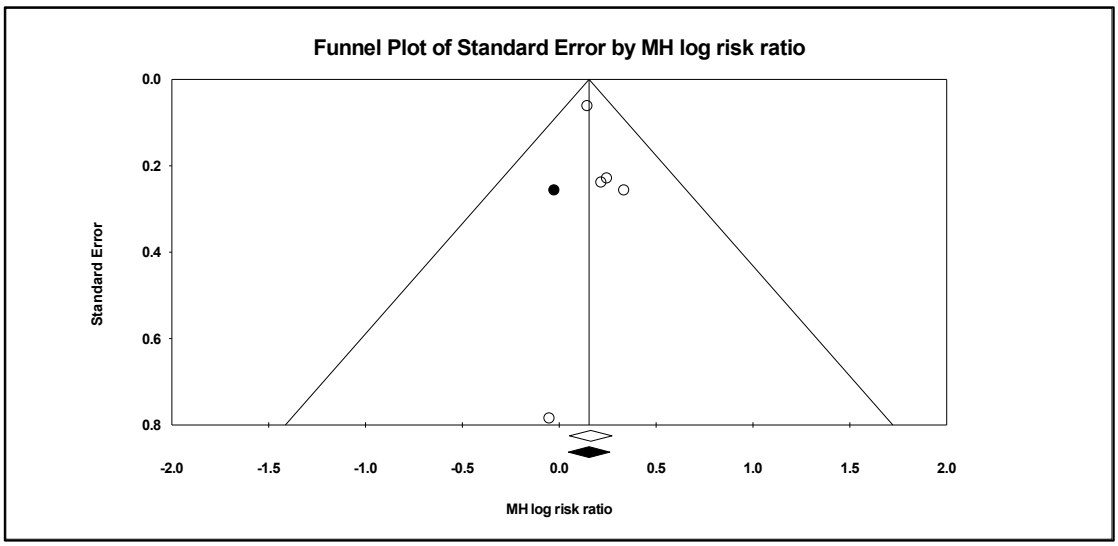


Figure 4.7b: Funnel plot comparison showing existing (o) and imputed (•) studies: microbiological/bacteriological cure

Secondary/super-infection: Nine articles (Feld et al., 1984; Hanes et al., 2000; McNabb et al., 2001; Georges et al., 2005; Roberts et al., 2007; Chytra et al., 2012; Laterre et al., 2015; Cotrina-Luque et al., 2016; Zhao et al., 2017) reported secondary/super-infection with a presumed or proven different organism. Eight of these articles reported studies investigating time-dependent antibiotics, one (Feld et al., 1984) investigated concentration-dependent. No statistically significant difference in secondary/super-infection was observed (n = 596, RR 1.120, 95% CI 0.662 to 1.896, P = 0.673). No evidence of statistical heterogeneity was found (df = 8, P = 0.548, I^2 = 0.0%).

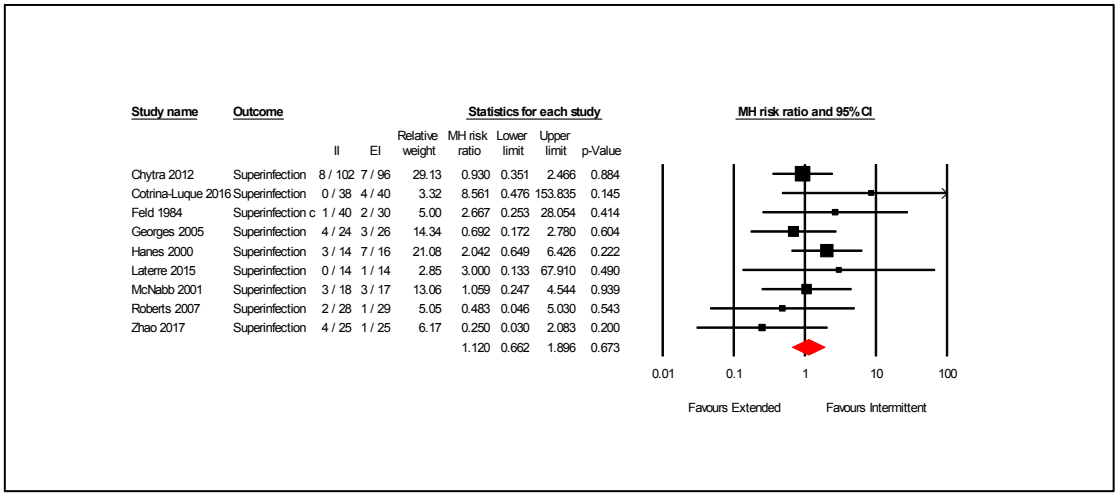


Figure 4.8a: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of super-infection of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test

Analysis of the funnel plot showing both observed (white) and imputed (black) studies suggests that some publication bias may exist favouring publication of articles showing a positive effect from extended infusions. Trim and Fill (Duval and Tweedie, 2000) only identifies 1 potentially missing study which doesn't alter the statistical significance of the result (random effects model, RR 1.044, 95% CI 0.622 to 1.753).

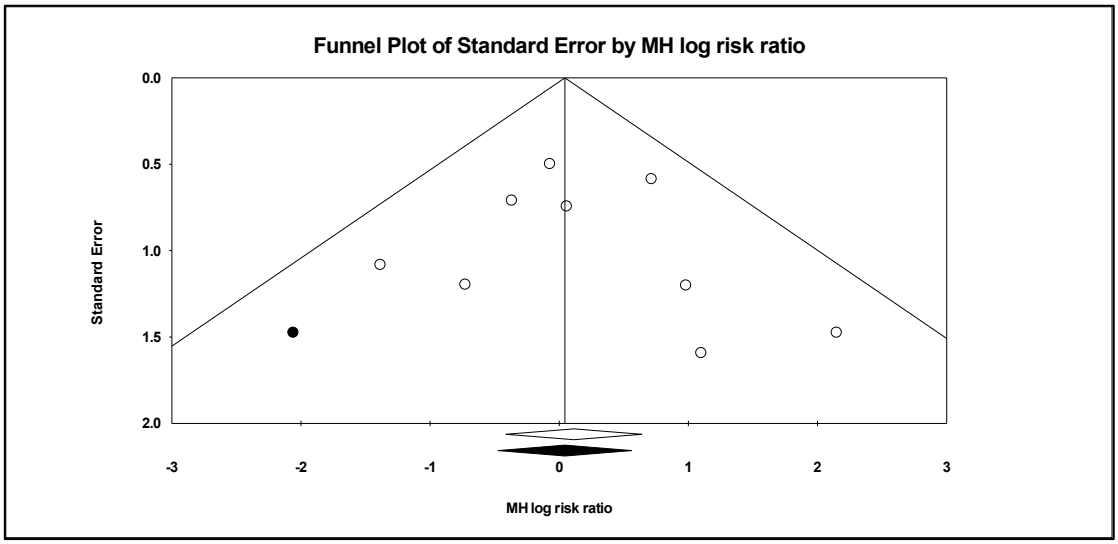


Figure 4.8b: Funnel plot comparison showing existing (o) and imputed (•) studies: super-infection

Number of patients withdrawing as a result of an adverse event (WAE): Four articles (Hanes et al., 2000; Lau et al., 2006; Chytra et al., 2012; Bao et al., 2017) reported WAE. Two articles (Hanes et al., 2000; Chytra et al., 2012) reported no WAEs for all patients assessed and are not represented visually in the forest plot. All of these articles reported studies investigating time-dependent antibiotics. No statistically significant difference in WAE was observed (n = 597, RR 0.970, 95% CI 0.243 to 3.877, P = 0.966). No evidence of statistical heterogeneity was found (df = 1, P = 0.455, I^2 = 0.0%)

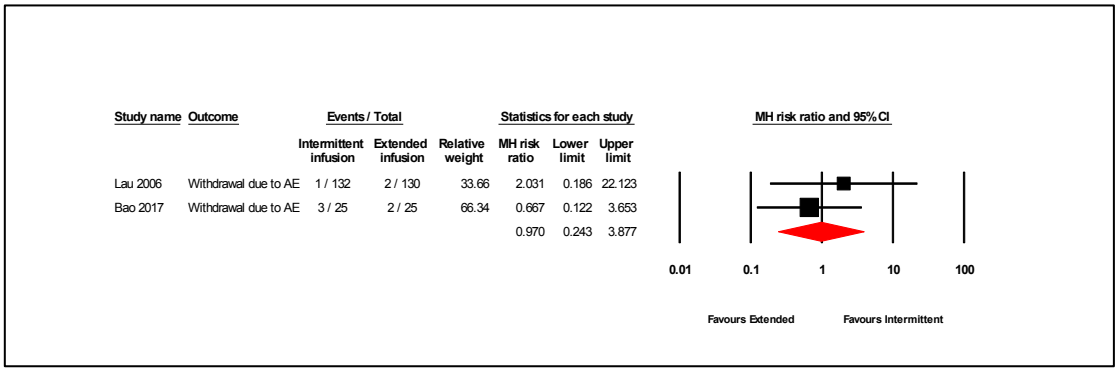


Figure 4.9: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of withdrawal due to adverse events of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test

The number of articles reporting WAE was insufficient to assess for publication bias.

Number of patients with at least one AE: Fourteen articles (Feld et al., 1984; Nicolau et al., 1999b; Wysocki et al., 2001; McNabb et al., 2001; Lau et al., 2006; Sakka et al., 2007; van Zanten et al., 2007; Schmelzer et al., 2013; Dulhunty et al., 2013a, 2015; Laterre et al., 2015; Abdul-Aziz et al., 2016; Bao et al., 2017; Fan et al., 2017) reported AE. Six articles (Nicolau et al., 1999b; Sakka et al., 2007; van Zanten et al., 2007; Dulhunty et al., 2013a; Abdul-Aziz et al., 2016; Fan et al., 2017) reported no AE in all patients assessed and are not represented visually in the forest plot. Eleven of these articles reported studies investigating time-dependent antibiotics, one (Feld et al., 1984) concentration-dependent and two (Wysocki et al., 2001; Schmelzer et al., 2013) MIC:AUC ratio. One article (Wysocki et al., 2001) reported nephrotoxicity separately from other adverse events and therefore no absolute number of patients suffering from an AE in each arm could be identified, this article was not included in the analysis. No statistically significant difference in AE was observed (n = 1625, RR 1.015, 95% CI

0.791 to 1.302, P = 0.907). No significant evidence of statistical heterogeneity was found (df = 6, P = 0.282, I^2 = 19.4%).

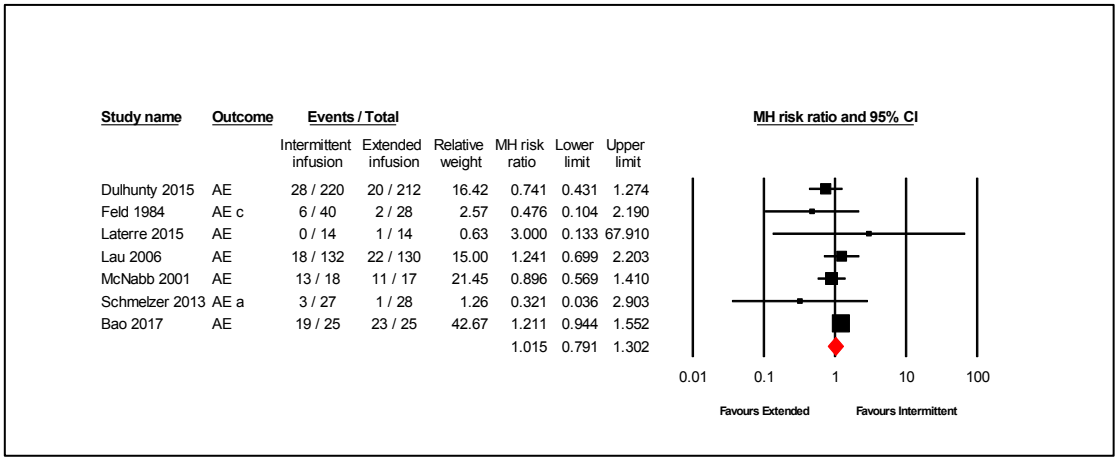


Figure 4.10a: Forest plot depicting the risk ratio and associated 95% confidence interval (95% CI) of adverse events (AE) of patients receiving "Extended" (extended intermittent or continuous infusions (EI)) versus "Intermittent" (bolus or short infusions (II)) of various antibiotics. MH = Mantel-Haenszel test

Analysis of the funnel plot showing both observed (white) and imputed studies suggests that no publication bias exists

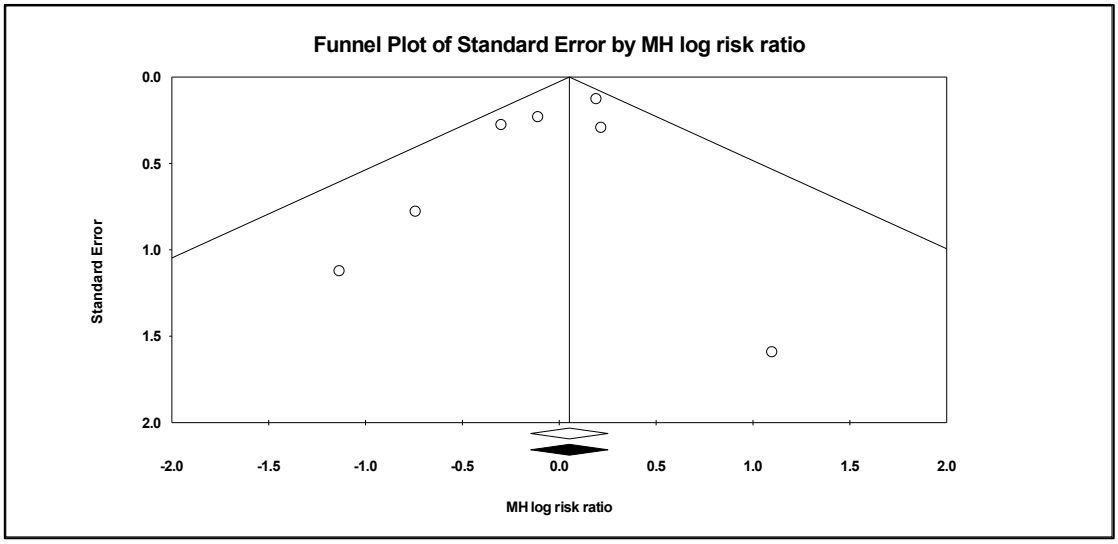


Figure 4.10b: Funnel plot comparison showing existing (o) and imputed (•) studies: adverse events

4.4.3.2 Subgroup analysis

Piperacillin (+/- tazobactam)

Thirteen articles (Pédeboscq et al., 2001; Buck et al., 2005; Lau et al., 2006; Roberts et al., 2009b, 2010, Dulhunty et al., 2013a, 2015; Lü et al., 2013; Abdul-Aziz et al., 2016; Cotrina-Luque et al., 2016; Bao et al., 2017; Fan et al., 2017; Ram et al., 2018) reported on piperacillin used in combination with tazobactam and one article (Rafati et al., 2006) piperacillin alone. The following outcomes were reported in at least one of the articles; AE, clinical cure, clinical response, mortality, microbiological/bacteriological cure, super-infection and WAE.

Adverse events (AE): Five articles (Lau et al., 2006; Dulhunty et al., 2013a, 2015; Abdul-Aziz et al., 2016; Fan et al., 2017) reported AE. Two articles (Dulhunty et al., 2013a, 2015) investigated more than one antibiotic and separate data for piperacillin/tazobactam was unavailable. Two articles (Abdul-Aziz et al., 2016; Fan et al., 2017) reported no AE in either group. No statistically significant difference was observed (n = 716, RR 1.241, 95% CI 0.699 to 2.203, p = 0.461). The number of articles reporting adverse events was insufficient to assess for statistical heterogeneity.

Clinical cure: Five articles (Roberts et al., 2009b; Dulhunty et al., 2013a, 2015; Abdul-Aziz et al., 2016; Cotrina-Luque et al., 2016) reported clinical cure. Two articles (Dulhunty et al., 2013a, 2015) investigated more than one antibiotic and although published data for piperacillin/tazobactam is unavailable the authors were able to provide a breakdown by antibiotic for the published outcomes. One article (Cotrina-Luque et al., 2016) contained discrepancies within the published article and therefore had to be excluded. One article (Roberts et al., 2009b) reported clinical cure in all patients. A statistically significant difference in clinical cure was observed (n = 424, RR 1.395, 95% CI 1.035 to 1.882, p = 0.029). There is evidence of moderate statistical heterogeneity between the studies (df = 2, P = 0.230, I^2 = 31.9%).

Clinical response: Five articles (Buck et al., 2005; Lau et al., 2006; Cotrina-Luque et al., 2016; Bao et al., 2017; Ram et al., 2018) reported clinical response. One article (Ram et al., 2018) investigated more than one antibiotic and separate data for piperacillin/tazobactam was unavailable. One article (Cotrina-Luque et al., 2016) contained discrepancies within the published article and therefore had to

be excluded. No statistically significant difference was observed (n = 332, RR = 0.973, 95% CI 0.869 to 1.090, p = 0.639). No evidence of statistical heterogeneity was found (df = 2, P = 0.521, I^2 = 0.0%).

All-cause mortality: Seven articles (Rafati et al., 2006; Roberts et al., 2010; Dulhunty et al., 2013a, 2015; Cotrina-Luque et al., 2016; Fan et al., 2017; Ram et al., 2018) reported mortality. Three articles (Dulhunty et al., 2013a, 2015; Ram et al., 2018) investigated more than one antibiotic and although published data for piperacillin/tazobactam is unavailable the authors of two articles (Dulhunty et al., 2013a, 2015) were able to provide a breakdown by antibiotic for the published outcomes. One article (Roberts et al., 2010) reported no deaths in either group. No statistically significant difference was observed (n = 824, RR 0.904, 95% CI 0.716 to 1.141, p = 0.396). No evidence of statistical heterogeneity was found (df = 4, P = 0.763, I^2 = 0.0%)

Microbiological/bacteriological cure: One article (Cotrina-Luque et al., 2016) reported microbiological cure and found no statistically significant difference (n = 78, RR 0.950, 95% CI 0.204 to 4.420, p = 0.948). The number of articles reporting microbiological/bacteriological cure was insufficient to assess for statistical heterogeneity.

Super-infection: One article (Cotrina-Luque et al., 2016) reported super-infection and found no statistically significant difference (n = 78, RR 8.561, 95% CI 0.476 to 153.835, p = 0.145). The number of articles reporting super-infection was insufficient to assess for statistical heterogeneity.

Withdrawal due to adverse events (WAE): One article (Lau et al., 2006) reported WAE and no statistically significant difference was observed (n = 262, RR 2.031, 95% CI 0.186 to 22.123, p = 0.561). The number of articles reporting WAE was insufficient to assess for statistical heterogeneity.

Meropenem

Seven articles (Okimoto et al., 2009; Roberts et al., 2009a; Chytra et al., 2012; Dulhunty et al., 2013a, 2015; Abdul-Aziz et al., 2016; Zhao et al., 2017) investigated meropenem. One article (Okimoto et al., 2009) was only available as an abstract in English and assessment of the outcomes was not possible so it was excluded from further analysis. The following outcomes were reported in at least one of the

articles; AE, clinical cure, clinical response, mortality, microbiological/bacteriological cure, super-infection and WAE.

Adverse events (AE): Four articles (Chytra et al., 2012; Dulhunty et al., 2013a, 2015; Abdul-Aziz et al., 2016) investigated AE. Two articles (Dulhunty et al., 2013a, 2015) investigated more than one antibiotic and separate data for meropenem was unavailable. One article (Abdul-Aziz et al., 2016) reported no adverse events in either treatment group. No statistically significant difference in AE was observed (n = 380, RR 0.833, 95% CI 0.374 to 1.855, p = 0.655). The number of articles reporting AE was insufficient to assess for statistical heterogeneity.

Clinical cure: Four articles (Chytra et al., 2012; Dulhunty et al., 2013a, 2015; Abdul-Aziz et al., 2016) reported clinical cure. Two articles (Dulhunty et al., 2013a, 2015) investigated more than one antibiotic and although published data for meropenem is unavailable the authors were able to provide a breakdown by antibiotic for the published outcomes. No statistically significant difference in clinical cure was observed (n = 428, RR 1.214, 95% CI 0.860 to 1.714, p = 0.271). Significant evidence of statistical heterogeneity was found (df = 3, P = 0.071, I^2 = 57.3%)

Clinical response: Three articles (Dulhunty et al., 2013a; Abdul-Aziz et al., 2016; Zhao et al., 2017) reported clinical response. One article (Dulhunty et al., 2013a) investigated more than one antibiotic and separate data for meropenem was unavailable. No statistically significant difference in clinical response was observed (n = 290, RR 1.093, 95% CI 0.936 to 1.276, p = 0.261). No evidence of statistical heterogeneity was found (df = 1, P = 0.837, I^2 = 0.0%)

All-cause mortality: Five articles (Roberts et al., 2009a; Chytra et al., 2012; Dulhunty et al., 2013a, 2015; Zhao et al., 2017) reported mortality. Two articles (Dulhunty et al., 2013a, 2015) investigated more than one antibiotic and although published data for meropenem is unavailable the authors were able to provide a breakdown by antibiotic for the published outcomes. One article (Dulhunty et al., 2013a) reported no deaths in either group. No statistically significant difference in mortality was observed (n = 445, RR 0.816, 95% CI 0.586 to 1.136, p = 0.229). No evidence of statistical heterogeneity was found (df = 3, P = 0.630, I^2 = 0.0%).

Microbiological/bacteriological cure: One article (Chytra et al., 2012) reported microbiological cure and no statistically significant difference between treatment groups was observed (n = 198, RR 1.148, 95% CI 0.936 to 1.408, p = 0.184). The number of articles reporting microbiological/bacteriological cure was insufficient to assess for statistical heterogeneity.

Super-infection: Two articles (Chytra et al., 2012; Zhao et al., 2017) reported super-infection and no significant statistical difference between treatment groups was observed (n 248, RR 0.682, 95% CI 0.227 to 2.049, p = 0.495). No evidence of statistical heterogeneity was found (df = 1, P = 0.267, I^2 = 18.9%)

Withdrawal due to adverse events (WAE): One article (Chytra et al., 2012) reported WAE but no events were observed in either group.

Vancomycin

Two articles (Wysocki et al., 2001; Schmelzer et al., 2013) investigated the use of vancomycin. The following outcomes were reported in at least one of the articles; AE, clinical response, all-cause mortality.

Adverse events (AE): Both articles reported the adverse events, specifically the incidence of nephrotoxicity. No statistically significant difference in nephrotoxicity was observed (n = 174, RR 0.775, 95% CI 0.372 to 1.612, p = 0.494). No evidence of statistical heterogeneity was found (df = 1, P = 0.403, I^2 = 0.0%).

Clinical response: One article (Wysocki et al., 2001) reported clinical response (n = 119, RR 0.971, 95% CI 0.811 to 1.163, p = 0.750)

All-cause mortality: One article (Wysocki et al., 2001) reported mortality (n = 119, RR 1.051, 95% CI 0.634 to 1.743, p = 0.847)

Ceftazidime

Nine articles (Lipman et al., 1999; Nicolau et al., 1999a, 1999b, 2001; Angus et al., 2000; Hanes et al., 2000; McNabb et al., 2001; Lubasch et al., 2003; Ram et al., 2018) investigated the use of ceftazidime.

One article (Ram et al., 2018) was primarily a study of piperacillin/tazobactam and only 6% (7/105) of patients received ceftazidime, a breakdown of results by antibiotic was unavailable at the time of thesis write up and so this study could not be further analysed. The following outcomes were reported in at least one of the articles; AE, clinical cure, clinical response, mortality, microbiological/bacteriological cure and super-infection.

Adverse events (AE): Six articles (Lipman et al., 1999; Nicolau et al., 1999a, 1999b, 2001; McNabb et al., 2001; Lubasch et al., 2003) reported adverse events. Two articles (Lipman et al., 1999; Nicolau et al., 1999a) reported adverse events but by event not patient and were therefore not assessable and so not included. Two articles (Nicolau et al., 2001; Lubasch et al., 2003) reported AE as a total number rather than by treatment arm however the events from Nicolau et al. 2001 are reported in full in McNabb et al. 2001. One article (Nicolau et al., 1999b) reported no adverse events in either treatment arm. No statistically significant difference in AE was observed (n = 59, RR 0.896, 95% CI 0.569 to 1.410, p = 0.635). The number of articles reporting AE was insufficient to assess for statistical heterogeneity.

Clinical cure: One article (Nicolau et al., 2001) reported clinical cure and no statistically significant difference between treatment groups was observed (n = 35, RR 1.235, 95% CI 0.520 to 2.936, p = 0.632). The number of articles reporting clinical cure was insufficient to assess for statistical heterogeneity.

Clinical response: Three articles (Hanes et al., 2000; Nicolau et al., 2001; Lubasch et al., 2003) reported clinical response. No statistically significant difference in clinical response was observed (n = 146, RR 1.021, 95% CI 0.906 to 1.152, p = 0.729). No evidence of statistical heterogeneity was observed (df = 2, P = 0.407, I^2 = 0.0%).

All-cause mortality: One article (Angus et al., 2000) reported mortality and a statistically significant difference in mortality was observed (n = 21, RR 0.367, 95% CI 0.137 to 0.984, p = 0.046). The number of articles reporting clinical cure was insufficient to assess for statistical heterogeneity.

Microbiological/bacteriological cure: One article stated "microbiological eradication" as a primary outcome but this was reported as "microbiological response" in the results of the article so no articles provided results analysable for this outcome.

Super-infection: Three articles (Hanes et al., 2000; McNabb et al., 2001; Nicolau et al., 2001) reported super-infection. One article (Nicolau et al., 2001) was not analysed further as it did not report the actual number of events in each treatment arm, results from this study for super-infection were available in the article by McNabb et al.. No statistically significant difference in super-infection rate was observed (n = 65, RR 1.588, 95% CI 0.645 to 3.910, p = 0.314). No evidence of statistical heterogeneity was found (df = 1, P = 0.487, I^2 = 0.0%).

Table 4.3: Summary of meta-analysis results

Outcome	Group	n	MH RR	95% CI		P value	Statistical heterogeneity		Assessment of publication bias		
				LL	UL		df	I^2 (%)	Imputed studies	Point estimate	95% CI
Clinical cure											
	All	1083	1.231	1.081	1.403	0.002	8	9.4	4	1.109	0.952 to 1.293
	Time only	1083	1.231	1.081	1.403	0.002	8	9.4	4	1.109	0.952 to 1.293
	P/T	424	1.395	1.035	1.882	0.029	2	31.9			
	M	428	1.214	0.860	1.714	0.271	3	57.3			
	V										
	C	35	1.235	0.520	2.936	0.632	NA	NA			
Clinical response											
	All	1132	1.027	0.974	1.083	0.319	11	0.0	2	1.007	0.958 to 1.058
	Time only	1013	1.033	0.977	1.092	0.254	10	0.0	3	1.011	0.960 to 1.064
	P/T	332	0.973	0.869	1.090	0.639	2	0.0			
	M	290	1.093	0.936	1.276	0.261	1	0.0			
	V	119	0.971	0.811	1.163	0.750	NA	NA			
	C	146	1.021	0.906	1.152	0.729	2	0.0			
All cause mortality											
	All	2165	0.868	0.743	1.014	0.075	20	0.0	0	0.868	0.743 to 1.014
	Time only	1861	0.844	0.713	0.999	0.049	16	0.0	0	0.844	0.743 to 0.999
	P/T	824	0.904	0.716	1.141	0.396	4	0.0			
	M	445	0.816	0.586	1.136	0.229	3	0.0			
	V	119	1.051	0.634	1.743	0.847	NA	NA			
	C	21	0.367	0.137	0.984	0.046	NA	NA			
AE											
	All	1625	1.015	0.791	1.302	0.907	6	19.4	0	1.015	0.791 to 1.302
	Time only	1502	1.068	0.859	1.329	0.551	4	11.1	0	1.068	0.859 to 1.329
	P/T	716	1.241	0.699	2.203	0.461	NA	NA			
	M	380	0.833	0.374	1.855	0.655	NA	NA			
	V										
	C	59	0.896	0.569	1.410	0.635	NA	NA			
SAE											
	All	482	0.858	0.515	1.431	0.558	1	0.0	NA	NA	NA
	Time only	482	0.858	0.515	1.431	0.558	1	0.0	NA	NA	NA
	P/T										
	M										
	V										
	C										
WAE											
	All	597	0.970	0.243	3.877	0.966	1	0.0	NA	NA	NA
	Time only	597	0.970	0.243	3.877	0.966	1	0.0	NA	NA	NA
	P/T	262	2.031	0.186	22.123	0.561	NA	NA			
	M										
	V										
	C										

Table 4.3: Summary of meta-analysis results (cont.)

Outcome	Group	n	MH RR	95% CI		P value	Statistical heterogeneity		Assessment of publication bias		
				LL	UL		df	I^2 (%)	Imputed studies	Point estimate	95% CI
Infection recurrence											
	All	152	1.024	0.219	4.793	0.976	2	0.0	1	0.500	0.145 to 1.718
	Time only	152	1.024	0.219	4.793	0.976	2	0.0	1	0.500	0.145 to 1.718
	P/T										
	M										
	V										
	C										
Microbiological/bacteriological cure											
	All	403	1.177	1.054	1.313	0.004	4	0.0	1	1.166	1.048 to 1.299
	Time only	403	1.177	1.054	1.313	0.004	4	0.0	1	1.166	1.048 to 1.299
	P/T	78	0.950	0.204	4.420	0.948	NA	NA			
	M	198	1.148	0.936	1.408	0.184	NA	NA			
	V										
	C										
Super-infection											
	All	596	1.120	0.662	1.896	0.673	8	0.0	1	1.044	0.622 to 1.753
	Time only	526	1.070	0.623	1.837	0.806	7	0.0	0	1.070	0.623 to 1.837
	P/T	78	8.561	0.476	153.835	0.145	NA	NA			
	M	248	0.682	0.227	2.049	0.495	1	18.9			
	V										
	C	65	1.588	0.645	3.910	0.314	1	0.0			

Key: n = number of patients, MH RR = Mantel-Haenszel risk ratio, 95% CI = 95% confidence interval, LL = lower limit, UL = upper limit, df = degrees of freedom, All = all antibiotics, Time only = time-dependent action antibiotics only, P/T = piperacillin (+/- tazobactam), M = meropenem, V = vancomycin, C = ceftazidime, grey shaded boxes = no data, NA = not enough data to run analysis

4.4.4 Sensitivity analysis for primary and significant outcomes

4.4.4.1 Effect of removing individual studies on outcomes

The removal of individual studies had no effect on the statistical significance of the primary outcomes. Clinical cure still favours CI (RR range 1.192 – 1.335 with associated p-value range of <0.001 to 0.012) and SAE shows no difference between administration methods (RR range 0.789 – 1.250 with associated p-value range of 0.411 to 0.714).

Mortality remains not statistically significant (RR range 0.846 – 0.889 with associated p-value range of 0.053 to 0.160). Analysis of mortality in articles investigating only time-dependent antibiotics had previously shown a difference between administration methods favouring CIs, re-analysis with individual studies removed renders a neutral result favouring neither method in 11 out of 17 instances (RR range 0.808 – 0.866 with associated p-value range of 0.036 to 0.114). In addition to the 17 articles analysed, two articles (De Jongh et al., 2008; Roberts et al., 2010) reported no deaths in either group. Only the removal of the study by Chytra et al affects the statistical significance of microbiological/bacteriological cure (RR range 1.170 to 1.287 with associated p-value range of 0.004 to 0.065)

4.4.4.2 Using fixed effect rather than random effect

The random effects model will potentially increase the role that smaller studies will play in a meta-analysis when compared to using fixed effects. Using fixed effect analysis on the primary outcomes of clinical cure and SAE has no affect on the statistical significance. Clinical cure remains in favour of CIs (RR 1.236, 95% CI 1.088 to 1.403, p-value 0.001) and SAE still shows no difference between administration methods (RR 0.853, 95% CI 0.513 to 1.421, p-value 0.542)

Mortality remains neutral (RR 0.879, 95% CI 0.753 to 1.026, p-value 0.102). However, using the fixed effects model on mortality associated with time-dependent antibiotics renders the previously statistically significant result neutral suggesting no difference between administration methods (RR 0.858, 95% CI 0.726 to 1.013, P = 0.071). Microbiological/bacteriological cure still favours CIs (RR 1.188, 95% CI 1.050 to 1.344, p-value 0.006).

4.4.4.3 Using odds ratio rather than risk ratio

Using odds ratio (OR) as the measure of effect on the primary outcomes of clinical cure and SAE has no affect on the statistical significance. Clinical cure remains in favour of CIs (OR 1.678, 95% CI 1.209 to 2.329, p-value 0.002) and SAE still shows no difference between administration methods (OR 0.836, 95% CI 0.469 to 1.488, p-value 0.542)

Mortality remains neutral (OR 0.832, 95% CI 0.672 to 1.030, p-value 0.091). However, using odd ratio to analyse mortality associated with time-dependent antibiotics renders the previously statistically significant result neutral, favouring neither method of administration (OR 0.802, 95% CI 0.637 to 1.010, P = 0.061). Microbiological/bacteriological cure still favours CIs (OR 2.036, 95% CI 1.204 to 3.444, p-value 0.008).

4.4.4.4 Analysing only articles looking at continuous infusions

Analysis of articles just reporting studies investigating continuous infusions, i.e. excluding those looking at extended intermittent infusions, did not affect the statistical significance of the primary outcomes; clinical cure still favours extended infusions (RR 1.231, 95% CI 1.081 to 1.403, p-value = 0.002) and SAE remained neutral (RR 0.789, 95% CI 0.448 to 1.389, p-value = 0.411).

Mortality remained neutral (RR 0.861, 95% CI 0.719 to 1.031, p-value = 0.103), the statistical significance of mortality associated with just time-dependent antibiotics however was affected; this result no longer favoured either administration method (RR 0.826, 95% CI 0.675 to 1.009, p-value = 0.062). Microbiological cure remained in favour of CIs (RR 1.178, 95% CI 1.055 to 1.315, p-value = 0.004).

4.4.4.5 Including vancomycin in "time only" analysis

Two articles investigated vancomycin (Wysocki et al., 2001; Schmelzer et al., 2013) and one Linezolid (Adembri et al., 2008), the remaining articles investigating time-dependent action antibiotics all investigated β-lactams. All though all time-dependent in action the efficacy of β-lactams and linezolid relates entirely or in part to T>MIC were as the efficacy of vancomycin relates solely to AUC:MIC. It

was decided *a priori* to exclude vancomycin from "time only" analysis as a major part of the justification for extended infusions is to increase the T>MIC.

Neither vancomycin article reported the primary outcomes or microbiological/bacteriological cure therefore the results for these outcomes remain unchanged. Analysis of mortality no longer favours extended infusions (RR 0.863, 95% CI 0.736 to 1.012, p-value = 0.071).

4.5 Discussion

4.5.1 Author's interpretation

4.5.1.1 Summary of the main findings

A statistical significant difference in both clinical cure and microbiological/bacteriological cure was observed between extended and intermittent infusions of antibiotics favouring extended infusions. No difference in all-cause mortality, clinical response, super-infection or infection recurrence was observed between administration methods. Nor was any difference in adverse events, serious adverse events or withdrawal due to adverse events found between administration methods. Analysis of only antibiotics exhibiting time-dependent action observed a statistically significant difference in all-cause mortality, clinical cure and microbiological/bacteriological cure between extended and intermittent infusions favouring extended infusions. Analysis of all other primary and secondary outcomes found no difference between administration methods. Sub-group analysis of all primary and secondary outcomes for individual antibiotics observed a statistically significant difference between administration methods associated with piperacillin (+/- tazobactam) and clinical cure and ceftazidime and all-cause mortality again favouring extended infusions. No differences were found for all other outcomes and the individual antibiotics investigated. Sensitivity analysis supported the positive findings associated with both clinical cure and microbiological/bacteriological cure and extended infusions as the difference was observed in both random and fixed effect models and with both odds and risk ratio analysis. This is however not the case for time-dependent action antibiotics and all-cause mortality, the difference was not observed in both random and fixed effects models nor was it seen when using odd ratio rather than risk ratio.

4.5.1.2 Overview of the nature of the articles included

As shown by this systematic review, interest in the potential benefits of extended infusions of antibiotics is wide reaching and the subject has been intensively investigate for at least the last four decades. Since 2003, on average, 2 RCTs have been published each year with 12 published in the last 5 years. Many different benefits have been postulated predominately focusing on two general themes, efficacy and safety. Investigators have also looked into other, non-clinical, outcomes such as length of stay, reducing the total amount of antibiotic used or cost savings. Reducing antimicrobial resistance is a newer emerging theme.

Forty articles were identified as suitable for inclusion in the systematic review and what was immediately apparent was the sheer diversity in the way the topic has been approached. Across the 40 articles, 16 different antibiotics have been investigated as extended infusions. This is usually as the only study drug but sometimes with a second antibiotic given to both groups by a standard method to increase the spectrum of activity. A number of more recent studies investigated more than one antibiotic under the umbrella of "β-lactams" (Dulhunty et al., 2013a, 2015; Abdul-Aziz et al., 2016) allowing individual sites in multi-centred international studies to use antibiotics in line with their local antimicrobial guidelines. Although there was a great number of antibiotics investigated the majority, thirty-three, of the articles focused solely on β-lactams. This is both logical and evidenced based as not only do β-lactams exhibit time-dependent action but the main pk/pd parameter aligned with efficacy is T>MIC (Ambrose et al., 2007). Of the remaining 7 articles 4 investigated aminoglycosides (Feld et al., 1977, 1984; Bodey et al., 1979; Wright et al., 1979). Although this would now seem illogical, at the time in the mid to late 1970s, the influence of the pk/pd relationship on the efficacy of antibiotics was poorly appreciated. Harry Eagle had postulated that continuous infusions of penicillins would be beneficial in the 1950s (Eagle et al., 1953) but it wasn't really until the 1990s that the different groups of antibiotics and their pk/pd parameters was being fully understood (Craig, 1998).

Aside from the antibiotic being investigated most studies either did not discuss or allowed concomitant prescribing of non-study antibiotics at the treating clinicians discretion. Where discussed, some articles compared additional antibiotics used by class in both treatment and control

groups to assess for significant differences between groups but many did not. One article described the need to prescribe non-study antibiotics as clinical failure (Bao et al., 2017). Substantial differences in the approach to concomitant antibiotic use make interpretation of the overall result of the meta-analysis complex. In many cases a microorganism isn't cultured and so it would be impossible to state categorically which antibiotic had been effective and therefore which infusion method is superior.

Another source of variation throughout the articles is the patient group selected. Although the systematic review identified articles investigating patients with sepsis, this is a very generic term. Some articles reported studies investigating sepsis in general regardless of the source (Dulhunty et al., 2015) others focused on specific end organ sites e.g. the lungs (van Zanten et al., 2007) and others on specific micro-organisms e.g. pseudomonas (Cotrina-Luque et al., 2016). The patient group selected also varied, frequently it focused on "critically ill" patients regardless of premorbid state but some articles looked at specific patient groups, for example with malignancies +/- neutropenia (Bodey et al., 1979), trauma (Hanes et al., 2000) or chronic co-morbidities such as pneumonia in the context of patients with chronic obstructive airways disease (van Zanten et al., 2007). To complicate this further, as described in chapter 1, the definition of sepsis has evolved over time. What an article pre-1992 describes as sepsis will potentially include a very different cohort of patients from those included in a study developed after the 2016 sepsis-3 definition (Singer et al., 2016). An article published between 1992 and 2016 may well describe a cohort of patients as having "severe sepsis" (Bone et al., 1992), a sub-group of septic patients that had not previously been defined, but that have now been removed from the most recent definition.

The affect that the factors described above will have on the results of the meta-analysis is hard to precisely quantify and can only really be highlighted so the reader can make their own judgement. However, due to the volume of RCTs in the literature future systematic reviews could afford to be more specific with their inclusion criteria and focus the review to specific groups of antibiotics, definitions of sepsis or sources/causes of sepsis.

4.5.1.3 Assessment of risk of bias within each study

It is no surprise that no single study was completely without some elements of bias. It isn't as simple as saying that many studies were poor quality and/or at a high risk of bias though. Approximately 50% of the individual assessments (136 out of 280, see table 4.1) were judged to be at unclear risk. This was generally because the information just wasn't available from the published article. There may be no excuse for articles published in the last few years, but the concept of reporting standard items in a randomised controlled trial is relatively new. The CONSORT statement in the mid 1990s set out to try to formalise how RCTs were reported and is now on its third incarnation (Schulz et al., 2010). It is also true to say that the idea of grouping RCTs together to look for effects that individual studies may not have been powered for is also relatively new. Although the meta-analysis has been around in medicine since the early 1900s (Pearson, 1904), the idea of a systematic review of the literature which is then analysed, was only really introduced with the formation of the Cochrane collaboration in the early 1990s. The tool for assessing the risk of bias in randomised trials currently used was only published in 2011 (Higgins et al., 2011).

The most common potential sources of bias were associated with blinding. This was primarily "performance bias" associated with the blinding of patients and researcher involved in direct patient care but also to a lesser extent with "detection bias" associated with those assessing the outcome of the study. The studies in this review all investigated different methods of intravenous administration of the same active agent rather than comparing an active agent to a placebo. To adequately blind these studies at the point of care both the treatment and control groups would require a placebo i.e. an active extended infusion and an inactive short infusion/bolus and visa versa. Trying to provide two placebos would generally be deemed prohibitively complicated and expensive. Only one study group in the articles included in the systematic review adequately described "double-blinding" their study, i.e. blind both at the point of care and at the point of assessment, to be judged at low risk of both performance and detection bias. After publishing the study protocol (Dulhunty et al., 2013b) the group then went on to do a small scale RCT in part aimed at validating the blinding process (Dulhunty et al., 2013a) before finally stepping up to an adequately powered study (Dulhunty et al., 2015). "Single-blinding", usually at the point of assessing the outcome to minimise detection bias, is

comparably easy as this assessment can be done away from the clinical environment but most articles either simply stated that they were open-label/un-blinded or did not comment on that aspect of the study. Three articles described their studies as single-blinded but one failed to state which part of the process was blinded/un-blinded. Although a lack of blinding is predictable this is none the less disappointing and it can be seen as a major flaw in these studies. Clinicians often feel strongly about the studies they are involved in and may have deeply ingrained opinions as to which therapy option they think is superior, this can lead to patients being withheld from studies for fear that they will be enrolled into the "inferior" arm.

Of the remaining areas of potential bias assessed "attrition bias", the loss of patients to follow up, was globally managed well with over 50% of articles clearly accounting for any patients that were not included in the final analysis and so deemed to be at low risk of bias. Many articles presented intention to treat (ITT) analysis, where all enrolled patients regardless of whether they complete the study or not, were included in the assessments of the result. When only the patients that complied fully with the study were assessed (referred to as "per protocol" assessment) frequently the missing patients were accounted for.

The catchall section entitled "other bias" is there to allow for the comparison of biases associated with the specific question being asked. The main areas of interest for this review were concomitant non-study antibiotic use and pharmaceutical industry influence. Only 4 articles were deemed to be at low risk of bias, three of which were published in the last 2 years, with the majority being deemed to be at unclear risk. As discussed previously non-study antibiotic use complicates interpretation of the results of the meta-analysis. As for funding and declarations, it would be unfair to say that just because a study or one of its authors has an association with the pharmaceutical industry it is therefore inherently biased and therefore at high risk. Large studies cost vast sums of money and would not be possible without external funding sources, be that national charitable/research organisations or the private sector. Both these examples will have their own reasons for providing funding but it is generally unclear what level of influence the funding organisation has had in the over all design and conduct of the study.

4.5.1.4 Review of outcomes

Clinical cure and clinical response

A statistical difference in clinical cure was observed favouring extended over intermittent infusions of antibiotics. This difference was still present when only time-dependent action antibiotics were analysed and was also seen in subgroup analysis of piperacillin/tazobactam but wasn't present in the other individual antibiotics examined. Sensitivity analysis carried out to assess the influence of choice of statistical methods appears to support the observed difference; the use of both random or fixed effects models and odds or risk ratio favour extended infusions.

This appears to be the first systematic review to separate out clinical cure from clinical response (a combination of both clinical cure and clinical improvement). Frequently previous systematic reviews have combined papers reporting cure with those reporting response. Other reviews have looked at clinical failure (usually defined as the opposite of clinical response i.e. no improvement, worsening or death). In keeping with previous reviews this meta-analysis has shown no difference in clinical response rate.

The different ways in which clinical success has been reported in the RCTs was not anticipated *a priori*. The decision to include both clinical cure and clinical response as separate results for analysis has unearthed a subtle but potentially important finding.

There are a number of reasons why these two outcomes may differ. Firstly, "response" is a much more general outcome than "cure". To be defined as responding positively to a treatment regimen a participant merely has to show some sign of improvement, be that biochemically, radiologically and/or clinically. This outcome is much more open to researcher interpretation than "cure" were generally all signs of the original infection need to have resolved. This leads on to the second point, even a sub-optimal treatment may lead to a positive clinical response and therefore improvement. This potentially generates background noise; in groups of less severely unwell patients, just looking for a positive response might not provide a rigorous enough test of the different administration methods to identify significant differences in efficacy.

Another important consideration is the RCTs themselves; eleven reported clinical cure and 12 reported clinical response but only 3 RCTs reported both outcomes (Nicolau et al., 2001; Roberts et al., 2007; Chytra et al., 2012). Considering the limited overlap there may have been fundamental differences between the 2 sets of RCTs, such as choice of antibiotic or patient group, that account for the differences seen between outcomes in the meta-analysis. All three articles reporting both outcomes favoured extended infusions when assessing for either clinical cure or clinical response, one article (Roberts et al., 2007) reported a statistically significant difference in cure favouring extended infusions. This last finding reinforces the idea that choice of clinical response in studies of antibiotic administration may not be sensitive enough to identify a clinically relevant difference in the methods.

Some articles reported on β-lactams in general. In practical terms this would have allowed for greater recruitment, as each participating hospital would have been able to follow its own antibiotics policy based on local resistance patterns. One such article (Abdul-Aziz et al., 2016) also reports the breakdown of outcomes by individual antibiotic. The authors of two further articles were contacted and were able to supply detailed breakdown. From these three RCTs a large amount of data from some of the biggest and more methodologically robust studies was available for analysis by antibiotic. Sub group analysis of individual antibiotics with respect to clinical cure revealed some interesting results to be considered. Firstly, although piperacillin, a penicillin, had shown a statistically significant difference between the administration methods the bigger the study the less of a favourable effect was found hence the unfavourable heterogeneity (I^2 = 31.9%). The second observation was that clinical cure with different methods of meropenem administration was not statistically significant; this raises the question of whether all β-lactams are "equal" and if studies should be investigating individual antibiotics rather than broader classes. This later consideration is potentially supported by the literature. It has been suggested that the amount of time different antibiotics need to spend above the MIC in each dosing interval varies with penicillins (e.g. piperacillin) requiring greater time above the MIC than carbapenems (e.g. meropenem) (Drusano, 2004). It is possible that a positive effect from one class is muted by an underwhelming effect by others. It is possible that a greater beneficial effect may be seen with longer infusions of penicillins compared to other β-lactams.

Clinical heterogeneity, the differences in design, participants, interventions, etc between studies, is low. The articles predominantly investigate continuous infusions of β-lactams and were published in the last decade. The risk of statistical heterogeneity, detectable if the variation between the results of the studies is greater than that expected by chance, is low. Visual assessment of the funnel plot looking for publication bias reveals asymmetry with a lack of studies on the left-hand side. Using the trim and fill method (Duval and Tweedie, 2000) to impute missing studies identifies 4 possible additional studies. Including these studies in the over all analysis and we now find no difference in clinical cure between the administration methods. This later point reduces the certainty with which one can support the overall finding.

Adverse events (AE, SAE and WAE)

No differences in the incidence of all types of adverse events were found between the different administration methods. There was however a high incidence of clinical heterogeneity between the articles. The rate and relevance of adverse events (AE), serious adverse events (SAE) and withdrawals due to adverse events (WAE) were hard to interpret for the following reasons,

1. The definition of an AE and whether it was serious or not differed greatly between articles.
2. Only one article (Bao et al., 2017) reported all 3 outcomes, i.e. AE, SAE and WAE.
3. Some articles reported all adverse events, others reported only the events that they thought were related to the study drug and yet another small group reported both.
4. Some articles only reported one type of adverse event e.g. nephrotoxicity (Schmelzer et al., 2013).
5. Frequently documented as events rather than the number per patient for example a study of 10 patients may have 5 AEs but all in one patient.

The first 4 factors listed above led to very different reporting rates and hence some studies showed no AE (Abdul-Aziz et al., 2016; Fan et al., 2017) and some suggesting nearly every patient suffers an AE (Bao et al., 2017).

As the unit of measure for this review was the patient and many adverse events were reported as events many data could not be included in the meta-analysis.

All cause mortality

Analysis including all antibiotics found no difference in mortality between the two methods of administration but analysis of just time-dependent action antibiotics revealed a positive benefit associated with extended infusions. Of the antibiotics analysed individually this benefit was also seen within the ceftazidime sub group, however this secondary result should be viewed with caution as only one ceftazidime article (Angus et al., 2000) reported mortality and the total number of patients analysed for this outcome was only 21.

Twenty three articles reported mortality as an outcome but the relative weighting allocated to the papers meant that slightly over 50% of the effect seen in the meta-analysis of all antibiotics came from just 2 articles (Dulhunty et al., 2015; Fan et al., 2017). When the 19 articles investigating time-dependent action antibiotics were analysed alone, 4 articles accounted for over 80% of the effect with the papers by Dulhunty et al and Fan et al accounting for approximately 30% each and two more articles contributing 11% each (Chytra et al., 2012; Abdul-Aziz et al., 2016). These 4 articles all report large, well-conducted RCTs published recently focusing predominantly on meropenem and piperacillin/tazobactam.

Unfortunately there was a lot of clinical heterogeneity between the articles. Mortality was reported over different time frames, some relating to variable time frames such as “ICU mortality” and “hospital discharge” and others picking a specific point in time, for example “90 days”. In a similar way to the reporting of AE, articles also varied in whether they reported every death i.e. “all-cause mortality” or death that was attributable to the infection and antibiotic failure. In both instances, analysis of all antibiotics and time-dependent only, the risk of statistical heterogeneity was very low (I^2 = 0%). There was no evidence of publication bias.

Sensitivity analysis however brings in to question the robustness of the positive relationship between extended infusions, time-dependent action antibiotics and mortality. Both the use of a fixed effects model or odds ratio finds no difference between infusion methods.

Secondary/super-infection with a presumed or proven different organism

Secondary and super-infection were included as reported in the articles and their incidence was similar between the administration methods. Many differences existed between articles in the way this information was reported, for example some articles included all patients (Feld et al., 1984) whilst other included just those patients from whom an organism had been isolated (Chytra et al., 2012). In general articles just reported super-infection regardless of the nature of the organism i.e. whether it was one that should have responded to the antibiotic being investigated or an organism that wouldn't have been sensitive, for example fungi; only one article sub-divided the two outcomes (Roberts et al., 2007). Due to the inconsistencies it is hard to really comment on the relevance of this as an outcome. It may add some detail to the more general outcome of clinical cure/response/failure but ideally future studies should only report this outcome for patients with a proven organism whom have then regrown the same organism or another opportunistic organism such as yeast whilst on the study antibiotic therapy.

Infection recurrence within 14 days of resolution of primary infection

Only 3 articles met the pre-define criteria for inclusion in analysis for this outcomes and no difference was found between methods of administration. Again there is a similar scenario to the one described above, there are many ways articles have approached this ranging from reporting all new infections post therapy regardless of whether or not an organism has been isolated at any point during the study through to just reporting the recurrence of the originally isolated and treated organism. These differences again make interpreting the combined results difficult and future systematic reviews could afford to be very specific *a priori* about what they choose to include in the meta-analysis.

Bacteriological/microbiological cure

Many studies didn't report this outcome and where it was reported the numbers of patients were smaller than the total enrolled as not every patient had a verified, culture positive infection. Again, the definition also varied from either proven eradication to overall eradication, the later including both proven and presumed.

Analysis of bacteriological/microbiological cure found a statistically significant difference in favour of extended infusions when examining articles reporting results for both all antibiotics and time-

dependent only antibiotics. However no difference between methods of administration was found when antibiotics where examined individual. Interestingly one of the 5 articles accounted for 83% of the weighting (Chytra et al., 2012). This article looked solely at meropenem and reported a statistically significant result in favour of continuous infusions (P = 0.020) for overall eradication but no difference when analysing solely proven or presumed eradication independently. Encouragingly it found significantly less persistence (i.e. on going infection) and no difference in resistance in the point of final assessment.

4.5.2 Comparison with other systematic reviews and meta-analyses

The first point of note is that there has been many new RCTs published over the last five years; this systematic review contains eleven more articles than the last similarly wide reaching review of the literature conducted for the Cochrane Collaboration in 2013 (Shiu et al., 2013). This review also analyses data for at least an additional 1700 patients (approximately 1600 patients in the review by Shiu et al compared to approximately 3300 in this review). Many of these additional articles are of higher quality, larger patient numbers and at lesser risk of bias than the earlier articles. These facts combined make this the most robust review to date.

Comparison of the articles included in this systematic review for the same time period as to that of the Cochrane review and the results are almost identical. This systematic review focused on only articles or abstracts published in English and the published peer reviewed data contained within them, Shiu et al obtained translations of non-English papers and invited authors to contributed unpublished data. For the purpose of this review authors were only contacted for clarification of anomalies in the data or for subdivision of the data for individual antibiotics where it was published by group e.g. β-lactams.

There are 2 main differences however between this systematic review and those that have come before it. Firstly, the definitions of the outcomes of interest set out *a priori* for the reviews and secondly differences in approach to data extraction. For example, this review has examined clinical cure rather than response or failure leading to a slightly different insight into the results. This review has interpreted and analysed adverse events differently to previous reviews. Secondly, previous

reviews have treated glycopeptides, specifically vancomycin, as time-dependent whereas as already discussed in this review, vancomycin has been excluded from the "time-dependent" analysis. Sensitivity analysis highlighted that this decision had an impact on the results, mortality no longer being positively influenced by extended infusions. The decision to exclude vancomycin from this analysis is however logical and as such the observed benefit remains valid. This mortality benefit is in keeping with the recent meta-analysis of individual patient data from RCTs comparing continuous and intermittent β-lactam infusions (Roberts et al., 2016).

4.5.3 Impact

This is the biggest systematic review and meta-analysis to date. It is the first review to treat clinical cure and clinical response as separate outcomes. In doing so it has highlighted a significant result when specifically looking at articles that reported clinical cure as apposed to assessing clinical cure and response under the same umbrella. In addition, this review has highlighted other previously unseen improvements in bacteriological cure rates and mortality. In doing so it has shown that there truly is potential benefits from extended infusions. Sub group analysis of individual antibiotics however has highlighted the potential folly of the new trend to investigate β-lactams rather than individual antibiotics and indicated the areas that future studies should focus.

4.5.4 Limitations and assumptions

Although statistical heterogeneity was generally low or non-existent throughout this meta-analysis clinical and methodological heterogeneity will have been very high. Firstly, these articles span over 40 years in which many aspects of clinical care have changed including effectiveness of other drug interventions, accuracy and types of monitoring equipment, quality of nursing interventions and even disease definitions. Secondly, there were many differences throughout the articles included in terms of definitions of the various outcomes and how outcome measures were applied. This makes generalising the outcomes very difficult. Many outcomes were reported over different time frames e.g. mortality reported at ICU discharge, hospital discharge, 30 days, 90 days or without a stipulated time frame. An example of how this may affect the overall outcome can be seen in the BLING II study (Dulhunty et al., 2015), hospital mortality was statistically significant but was no longer significant

when assessed at 90 days. Another example, this time of data unavailable for the meta-analysis, is that many articles described adverse events by event rather than the number of patients that suffered one or more events and so this data could not be included in the analysis. A final problem, which was unforeseen, was the issue of the inconsistency of the data within some articles where data in tables did not correlate with the same data in the text of the article and this data therefore needed to be exclude.

4.6 Conclusion

This large systematic review identified 40 eligible randomised controlled trials investigating extended infusions of antibiotics in adult patients with presumed or proven sepsis. Statistically significant differences in clinical cure and microbiological/bacteriological cure were found in favour of extended infusion methods. No difference in adverse events was identified between the administration methods. Although a difference in mortality was seen when time-dependent antibiotics were analysed separately this result may have been influenced by the choice of method of statistical analysis. Sub group analysis showed statistically significant differences in benefits between antibiotics suggesting that future studies should focus on individual antibiotics, for example piperacillin, rather than classes or groups such as β-lactams.

5 Discussion and overall conclusion

The overall aim of this thesis was to investigate the evidence base for current UK intravenous antibiotic administration practice. A questionnaire was circulated to critical care pharmacists via the United Kingdom Clinical Pharmacy Associations' Critical Care Group message board to ascertain what current practice existed and if any critical care units (CCUs) were adopting extended infusion methods of administration in their usual practice. At the same time a systematic review was performed of the randomised controlled trials (RCTs) in the published literature and with knowledge of the articles in the pipeline at the time it was decided to update the review in April 2018. A meta-analysis was performed investigating the evidence base for all antibiotics and sub-group analysis focused on the antibiotics shown by the survey to be given commonly on UK CCUs by extended methods of administration.

5.1 Overview

The results of both phases of the study have shown a wide-ranging interest in the literature and in practice for extended methods of administration. Aside from the RCTs described in the systematic review there is a large number of observational studies in patients and pk/pd studies in both animal models and humans that have shown a scientific basis for, and a potential benefit to be gained from, extending the duration over which an antibiotic infusion is administered. The systematic review revealed that the focus of the literature is predominantly on β-lactam antibiotics and although extended infusions of antibiotics in this class are popular, vancomycin is by far the most commonly administered extended infusion in practice across CCUs in the UK. This is despite there being only two RCTs assessing its safety and only one (Wysocki et al., 2001) investigating efficacy, compared to 14 articles reporting studies investigating piperacillin. From the results of the survey it is clear that the reasons for adopting extended infusions differed between vancomycin and β-lactams, with the latter being almost exclusively about efficacy whereas the former is about a combination of efficacy, safety and ease of administration. Where practice and the literature are markedly different is in the method of extended administration utilised.

5.2 Continuous (CI) versus extended intermittent (EII) infusions

The majority of the published RCTs, 34 out of the 40 articles, investigated continuous infusions (CI). Four of the 6 articles focussing on extended intermittent infusions (EII) have been published since the beginning of 2017. The survey of practice conducted at the end of 2013 revealed that those CCUs using extended methods of administration exclusively used EIIs for β-lactams and vancomycin was given only by CI. These findings were not anticipated during the study design phase and therefore the questionnaire was not designed to collect data to investigate this aspect further. The following reasons can be postulated though as to why EIIs of β-lactam antibiotics may be the administration method of choice rather than CIs.

Firstly, there may be many more articles investigating extended administration methods that are not RCTs and so therefore not included in the meta-analysis. One such article that stands out is a cohort study comparing 30 minute infusions of piperacillin/tazobactam given every 4 or 6 hours with 4-hour infusions given every 8 hours to treat *Pseudomonas aeruginosa* infection (Lodise et al., 2007a). The two groups comprised 194 patients in total and the authors state the groups were evenly matched. Even though a lower total daily dose of antibiotic was used in the EII group this group had better target attainment, spending longer above the MIC, and showed a significantly lower mortality rate than the intermittent group (12.2% compared to 31.6%; P=0.04) and a shorter length of stay (21 days compared to 38 days; P=0.02). *Pseudomonas spp.* are often used in pk/pd studies of β-lactams as they have a relatively high MIC, are relatively common in the ICU patient population (Vincent et al., 2009) and have a high associated mortality so represent a "worst-case" scenario.

Secondly are the practical aspects of the different types of infusions. A CI requires the patient to have intravenous access dedicated to the administration of that one drug. EIIs have periods were that IV access port is not needed so can be utilised for the administration of other medicines. In the most critically ill patients this intravenous access may be at a premium and many other medicines, such as sedatives, analgesics, insulin, and feeds are also administered by CI hence the option of EIIs appearing favourable.

Lastly are pharmaceutical issues, such as stability of the antibiotic in a diluent at room temperature. This has not yet been widely investigated but for example one study has shown that meropenem

1g/100mL of diluent is only stable at 25^{o}C for 12 hours and then degrades (Berthoin et al., 2010) and that at higher concentrations and/or temperatures the rate of degradation of meropenem is much higher. For this reason studies investigating meropenem have run three back-to-back 8-hour infusions in a 24 hour period to provide the "continuous" infusion (Chytra et al., 2012; Dulhunty et al., 2015). This is therefore as labour intensive for nursing staff as three 30-minute or 4-hour infusions per day and therefore confers no non-clinical benefits over the other administration methods such as cost and consumable savings.

5.3 Piperacillin/tazobactam and meropenem

The β-lactams make an obvious choice to investigate as their efficacy depends solely on the amount of time they spend above the minimum inhibitory concentration (T>MIC). Since their release on to the world market, piperacillin and meropenem have formed the mainstay of empirical treatment for patients with sepsis or septic shock; they are both broad spectrum including those microorganisms not sensitive to other β-lactams such as *pseudomonas aeruginosa,* and face comparably low levels of resistance. Interest in maintaining their effectiveness has led to their empirical use in the UK largely being restricted to the critical care environment. International sepsis guidelines encourage their use in accordance with their pk/pd properties (Rhodes et al., 2017).

Piperacillin, in all but one instance combined with tazobactam, was both the most commonly investigated antibiotic in the RCTs included in the systematic review. It is also the β-lactam most commonly administered by an extended infusion method on UK CCUs. Meropenem, although third in terms of the number of published RCTs, was usually prescribed for extended infusion on a similar number of CCUs as piperacillin. In total, across all of the patients enrolled in the RCTs, approximately 1400 received piperacillin and more than 500 received meropenem. Between them they accounting for nearly 2/3 of the total number of patients investigated in the studies. These two antibiotics are now commonly being investigated in the same studies under the umbrella term of β-lactams (Dulhunty et al., 2015; Abdul-Aziz et al., 2016).

The large number of studies, the pk/pd logic and evidence pointing towards their potential benefit, along with the fact that they are first-line empirical therapies for septic patients on UK CCUs means that it is no surprise that these two antibiotics have been the first to be widely adopted as EIIs.

The meta-analysis showed a favourable clinical cure rate for extended methods of administration of time-dependent action antibiotics, a reduction in mortality, and improved microbiological/bacteriological cure rates over standard methods, but no difference between administration methods for any of the adverse events. All but one of the articles included in the time-dependent analysis investigated β-lactams, however individual analysis by antibiotic failed to show any positive difference in any outcomes for meropenem, and only a superior clinical cure rate but no mortality benefit for piperacillin/tazobactam.

Another point of note is that, as described above, the majority of articles reported studies investigating continuous infusions but all of the practice in UK CCUs for these two antibiotics is extended intermittent infusions.

Although the evidence base points towards a benefit from extended infusions, the articles included in the systematic review show a large amount of clinical heterogeneity and analyses of individual antibiotics for the most part do not show any statistically significant results. Only the administration of piperacillin/tazobactam by continuous infusion is supported by the available published literature.

5.4 Vancomycin

The benefit of CIs of vancomycin may initially seem to be less obvious than that of β-lactams but this survey showed that they are by in far the most popular extended infusion being given on UK CCUs and the only antibiotic given by CI. 50% of CCUs give vancomycin by extended infusion with the next most popular antibiotic, piperacillin/tazobactam, being given on just over 20%.

As previously described vancomycin pk/pd still isn't fully understood (Löwdin et al., 1998; Moise-Broder et al., 2004; Vandecasteele et al., 2012). It is now widely accepted that although it exhibits elements of both time- and concentration-dependent action the pk/pd parameter that best aligns with efficacy is the total exposure over time (AUC:MIC ratio) (Holmes et al., 2013). Although this

systematic review only found two RCTs there have been many other articles reviewing the use of vancomycin as a CI. Even though to date no benefit in efficacy has been shown, CIs appear to be simpler to administer, cheaper and have less adverse events (Cataldo et al., 2012; Hao et al., 2016). The responses to the questionnaire confirm that these factors have been taken into account when adopting this practice.

The benefits largely revolve around the ability to do therapeutic drug monitoring (TDM) of serum vancomycin levels. Unlike the β-lactams, which as a general rule, have a large therapeutic window and are generally deemed to be safe, vancomycin has a narrow therapeutic window and overdose or accumulation can lead to severe complications such as nephrotoxicity. Due to vancomycin's side effect profile TDM has always been both advisable and readily available in all clinical situations in which vancomycin is used in the UK. As shown in the survey, TDM is used ubiquitously in the management of patients on vancomycin throughout UK CCUs.

CIs allow dosing and administration to be simplified. This not only makes the job of the nursing staff easier, but also removes any elements of doubt in the pharmacist's mind when trying to interpret TDM levels, which are otherwise more complex with standard intermittent dosing.

Another important factor is safety. A study in 2009 showed that nephrotoxicity increases as trough vancomycin levels increase in patients receiving standard dosing. A 5% incidence was seen when initial trough was <10 mg/L compared with 33% if the trough was >20 mg/L (Lodise et al., 2009). This is worrying as target levels of 15-25mg/L are often used in CI protocols (James et al., 1996; Barton, 2009) but the negative effect observed may be due to higher peak concentrations associated with high troughs or a larger AUC:MIC ratio rather than the trough *per se*. This is supported by a number of studies and reviews that have shown a lower incidence of nephrotoxicity with CIs compared to intermittent infusions (Schmelzer et al., 2013; Tafelski et al., 2015; Hao et al., 2016).

Finally, potential cost saving is a very real factor for healthcare budgets. Although cost saving in practice have been shown (Wysocki et al., 2001) this seems unlikely as a large cost associated with administration by either method is TDM. Checking levels starts earlier in therapy and more frequently with suggested CI protocols compared with intermittent dosing. The questionnaire responses seem to

agree with this, with only two respondents suggesting that cost savings were a consideration with any antibiotic and CIs. These responses may have related to articles reporting studies using smaller doses of β-lactams in the CI group and achieving similar efficacy.

In summary, although in terms of RCTs the evidence is limited, the people have spoken and the perceived benefits associated with ease of dosing and reducing toxicity have meant that vancomycin CIs are now common place on UK CCUs.

5.5 The use of extended infusions of β-lactams in practice

Many other β-lactam antibiotics have been investigated in RCTs over the years but very little interest appears to be shown in using them as extended infusions on UK CCUs. From the results of the questionnaire it is apparent that the only CCUs using any other β-lactam antibiotics by extended infusions are large Trusts with multiple CCUs, a lot of level 3 beds and a senior pharmacist integrated into the CCU team. There may be two reasons for this; the first is that meropenem and piperacillin/tazobactam are used empirically for a wide range of suspected micro-organisms and source sites. Most of the other β-lactams are used for very specific infections, for example flucloxacillin for a suspected *staphylococcal spp.* soft tissue infection. With this in mind even the smallest CCU will frequently use piperacillin/tazobactam and meropenem but may rarely if ever use some of the more niche β-lactams. The second possible reason is related to the first; the largest CCUs which are administering piperacillin/tazobactam and meropenem by EII will also use a number of other β-lactams by nature of their size and specialist areas, e.g. neurology, cardiothoracics, etc. They therefore may approach the subject in a more enthusiastic manner developing guidelines for all of the β-lactams they use commonly across the larger departments. However, big doesn't necessarily mean better; flucloxacillin is reportedly used in one Trust on its 4 CCUs despite there not being a single RCT investigating its efficacy or safety.

5.6 Professional influence on the adoption of extended administration methods

The adoption of extended infusions of antibiotics correlates with whether or not the CCU has an experienced pharmacist(s) integrated into the team, attending multi-professional ward rounds and providing seven-day service. This could be an unforeseen advantage of having a senior, experienced

pharmacist as part of the wider multi-professional team, driving novel, evidence-based medicines change for patient benefit that otherwise would at least initially go largely under the radar.

5.7 Drawbacks affecting adoption of extended infusions

Although the meta-analysis showed statistically significant differences in some outcomes, sub analysis revealed that this was less convincing in more specific areas. Despite this, many CCUs are using extended infusions, so one is led to ask if there is a risk of this resulting in patient harm. The evidence from the RCTs suggests not, the overall outcomes suggested that at worst there is no difference between the effectiveness and safety of the different methods. This fact combined with the large amount of evidence and pk/pd data suggests that extended infusions are at least as good as, and in some instances more effective/safer than standard licensed methods of administration.

5.8 The use of extended infusions in specific patient groups

Many of the RCTs focus on targeting the "worst-case" scenario such as infection with *pseudomonas aeruginosa* or in the case of vancomycin methicillin resistant *staphylococcus aereus,* but many critically ill patients do not have these infection. Articles frequently reported exclusion of patients from the study who had renal failure, but these patients form a large cohort of the patients that are to be found every day on CCUs. Some of the responses to the questionnaire addressed this and although extended infusions may not be used by some in their regular practice, patients treated with extended infusions may be considered to be at high risk of renal failure, especially those with *pseudomonas aeruginosa* or large burns. Conversely, those using extended infusions as their usual practice would convert back to licensed dosing in the face of renal impairment.

5.9 Combining extended infusions with TDM in practice

The survey showed that every CCU using vancomycin relied upon TDM to monitor serum levels; it also showed that apart from aminoglycosides there was no other TDM taking place. Historically TDM has only ever been available for drugs with poor side effect profiles such as vancomycin and the aminoglycosides. Antibiotics that are deemed to be safe have therefore never had TDM systems developed. However, as described above it has now become common practice to use TDM to confirm

that vancomycin serum levels are therapeutic throughout the dosing interval rather than to monitor for toxicity. Ideally all commonly used antibiotics would have a means of TDM available, preferably a point-of-care system that would facilitate rapid turnaround of results to guide therapy in a meaningful way. This could be used in combination with knowledge of the MIC of the antibiotic/micro-organism combination the clinician is faced with, to then tailor the antibiotic therapy for the patient being treated. What this would mean is that for the most part patients would receive antibiotics by licensed administration methods or where extended infusions are usual practice therapy can be rationalised.

5.10 Limitations

The most important potential limitation in this study is the time between the two elements, the questionnaire was launched towards the end of 2013 and the meta-analysis completed in April 2018. Just by looking at the number of new RCTs published in the last 5 years it is evident that the level of interest is growing. In line with this, anecdotally the number of posts on the UKCPA CCG message board asking for both advice and/or guidelines is on the increase. Although the overall aim of this piece of work was to ascertain if UK CCU practice is in line with the evidence base this required two fundamental unknowns to be answered, what is UK CCU practice and what is the up to date evidence. Both of these elements have been addressed and the question of how does UK practice compare to the evidence answered.

5.11 Future research

On the face of it no more studies should be required. The systematic review identified 40 RCTs and within the meta-analysis many of the major outcomes such as mortality showed no publication bias, statistical heterogeneity or statistical need for further research. However there is a big but and it surrounds the clinical heterogeneity in the articles. There is a lot of diversity in the antibiotics investigated, the underlying condition being treated, the target microorganisms and the use of non-study antibiotics to name just a few variables. To add to this many studies pre-date both the Cochrane collaboration advice on assessing for within study bias (Higgins et al., 2011) and the CONSORT guidelines advising on what RCTs should ideally report (Schulz et al., 2010). All these factors

point towards more data being required for individual antibiotics in scenarios clinically relevant to the UK patient population.

The β-lactam infusion study group (BLING) are just starting to enrol on their phase III randomised controlled trial of continuous β-lactam infusions compared with intermittent β-lactam dosing in critically ill patients (BLING III). This study aims to enroll 7000 patients across 100 CCUs worldwide and give the definitive answer to the question do CIs of β-lactam antibiotics improve mortality. The study hopes to complete enrollment at the end of 2021. Even this major study will leave some questions unanswered though. Firstly the group are investigating CIs so the question will remain over the efficacy and safety of EIIs, which are currently commonly used on UK CCUs. Again piperacillin (a penicillin) and meropenem (a carbopenem) are lumped together as "β-lactams" and how this will affect the results is unknown, as the meta-analysis in chapter 4 has shown there may be an argument for investigating antibiotics individually. This study will only answer the question about the effectiveness of the antibiotics it investigates so further studies will be required to investigate other agents but most notably vancomycin. Lastly BLING III may struggle to recruit to schedule as many large centres in the UK where the majority of patients may have been recruited are already using extended infusion and may not be willing to engage with the study.

6 Conclusion

Current UK critical care practice of intravenous antibiotic administration is in line with the evidence base. This meta-analysis shows that extended infusions are both safe and at least as effective as standard licensed administration methods. There is a significant benefit seen in clinical cure, microbiological cure and reduction in mortality associated with time-dependent action antibiotics. By far the most commonly investigated antibiotics are piperacillin/tazobactam and meropenem and it is these two antibiotics we see most usually prescribed by extended infusions on UK CCUs. Experienced senior pharmacists are leading the way by influencing the adoption of administration by extended infusions. There is however one dichotomy between the evidence and practice, the RCTs have almost exclusively investigating piperacillin/tazobactam and meropenem as CI but 100% of the CCUs giving either of these antibiotics do so by EII.

Vancomycin is given as a CI on approximately 50% of UK CCUs and although there are only 2 RCTs investigating its administration by this method factors other than just efficacy have been sited for its adoption. It is perceived to be easier to manage and has been proven to have less nephrotoxicity when administered in this way.

Future large studies and the availability of point-of-care TDM for more antibiotics will no doubt influence the long term uptake of extended infusion on UK CCUs.

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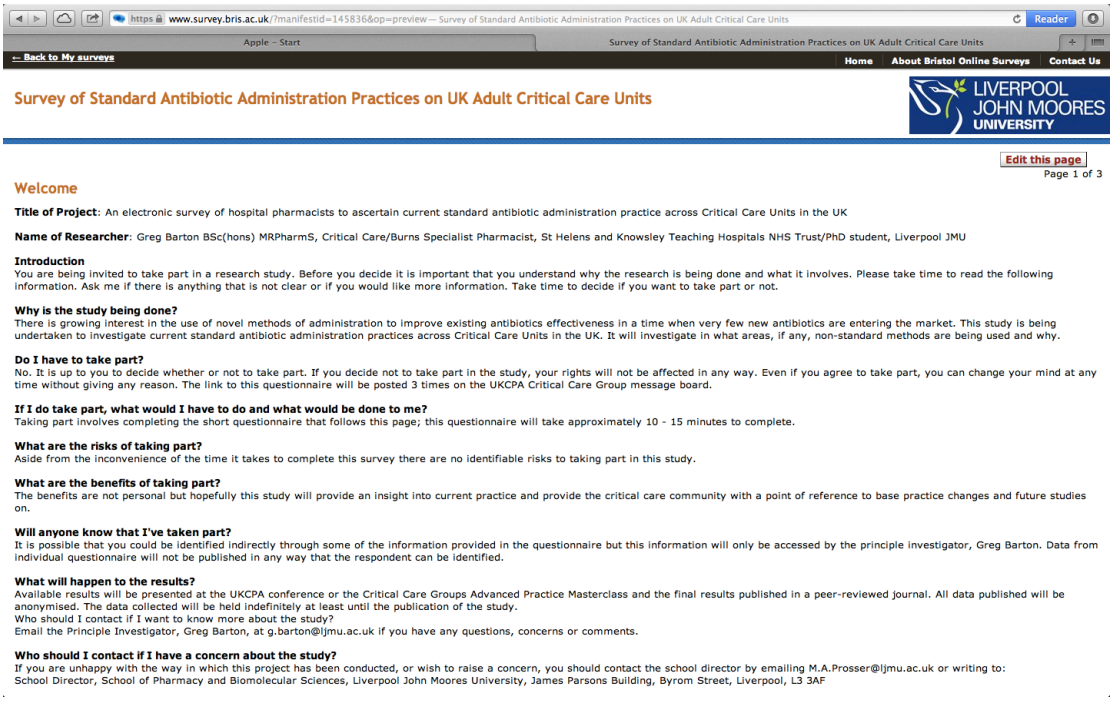
Appendix 1: Questionnaire literature search

Medline	(exp "CRITICAL CARE"/ AND exp "ANTI-BACTERIAL AGENTS"/) AND exp "HEALTH CARE SURVEYS"/	10
EMBASE	(exp "INTENSIVE CARE"/ AND exp "HEALTH CARE SURVEY"/) AND exp "ANTIBIOTIC AGENT"/	27
CINAHL	(exp SURVEYS/ AND exp "CRITICAL CARE"/) AND exp ANTIBIOTICS/	8

Appendix 2: Electronic questionnaire (screen shots)



https www.survey.bris.ac.uk/?manifestid=145836&op=preview— Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units Reader

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Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units

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Welcome

Title of Project: An electronic survey of hospital pharmacists to ascertain current standard antibiotic administration practice across Critical Care Units in the UK

Name of Researcher: Greg Barton BSc(hons) MRPharmS, Critical Care/Burns Specialist Pharmacist, St Helens and Knowsley Teaching Hospitals NHS Trust/PhD student, Liverpool JMU

Introduction
You are being invited to take part in a research study. Before you decide it is important that you understand why the research is being done and what it involves. Please take time to read the following information. Ask me if there is anything that is not clear or if you would like more information. Take time to decide if you want to take part or not.

Why is the study being done?
There is growing interest in the use of novel methods of administration to improve existing antibiotics effectiveness in a time when very few new antibiotics are entering the market. This study is being undertaken to investigate current standard antibiotic administration practices across Critical Care Units in the UK. It will investigate in what areas, if any, non-standard methods are being used and why.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you decide not to take part in the study, your rights will not be affected in any way. Even if you agree to take part, you can change your mind at any time without giving any reason. The link to this questionnaire will be posted 3 times on the UKCPA Critical Care Group message board.

If I do take part, what would I have to do and what would be done to me?
Taking part involves completing the short questionnaire that follows this page; this questionnaire will take approximately 10 - 15 minutes to complete.

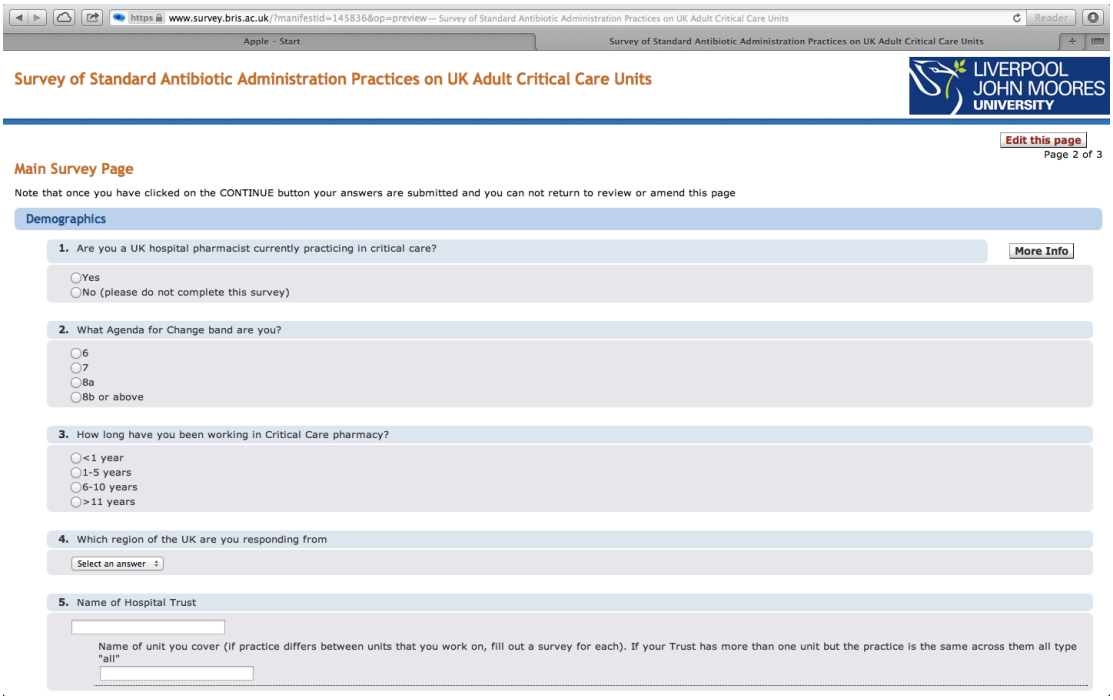
What are the risks of taking part?
Aside from the inconvenience of the time it takes to complete this survey there are no identifiable risks to taking part in this study.

What are the benefits of taking part?
The benefits are not personal but hopefully this study will provide an insight into current practice and provide the critical care community with a point of reference to base practice changes and future studies on.

Will anyone know that I've taken part?
It is possible that you could be identified indirectly through some of the information provided in the questionnaire but this information will only be accessed by the principle investigator, Greg Barton. Data from individual questionnaire will not be published in any way that the respondent can be identified.

What will happen to the results?
Available results will be presented at the UKCPA conference or the Critical Care Groups Advanced Practice Masterclass and the final results published in a peer-reviewed journal. All data published will be anonymised. The data collected will be held indefinitely at least until the publication of the study.
Who should I contact if I want to know more about the study?
Email the Principle Investigator, Greg Barton, at g.barton@ljmu.ac.uk if you have any questions, concerns or comments.

Who should I contact if I have a concern about the study?
If you are unhappy with the way in which this project has been conducted, or wish to raise a concern, you should contact the school director by emailing M.A.Prosser@ljmu.ac.uk or writing to:
School Director, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool, L3 3AF



https www.survey.bris.ac.uk/?manifestid=145836&op=preview— Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units Reader

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Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units

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Main Survey Page

Note that once you have clicked on the CONTINUE button your answers are submitted and you can not return to review or amend this page

Demographics

1. Are you a UK hospital pharmacist currently practicing in critical care? More Info

- ○ Yes
- ○ No (please do not complete this survey)

2. What Agenda for Change band are you?

- ○ 6
- ○ 7
- ○ 8a
- ○ 8b or above

3. How long have you been working in Critical Care pharmacy?

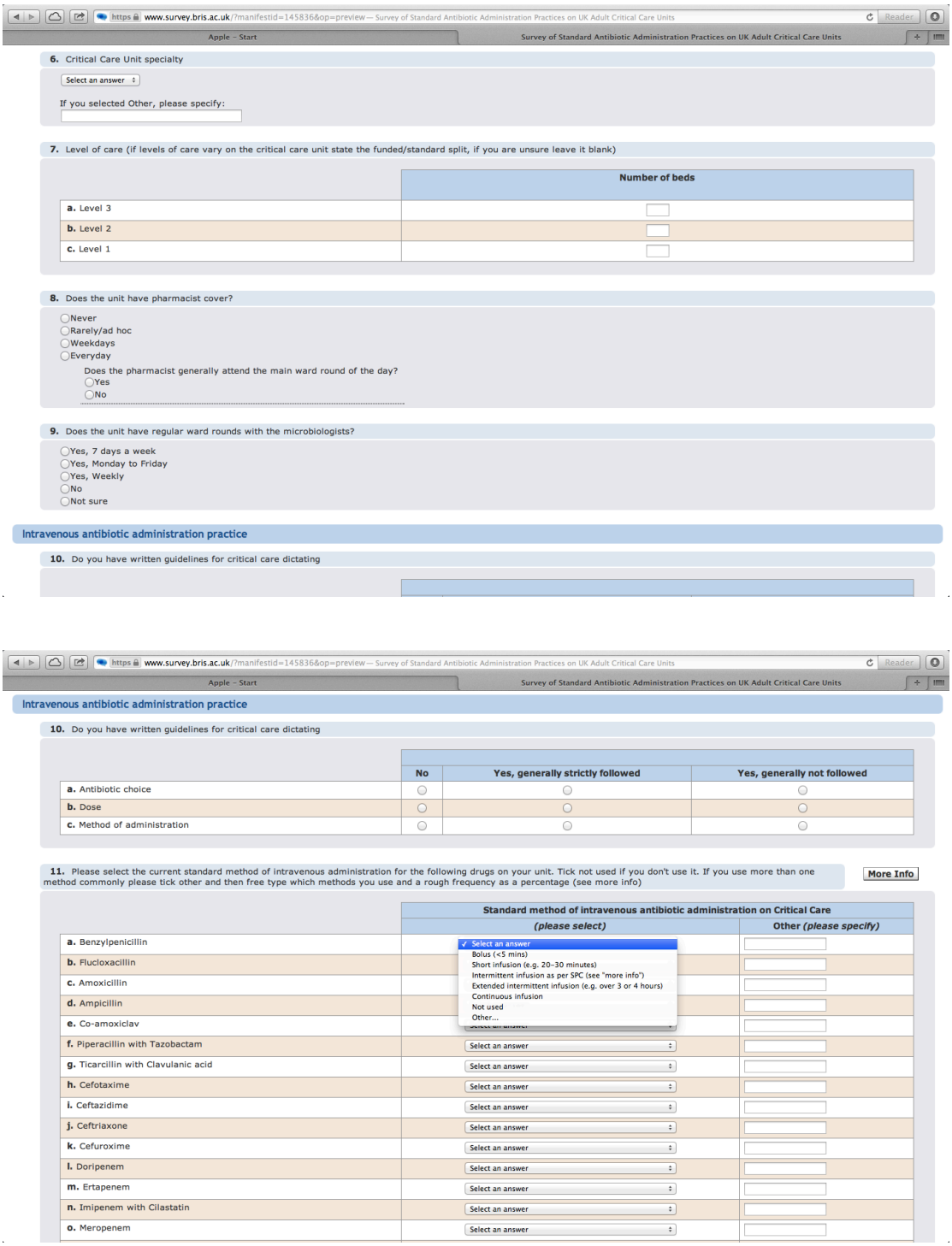
- ○ <1 year
- ○ 1-5 years
- ○ 6-10 years
- ○ >11 years

4. Which region of the UK are you responding from

Select an answer

5. Name of Hospital Trust

Name of unit you cover (if practice differs between units that you work on, fill out a survey for each). If your Trust has more than one unit but the practice is the same across them all type "all"



6. Critical Care Unit specialty

Select an answer

If you selected Other, please specify:

7. Level of care (if levels of care vary on the critical care unit state the funded/standard split, if you are unsure leave it blank)

	Number of beds
a. Level 3	
b. Level 2	
c. Level 1	

8. Does the unit have pharmacist cover?

- Never
- Rarely/ad hoc
- Weekdays
- Everyday

Does the pharmacist generally attend the main ward round of the day?

- Yes
- No

9. Does the unit have regular ward rounds with the microbiologists?

- Yes, 7 days a week
- Yes, Monday to Friday
- Yes, Weekly
- No
- Not sure

Intravenous antibiotic administration practice

10. Do you have written guidelines for critical care dictating

Intravenous antibiotic administration practice

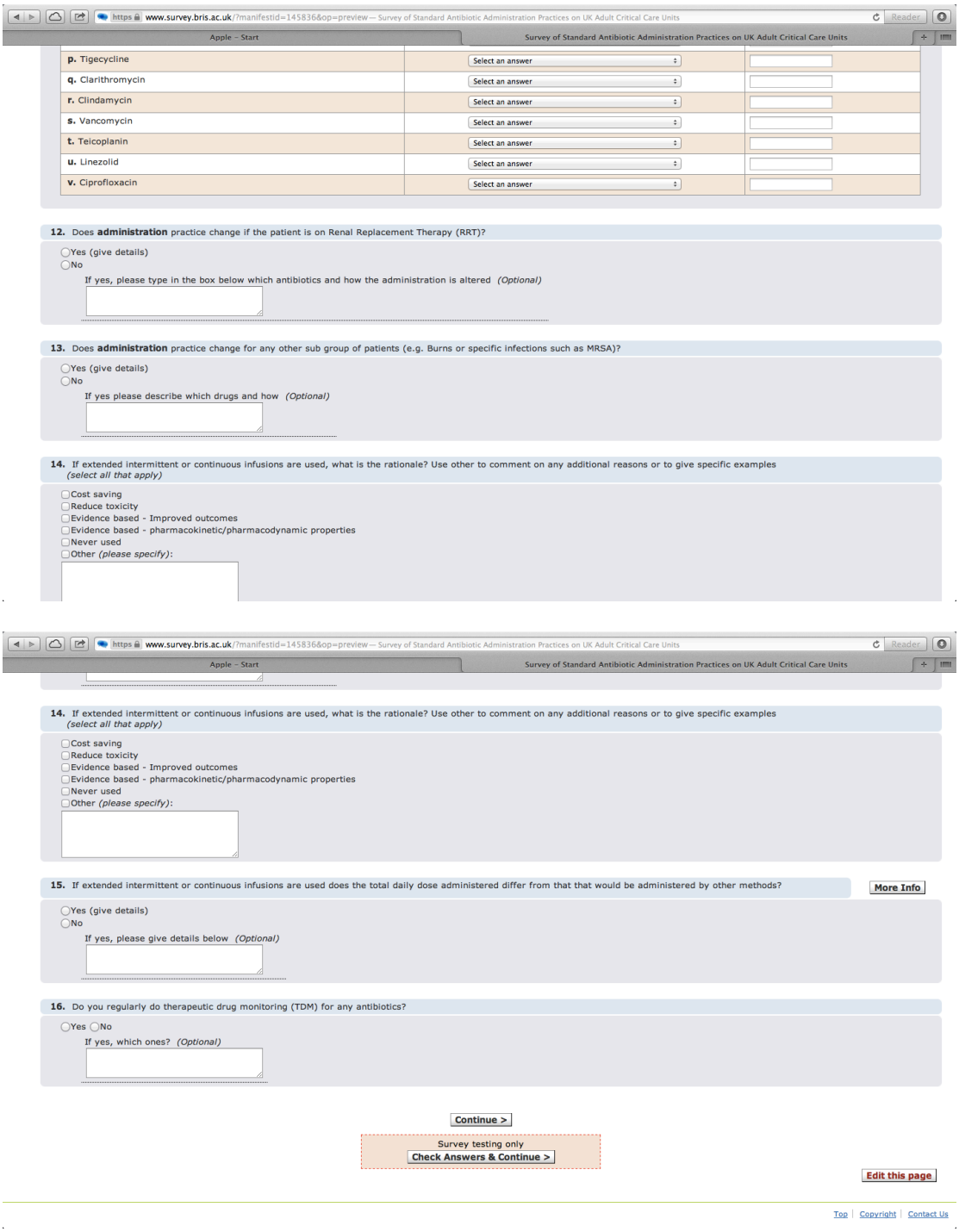
10. Do you have written guidelines for critical care dictating

	No	Yes, generally strictly followed	Yes, generally not followed
a. Antibiotic choice			
b. Dose			
c. Method of administration			

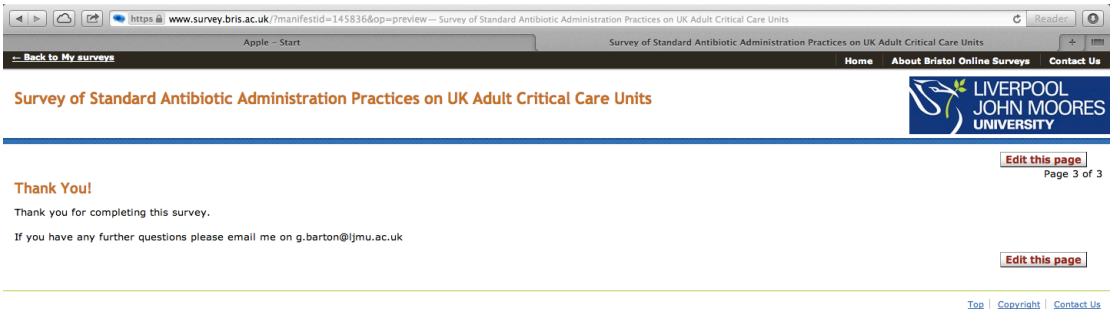
11. Please select the current standard method of intravenous administration for the following drugs on your unit. Tick not used if you don't use it. If you use more than one method commonly please tick other and then free type which methods you use and a rough frequency as a percentage (see more info)

More Info

	Standard method of intravenous antibiotic administration on Critical Care (please select)	Other (please specify)
a. Benzylpenicillin	✓ Select an answer Bolus (<5 mins) Short infusion (e.g. 20-30 minutes) Intermittent infusion as per SPC (see "more info") Extended intermittent infusion (e.g. over 3 or 4 hours) Continuous infusion Not used Other...	
b. Flucloxacillin	Select an answer	
c. Amoxicillin	Select an answer	
d. Ampicillin	Select an answer	
e. Co-amoxiclav	Select an answer	
f. Piperacillin with Tazobactam	Select an answer	
g. Ticarcillin with Clavulanic acid	Select an answer	
h. Cefotaxime	Select an answer	
i. Ceftazidime	Select an answer	
j. Ceftriaxone	Select an answer	
k. Cefuroxime	Select an answer	
l. Doripenem	Select an answer	
m. Ertapenem	Select an answer	
n. Imipenem with Cilastatin	Select an answer	
o. Meropenem	Select an answer	


https www.survey.bris.ac.uk/?manifestid=145836&op=preview — Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units
Reader
Apple – Start
Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units
p. Tigecycline
q. Clarithromycin
r. Clindamycin
s. Vancomycin
t. Teicoplanin
u. Linezolid
v. Ciprofloxacin
Select an answer
12. Does administration practice change if the patient is on Renal Replacement Therapy (RRT)?
Yes (give details)
No
If yes, please type in the box below which antibiotics and how the administration is altered (Optional)
13. Does administration practice change for any other sub group of patients (e.g. Burns or specific infections such as MRSA)?
Yes (give details)
No
If yes please describe which drugs and how (Optional)
14. If extended intermittent or continuous infusions are used, what is the rationale? Use other to comment on any additional reasons or to give specific examples (select all that apply)
Cost saving
Reduce toxicity
Evidence based - Improved outcomes
Evidence based - pharmacokinetic/pharmacodynamic properties
Never used
Other (please specify):

https www.survey.bris.ac.uk/?manifestid=145836&op=preview — Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units
Reader
Apple – Start
Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units
14. If extended intermittent or continuous infusions are used, what is the rationale? Use other to comment on any additional reasons or to give specific examples (select all that apply)
Cost saving
Reduce toxicity
Evidence based - Improved outcomes
Evidence based - pharmacokinetic/pharmacodynamic properties
Never used
Other (please specify):
15. If extended intermittent or continuous infusions are used does the total daily dose administered differ from that that would be administered by other methods?
More Info
Yes (give details)
No
If yes, please give details below (Optional)
16. Do you regularly do therapeutic drug monitoring (TDM) for any antibiotics?
Yes
No
If yes, which ones? (Optional)
Continue >
Survey testing only
Check Answers & Continue >
Edit this page
Top | Copyright | Contact Us


https www.survey.bris.ac.uk/?manifestid=145836&op=preview — Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units
Reader
Apple – Start
Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units
← Back to My surveys
Home
About Bristol Online Surveys
Contact Us
Survey of Standard Antibiotic Administration Practices on UK Adult Critical Care Units
LIVERPOOL JOHN MOORES UNIVERSITY
Edit this page
Page 3 of 3
Thank You!
Thank you for completing this survey.
If you have any further questions please email me on g.barton@ljmu.ac.uk
Edit this page
Top | Copyright | Contact Us

Appendix 3: Participant information sheet

LIVERPOOL JOHN MOORES UNIVERSITY
PARTICIPANT INFORMATION SHEET

Title of Project: An electronic survey of hospital pharmacists to ascertain current usual antibiotic administration practice across Critical Care Units in the UK

Name of Researcher: Greg Barton BSc(hons) MRPharmS, Critical Care/Burns Specialist Pharmacist, St Helens and Knowsley Teaching Hospitals NHS Trust/PhD student, Liverpool JMU

Introduction
You are being invited to take part in a research study. Before you decide it is important that you understand why the research is being done and what it involves. Please take time to read the following information. Ask me if there is anything that is not clear or if you would like more information. Take time to decide if you want to take part or not.

Why is the study being done?
There is growing interest in the use of novel methods of administration to improve existing antibiotics effectiveness in a time when very few new antibiotics are entering the market. This study is being undertaken to investigate current standard antibiotic administration practices across Critical Care Units in the UK. It will investigate in what areas, if any, non-standard methods are being used and why.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you decide not to take part in the study, your rights will not be affected in any way. Even if you agree to take part, you can change your mind at any time without giving any reason. The link to the study questionnaire will be posted 3 times on the UKCPA Critical Care Group message board.

If I do take part, what will I have to do and what will be done to me?
Taking part involves completing the short questionnaire that follows this page; this questionnaire will take approximately 10 minutes to complete. By completing and returning this questionnaire, you consent to participating in this research study and for your data to be used as described in this information sheet.

What are the risks of taking part?
There are no identifiable risks to taking part in this study.

What are the benefits of taking part?
The benefits are not personal but hopefully this study will provide an insight into current practice and provide the critical care community with a point of reference to base practice changes and future studies on.

Will anyone know that I've taken part?
It is possible that you could be identified indirectly through some of the information provided in the questionnaire but this information will only be accessed by the principle investigator, Greg Barton and his supervisory team at Liverpool John Moores University. Data from individual questionnaires will be published in a way that the respondent cannot be identified.

What will happen to the results?
The results of this study will feed into the design of the main phase of my PhD, a patient outcome-orientated investigation comparing current usual practice of antibiotic administration in the UK and extended intermittent infusions. Available results will be presented at the UKCPA conference or the Critical Care Groups Advanced Practice Masterclass and the final results published in a relevant critical care/anaesthesia journal. All data published will be anonymised. The data collected will be held indefinitely at least until the publication of the study.

Who should I contact if I want to know more about the study?
Email the Principle Investigator, Greg Barton, at g.barton@ljmu.ac.uk if you have any questions, concerns or comments.

Who should I contact if I have a concern about the study?
If you are unhappy with the way in which this project has been conducted, or wish to raise a concern, you should contact my director of studies by emailing N.C.Henney@ljmu.ac.uk or writing to*: Neil Henney, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool, L3 3AF*

Version
This participant information sheet was last updated: 24/9/13

This project has been looked at and approved by the University Research Ethics Committee and has been assigned the reference number Insert your reference number (from your screening email) here

Appendix 4: UKCPA message board posts (initial, week 2 and week 6)

Initial:

Dear Colleague,

I would be most grateful if you would complete this survey on antibiotic administration practice in the Critical Care setting.

The link is:-

www.BOS

(you may have to copy and paste it if it does not work automatically)

On the opening page you will be asked some simple demographic details about yourself and your Critical Care Unit (ICU/HDU). Information about the grade of pharmacist and the name of the hospital/unit are included to manage duplication of responses from the same unit, duplicate responses will be removed and if there are discrepancies between forms from the same unit then as a default the most senior pharmacists response will be taken. This information will **not** be included in any publications. All other information, such as specialty of the unit, will be used to analyse trends in the final data. If you don't know the answer please don't let this hinder you completing the rest of the survey, choose 'don't know'.

If you do not wish to be contacted as part of the follow up of none responders, please contact me on the following email address, g.barton@ljmu.ac.uk

If you work in a Trust with more than one ICU/HDU that have different standard practices, I would be most grateful if you would complete one survey per unit.

There are also some basic workforce questions on pharmacy practice which or may or may not influence prescribing practice in the intensive care.

The survey should take less than 10 minutes to complete.

Thank you all so much, for helping me undertake this research. I intend to present the results at a UKCPA meeting and publish in a peer reviewed journal.

Should you require information or feedback then please do not hesitate to contact me.

Best wishes,
Greg Barton,
Critical Care/Burns specialist pharmacist,
St Helens and Knowsley Teaching hospitals NHS Trust
Liverpool John Moores University

2 week follow up:

Dear All,

Thank you so much to all of you who have completed this survey on antibiotic administration practice in the Critical Care setting.

To date we have had **x** complete replies which is excellent. For the results to be valid, we really need a response rate of above 70 %. There are (approximately) 240 intensive care units in the UK. We are therefore looking for around 170 responses. Ideally more.

Please consider completing this survey.

The link is:-

www.BOS

(you may have to copy and paste it if it does not work automatically)

On the opening page you will be asked some simple demographic details about yourself and your Critical Care Unit (ICU/HDU). Information about the grade of pharmacist and the name of the hospital/unit are included to manage duplication of responses from the same unit, duplicate responses will be removed and if there are discrepancies between forms from the same unit then as a default the most senior pharmacists response will be taken. This information will **not** be included in any publications. All other information, such as specialty of the unit, will be used to analyse trends in the final data. If you don't know the answer please don't let this hinder you completing the rest of the survey, choose 'don't know'.

If you do not wish to be contacted as part of the follow up of none responders, please contact me on the following email address, g.barton@ljmu.ac.uk

If you work in a Trust with more than one ICU/HDU that have different standard practices, I would be most grateful if you would complete one survey per unit.

There are also some basic workforce questions on pharmacy practice which or may or may not influence prescribing practice in the intensive care.

The survey should take less than 10 minutes to complete.

Thank you all so much, for helping me undertake this research. I intend to present the results at a UKCPA meeting and publish in a peer reviewed journal.

Should you require information or feedback then please do not hesitate to contact me.

Best wishes,
Greg Barton,
Critical Care/Burns specialist pharmacist,
St Helens and Knowsley Teaching hospitals NHS Trust
Liverpool John Moores University

6 week follow up:

Dear All,

Thank you so much to all of you who have completed this survey on antibiotic administration practice in the Critical Care setting.

For the record, we have had **y** completed surveys to date, which is excellent. For those of you who have not had time to complete yet. There is still time left. We intend to keep the survey open for at least 4 more weeks.

Please complete, the results to date are very interesting. For those of you who work with colleagues who do not have access to this site, we would be most grateful if you could pass on.

Please consider completing this survey.

The link is:-

www.BOS

(you may have to copy and paste it if it does not work automatically)

On the opening page you will be asked some simple demographic details about yourself and your Critical Care Unit (ICU/HDU). Information about the grade of pharmacist and the name of the hospital/unit are included to manage duplication of responses from the same unit, duplicate responses will be removed and if there are discrepancies between forms from the same unit then as a default the most senior pharmacists response will be taken. This information will **not** be included in any publications. All other information, such as specialty of the unit, will be used to analyse trends in the final data. If you don't know the answer please don't let this hinder you completing the rest of the survey, choose 'don't know'.

If you do not wish to be contacted as part of the follow up of none responders, please contact me on the following email address, g.barton@ljmu.ac.uk

If you work in a Trust with more than one ICU/HDU that have different standard practices, I would be most grateful if you would complete one survey per unit.

There are also some basic workforce questions on pharmacy practice which or may or may not influence prescribing practice in the intensive care.

The survey should take less than 10 minutes to complete.

Thank you all so much, for helping me undertake this research. I intend to present the results at a UKCPA meeting and publish in a peer-reviewed journal.

Should you require information or feedback then please do not hesitate to contact me.

Best wishes,
Greg Barton,
Critical Care/Burns specialist pharmacist,
St Helens and Knowsley Teaching hospitals NHS Trust
Liverpool John Moores University

Appendix 5: Initial PROSPERO entry

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Extended versus intermittent infusions of antibiotics for the treatment of patients with sepsis: A systematic review and meta-analysis

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.
English

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
16/06/2016

4 Anticipated completion date
Give the date by which the review is expected to be completed.
01/08/2017

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	No	Yes
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Greg Barton

7 Named contact email
Enter the electronic mail address of the named contact.
g.barton@ljmu.ac.uk

8 Named contact address
Enter the full postal address for the named contact.
pharmacy department, Whiston hospital, Warrington road, Prescot, L35 5DR

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
00441514261600

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
None
Website address:

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Mr	Greg	Barton	Pharmacy department, St Helens and Knowsley Teaching Hospitals NHS Trust; School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University
Mr	Michael	Lloyd	Pharmacy department, St Helens and Knowsley Teaching Hospitals NHS Trust

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
None

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
Professor	Charles	Morecroft	School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University
Dr	Neil	Henney	School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

To compare the clinical efficacy and safety of extended intravenous administration of antibiotics with standard intravenous administration practice in patients with a severe acute bacterial (presumed or proven) infection.

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The search will use the following terms in each data base as a starting point, (antibiotic OR antibacterial OR anti-infective OR beta lactam OR penicillin OR cephalosporin OR carbopenem OR glycopeptides OR vancomycin OR I could go on a bit here….) AND (intensive care OR critical care OR sepsis OR septic shock OR critical illness) AND (pharmacokinetic OR pharmacodynamics OR drug schedule OR intermittent OR interval OR continuous OR discontinuous) These terms will be searched in each database as they are and also matched to the thesaurus. Where appropriate the term will be exploded and/or astrixed to find all possibilities with the same root (e.g. antibiotic*) and/or hyphenated (e.g. anti-bacterial). Searches will not be restricted by limits applied to age, date or language. The search will utilise the following databases, Cochrane Central Register of Controlled Trials (The Cochrane Library), Medline, Embase. References from relevant papers will also be reviewed, as will the investigators own library. Expert opinion will be sort to identify other papers including those in press.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

No

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Antibiotic management of sepsis

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: Male or non-pregnant females aged 18 years or over with a presumed or proven bacterial infection requiring intravenous antibiotics. Exclusion: Under 18 years of age and/or pregnancy

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

Treatment with antibiotics using an extended or continuous infusion as the method of administration.

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Compared to licensed intermittent infusions or bolus methods of antibiotic administration of the same antibiotic as the intervention arm.

22 Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Inclusion criteria: This systematic review and meta-analysis will include open label or blinded parallel group randomised controlled trials (RCTs). Exclusion criteria: Studies will be excluded from the systematic review based on the following conditions: all studies in humans under the age of 18, RCTs involving cross-over of participants, all non-RCTs (e.g. retrospective studies, commentaries, meeting abstracts, editorials, review articles and book chapters).

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)

Give the most important outcomes.

1) Clinical cure (any pre-defined criteria specific to the infection being studied that addresses signs and symptoms if infection) 2) Number of participants who experienced at least one serious adverse event (AE) (result in death, is life threatening, involved or prolonged hospitalisation, involved persistent or significant disability or incapacity, is another condition that investigators judge to represent significant harm/hazard)

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

1) All cause mortality 2) Infection recurrence with 14 days of resolution of primary infection 3) Time to clinical cure (defined as the time from initiation of antibiotics to attainment of clinical cure) 4) Microbiological cure (any pre-defined criteria that assessed microbiological outcomes) 5) Secondary/super infection (a new infection with different organisms from those observed in the primary infection) 6) Number of participants withdrawing as a result of an AE 7) Number of participant with at

26 Data extraction (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources (such as references and the investigators' personal library) with be screened by the primary investigator. A second investigator will review a randomly generated sample of 10% of titles and/or abstracts. The random list will be generated by listing all retrieved titles alphabetically and selecting every tenth paper for secondary review.The full texts of the potentially eligible studies will be retrieved and independently assessed for eligibility by both investigators. Any disagreement will be resolved through discussion (involving a third member of the team if necessary). A standardised form will be used to extract data from the included studies for assessment of study quality/risk of bias and evidence synthesis. Two investigators will extract the data independently and any discrepancies identified will be resolved through discussion (with a third member of the team if necessary). Missing data will NOT be requested from the study authors (only peer-reviewed published data will be included in the study).

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two investigators will independently assess the risk of bias in included studies by using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (as described below): 1) Selection Bias i) Randomisation sequence generation: was the allocation sequence adequately generated? ii) Treatment allocation concealment: was the allocated treatment adequately concealed from study participants and clinicians and other healthcare or research staff at the enrolment stage? 2) Performance Bias Blinding of participants and personnel: were the participants and researchers sufficiently blinded from knowledge of which intervention a participant received? 3) Detection Bias Blinding of outcome assessment: Where the researchers assessing outcomes and analysing data sufficiently blinded to the intervention allocation throughout the trial? 4) Attrition bias Incomplete outcome data: were participant exclusions, attrition and incomplete outcome data adequately addressed in the published report? 5) Reporting bias Selective outcome reporting: is there evidence of selective outcome reporting and might this have affected the study results? 6) Other sources of bias: was the trial apparently free of any other problems that could produce a high risk of bias? Disagreements between the investigators over the risk of bias in particular studies will be resolved by discussion, with involvement of a third member of the team where necessary.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

The Meta-analysis will be performed using Comprehensive Meta-Analysis (enter details here). Publication bias will be assessed by visual inspection of the funnel plot. Risk ratio with an associated 95% confidence interval using a random effects model will be used to measure treatment effect. Heterogeneity of included studies will be assess using

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. ‘None planned’ is a valid response if no subgroup analyses are planned.

Any antibiotic for which there are 5 or more published RCTs

Review general information

30 Type and method of review

Select the type of review and the review method from the drop down list.

Meta-analysis, Systematic review

Infections and infestations

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

England

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available

Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

intend to publish in a peer-reviewed journal widely read within critical care.

Do you intend to publish the review on completion?

Yes

36 Keywords

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

Appendix 6: Systematic review search strategies and results

Medline:

1. Medline; exp ANTI-INFECTIVE AGENTS/; 1651437 results.
2. Medline; exp ANTI-BACTERIAL AGENTS/; 609040 results.
3. Medline; (anti-infect* OR antiinfect* OR anti-bact* OR antibact* OR anti-biot OR antibiot OR anti-microbi* OR antimicrobi*).ti,ab; 157538 results.
4. Medline; exp BETA-LACTAMS/; 116390 results.
5. Medline; (beta-lactam* OR betalactam* OR (ß lactam*) OR B-lactam OR (B lactam*) OR ß-lactam* OR (beta lactam)).ti,ab; 29353 results.
6. Medline; exp GLYCOPEPTIDES/; 54743 results.
7. Medline; exp AMINOGLYCOSIDES/; 138154 results.
8. Medline; 1 AND 2 AND 3 AND 4 AND 5 AND 6 AND 7; 23 results.
9. Medline; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7; 1802624 results.
10. Medline; exp ADMINISTRATION, INTRAVENOUS/; 130657 results.
11. Medline; (infusion* OR injection* OR intravenous* OR drip*).ti,ab; 862210 results.
12. Medline; 10 OR 11; 903387 results.
13. Medline; 9 AND 12; 134917 results.
14. Medline; exp BACTERIAL INFECTIONS/ OR exp SEPSIS/; 858167 results.
15. Medline; exp CARDIOVASCULAR INFECTIONS/ OR exp CATHETER-RELATED INFECTIONS/ OR exp INTRAABDOMINAL INFECTIONS/ OR exp RESPIRATORY TRACT INFECTIONS/ OR exp SOFT TISSUE INFECTIONS/ OR exp URINARY TRACT INFECTIONS/ OR exp WOUND INFECTION/; 483375 results.
16. Medline; infect*.ti,ab; 1358989 results.
17. Medline; CRITICAL ILLNESS/; 19880 results.
18. Medline; (critical AND illness).ti,ab; 10190 results.
19. Medline; 14 OR 15 OR 16 OR 17 OR 18; 2146996 results.
21. Medline; PHARMACOKINETICS/; 259435 results.
22. Medline; exp DRUG ADMINISTRATION SCHEDULE/; 90822 results.
23. Medline; (continuous* OR intermittent* OR discontinuous* OR bolus* OR interval*).ti,ab; 1007265 results.
24. Medline; 21 OR 22 OR 23; 1308849 results.
25. Medline; 20 AND 24; 8028 results.
26. Medline; randomised AND controlled AND trial.pt; 416907 results.
27. Medline; controlled AND clinical AND trial.pt.; 402788 results.
28. Medline; randomized.ab.; 410610 results.
29. Medline; placebo.ab.; 168451 results.
30. Medline; drug AND therapy.fs.; 1967548 results.
31. Medline; randomly.ab; 247239 results.
32. Medline; trial.ab.; 344942 results.
33. Medline; groups.ab.; 1536018 results.
34. Medline; 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33; 3817721 results.
35. Medline; exp ANIMALS/ NOT humans.sh.; 4221082 results.
36. Medline; 34 NOT 35; 3288156 results.
37. Medline; 25 AND 36; 5138 results.
38. Medline; 37 [Limit to: (Age group Young Adult or Adult or Middle aged or Aged or Aged, 80 and over)]; 3084 results.

Embase:

137. EMBASE; exp ANTIINFECTIVE AGENT/ OR exp ANTIBIOTIC AGENT/; 0 results.
138. EMBASE; exp ANTIINFECTIVE AGENT/; 0 results.
139. EMBASE; (anti-infect* OR antiinfect* OR anti-bact* OR antibact* OR anti-biot OR antibiot OR anti-microbi* OR antimicrobi*).ti,ab; 207524 results.
140. EMBASE; (beta-lactam* OR betalactam* OR (ß lactam*) OR B-lactam OR (B lactam*)

OR ß-lactam* OR (beta lactam)).ti,ab; 44207 results.
141. EMBASE; (glycopeptide OR vancomycin).ti,ab; 32901 results.
142. EMBASE; aminoglycoside*.ti,ab; 18770 results.
143. EMBASE; (glycopeptide* OR vancomycin).ti,ab; 36565 results.
144. EMBASE; 138 OR 139 OR 140 OR 142 OR 143; 2520517 results.
145. EMBASE; exp INTRAVENOUS DRUG ADMINISTRATION/; 313831 results.
145. EMBASE; exp INTRAVENOUS DRUG ADMINISTRATION/; 313831 results.
146. EMBASE; (infusion* OR injection* OR intravenous* OR drip*).ti,ab; 1050739 results.
147. EMBASE; 145 OR 146; 1238934 results.
148. EMBASE; exp INFECTION/; 2810888 results.
149. EMBASE; exp SEPSIS/; 195449 results.
150. EMBASE; CRITICAL ILLNESS/; 24067 results.
151. EMBASE; infect*.ti,ab; 1644492 results.
152. EMBASE; ((critical illness)).ti,ab; 15685 results.
153. EMBASE; 148 OR 149 OR 150 OR 151 OR 152; 3302485 results.
154. EMBASE; 147 AND 153; 182558 results.
155. EMBASE; PHARMACOKINETICS/; 114592 results.
156. EMBASE; PHARMACODYNAMICS/; 22406 results.
157. EMBASE; exp DRUG INFUSION/; 13797 results.
158. EMBASE; (continuous* OR intermittent* OR discontinuous* OR bolus* OR interval*).ti,ab; 1232809 results. 159. EMBASE; 155 OR 156 OR 157 OR 158; 1362270 results.
160. EMBASE; 154 AND 159; 25883 results.
161. EMBASE; (random* OR factorial* OR crossover* OR cross AND over* OR cross-over* OR placebo* OR doubl* ADJ blind* OR singl* ADJ blind* OR assign* OR allocate* OR volunteer*).ti,ab; 553198 results.
162. EMBASE; exp RANDOMIZED CONTROLLED TRIAL/; 405905 results.
163. EMBASE; 161 OR 162; 854501 results.
164. EMBASE; 160 AND 163; 3261 results.
165. EMBASE; 164 [Limit to: Human]; 2975 results.
166. EMBASE; 165 [Limit to: Human and (Human Age Groups Adult 18 to 64 years or Aged 65+ years)]; 2069 results.

Appendix 7: Definitions of low, high and unclear risk of bias for each category

Sequence generation (selection bias)	Was sequence generation adequate?	Low risk	Random sequence generation is described (for example by computer generation or random number tables)
		High risk	Sequence generation is in part or completely non-randomised (for example patients allocated by clinician or order of admission into the study)
		Unclear	Insufficient information to judge low or high risk of bias
Allocation concealment (selection bias)	Was allocation concealment adequate?	Low risk	Neither patients nor enrolling investigators could predict assignment (e.g. opaque sealed envelopes, off-site randomisation)
		High risk	Either patients and or enrolling investigators could predict assignment (e.g. unsealed envelopes, alternation, allocation by patient identifier e.g. hospital/NHS number)
		Unclear	Insufficient information to judge low or high risk of bias
Blinding of participants and personnel (performance bias)	Was blinding of participants and personnel adequate?	Low risk	Blinding of patients and key study personnel stated and appears to be robust
		High risk	No or incomplete blinding, or blinding attempted but likely to have been broken
		Unclear	Insufficient information to judge low or high risk of bias

Blinding of outcome assessment (detection bias)	Was blinding of outcome assessors adequate?	Low risk	Blinding of outcome assessors stated and appears to be robust
		High risk	No or incomplete blinding, or blinding attempted but likely to have been broken
		Unclear	Insufficient information to judge low or high risk of bias
Incomplete outcome data (attrition bias)	Was incomplete outcome data adequately addressed?	Low risk	Any of the following, • No missing outcome data • Reasons for missing outcome data unlikely to be related to true outcome • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. • For dichotomous outcomes data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate • Appropriate method used for imputing missing data
		High risk	Any of the following, • Reason for missing outcome data likely to be related to true outcome, with imbalance in numbers of or reasons for missing data across intervention groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation • Potentially inappropriate application of simple imputation.
		Unclear	Insufficient information to judge low or high risk of bias

Selective reporting (reporting bias)	Are reports free of selective outcome reporting?	Low risk	All outcomes stated *a priori* that are of interest in the review have been reported in the pre-specified way
		High risk	Any of the following: • Not all outcomes of the study stated *a priori* have been reported • One or more of the outcomes are reported using measurements, analysis methods, or subsets of the data that were not pre-specified • One or more reported outcome was not stated *a priori* without clear justification for their reporting is provided, such as an unexpected adverse effect • One or more outcomes of interest in the review are reported incompletely, incorrectly or ambiguously as so cannot be entered in the meta-analysis • Study report fails to include results for a key outcome that would be expected to have been reported for such a study
		Unclear	Insufficient information to judge low or high risk of bias
Other bias	Was study free from other potential sources of bias not covered elsewhere	Low risk	Study appears to be free from other sources of bias including funding sources, conflicts of interest, use of open label antibiotics, noticeable differences in baseline demographics between study groups such as age, severity of illness
		High risk	One or more important factor providing a risk of bias such as industry funding, notable conflicts of interest, lack of clarity around open label antibiotic use, noticeable differences in baseline demographics between study groups such as age, severity of illness
		Unclear	Insufficient information to judge low or high risk of bias

Appendix 8: Individual bias assessments of each of the included articles

Abdul-Aziz 2016	**Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis**	
Method	Prospective, two-centre, open-labelled randomised controlled trial	
Participants	140 ICU patients (males 66% intervention group, 71% control, age range 41-68; average 54 years old intervention group, 56 control) were eligible for inclusion after meeting the following criteria: (1) adult (C18 years); (2) developed severe sepsis (defined as presumed or confirmed infection with new organ dysfunction) [24] in the previous 48 h; (3) indication for cefepime, meropenem or piperacillin/tazobactam with \24 h therapy at time of assessment; and (4) expected ICU stay greater than 48 h. Patients were excluded if they (1) were receiving renal replacement therapy (RRT); (2) had impaired hepatic function (defined as total bilirubin[100 mmol/mL); (3) were receiving palliative treatment; (4) had inadequate central venous catheter access; or (5) death was deemed imminent.	
Interventions	Participants currently receiving, or about to receive, cefepime, meropenem or piperacillin/tazobactam were randomly allocated to either a CI (intervention arm) or IB (control arm) treatment arm. Each antibiotic dose was prepared by an on-duty, unblinded ICU pharmacist in accordance with standard pharmacy practice. The dosing regimen was determined by the treating intensivist, with guidance from a local dosing protocol. To ensure early achievement of therapeutic beta-lactam exposures in the intervention arm, a single loading dose infused over 30 min was given at initiation of antibiotic therapy meaning that the continuous infusion group received a larger antibiotic dose on day 1 post-randomisation compared to those in the control arm. The study antibiotic was administered until (1) the treating intensivist decided to cease the drug; (2) the participant withdrew from the study; (3) ICU discharge; or (4) ICU death. All subsequent patient management including addition of other antibiotics and non-study drugs was at the treating intensivist's discretion.	
Outcomes	The primary endpoint investigated in this study was clinical cure at 14 days after antibiotic cessation. Clinical outcome was rated as either (1) resolution: complete disappearance of all signs and symptoms related to infection; (2) improvement: a marked or moderate reduction in disease severity and/or number of signs and symptoms related to infection; or (3) failure: insufficient lessening of the signs and symptoms of infection to qualify as improvement, death or indeterminate for any reason. Clinical cure was scored as a ''Yes'' for resolution and a ''No'' for all other findings (i.e. sum of 2 and 3 above). Secondary endpoints investigated in this study include (1) PK/PD target attainment; (2) ICU-free days at day 28; (3) ventilator-free days at day 28; (4) survival at day 14; (5) survival at day 30; (6) time to white cell count (WCC) normalisation	
Notes	sample size calculation suggested 120, enrolled 140 to allow for drop out and ended with 126 getting >3days of drug. Both groups very similar in terms of sex, age, sickness severity, etc. main reason for drop out was need for RRT	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	"Randomisation was performed using a computer program (http://www.randomization.com) based on blocks of four with an allocation ratio of 1:1 stratified by participating sites"
Allocation concealment (selection bias)	Low risk	"Opening sequentially numbered opaque, sealed and stapled envelopes" "tamper evident envelopes"
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	No patients were lost to follow up. Analysis was performed primarily on an ITT basis and then a mITT including all patients that received at least one dose of antibiotics. Per-protocol analysis was performed on all patients receiving >3day antibiotics. Sample size calculation required 120 participants and 140 were randomised to allow for drop out. 126 received >3days antibiotics therefore sample size was adequate
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes were reported
Other bias	Low risk	No conflicts of interest or funding issues of note. Open label antibiotic use clear documented

Adembri 2008	**Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion**	
Method	Prospective, open-label, randomised controlled trial	
Participants	18 Septic ICU patients with a microbiologically documented infection caused by either glycopeptide-resistant or glycopeptide-sensitive Gram-positive strains but with no clinical improvement after 5 days of glycopeptide therapy were considered eligible for enrolment in the study.Exclusion criteria were the following: age <18 years;pregnancy; previous knownallergic reaction to linezolid; creatinine clearance <40 mL/min; platelet count <80 000; and the simultaneous administration of other drugs (such as erythromycin) capable of interfering with the linezolid assay	
Interventions	Group I (n=9) received linezolid as a 30-min intermittent intravenous (i.v.) administration (600mg q12h); and Group C(n=9) received linezolid as 300mg i.v. loading dose (given in 30 min)+900mg continuous infusion on Day 1, followed by continuous infusion of 1200 mg/daily. Mean duraction of therapy 10 dyas (7-15 days)	
Outcomes	Global response (clinical success/failure), Microbiological efficacy (eradication vs failure where culture were available)	
Notes	69% male, mean age range 57-64 years old, no significant physiological differences between groups. One patient died before completing serum sample collection and one was excluded because he developed renal failure with ClCR <40 mL/min during the sampling period. Clinical success included resolution AND IMPROVEMENT, failure was persistance or new infection	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	"By closed envolope method" but opacity of envolope not stated
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	18 patients enrolled. None lost to follow up but 2 excluded - one died before completing sample collection and one developed renal failure (CrCl <40mL/min) during sample collection.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Open label antibiotics with similar antibacterial cover permitted but numbers not reported

Angus 2000	**Pharmacokinetic-pharmacodynamic evaluation of ceftazidime continuous infusion vs intermittent bolus injection in septicaemic melioidosis**	
Method	Prospective, single centred, randomised controlled trial	
Participants	34 patients with clinically suspected septicaemic melioidosis (age range 18 to 73, 47% male, average body weight 49kg (35-75kg)). "Pregnant women, patients who had already received effective antimicrobial therapy and those with known hypersensitivity to beta-lactam antibiotics were excluded"	
Interventions	Patients were randomised to receive ceftazidime 120mg/kg/day in 0.9% NaCl by either continuous infusion or bolus injection for 10 days	
Outcomes	Not clearly stated but "… study of the pharmacokinetics and in vivo bacterial killing rates….."	
Notes	A typical 50kg patient received 6g/day in the continuous infusion group vs 5.4g on day one then 4.8g/day in the bolus group. Average APACHE II score 21 in bolus group but 15 in infusion group	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear	Patients were randomised but method of randomisation not stated
Allocation concealment (selection bias)	Unclear	Not stated
Blinding of participants and researchers (performance bias)	Unclear	Not stated
Blinding of outcome assessment (detection bias)	Unclear	Not stated
Incomplete outcome data (attrition bias)	High risk	34 patients enrolled, data from 21 suitable for pharmacokinetic analysis (8 patients from the infusion and 5 from the bolus groups excluded). Of these 21, 15 had septic melioidosis, 5 had non-septic melioidosis and 7 didn't have melioidosis (numbers not consistant). Stated mortality not consistant between text and table 1. 11 of the 13 excluded patients died but it is not stated which group (infusion vs bolus) these patients where in.
Selective reporting (reporting bias)	High risk	Outcomes not clearly stated in the paper. In the discussion the authors state that "the objective of this study was to devise the optimum cost-effectiveness intraveneous regimen for ceftazidime administration…..". Authors also state "the original objective of the study to compare bacterial clearance rates between the two regemins could not be fulfilled....."
Other bias	High risk	groups not well matched, bolus group appeared to be more unwell at enrollment (APACHE score 21 vs 15, CrCl (mL/min) 23 vs 38). Patients received considerably different doses between the groups

Bodey 1979	**A randomized study of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients**	
Method	Prospective, single centre, randomised controlled trial	
Participants	Patients with malignancy who were neutropenic and had a fever associated with a proven or suspected bacterial infection was eligible for inclusion. 490 febrile episodes (number of patients not stated) were entered into the study. Final analysis was carried out on 235 documented infections in 204 patients (56% male, 42% > 50years old). Some afebrile but proven infection episodes were included as were some non-neutropenic episodes (were patients were expected to develop neutropenia). Patients with penicillin allergy or whose fever was considered to be from a non-infective cause (e.g. recent blood transfusion) were considered ineligible.	
Interventions	Patients received carbenicillin (5g over 2 hours every 4 hours) plus one of the following three regimens. Either cefamandole as an intermittent infusion (3g over 30 minutes every 6 hours), a continuous infusion (12g over 24 hours), or tobramycin (loading dose of 90mg/m2 over 30 minutes followed immediately a continuous infusion of 360mg/m2/24hours)	
Outcomes	Predefined outcomes were "cure", "relapse" and "super-infection"	
Notes	Outcomes expressed by episode not patient	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	Sequence generated from random number tables
Allocation concealment (selection bias)	Unclear	Sealed envolope but opacity of envolope not stated
Blinding of participants and researchers (performance bias)	Unclear	Not stated
Blinding of outcome assessment (detection bias)	Unclear	Not stated
Incomplete outcome data (attrition bias)	High risk	Of the 490 febrile episodes only 450/460 (contradiction in the paper so unclear) could be evaluated. 234 febrile episodes couldn't be demonstrated as being caused by infection and so were excluded from further analysis. 216 febrile episodes (235 infections, 19 patients had 2 simultaneous infections) were assessed. 10 patients had 2 epidoes and 1 had 3. Participants receiving less than 12 hours of antibiotics were excluded from evaluation
Selective reporting (reporting bias)	High risk	Reported on all predefined outcomes and some extra (e.g. respose by organism) but on approximately half of the enrolled episodes (235 infections out of 460 episodes receiving antibiotics)
Other bias	Unclear risk	Funding and declarations of interest not stated. Cefamandole supplied by Eli Lilly &Co

Buck 2005	**Pharmacokinetics of piperacillin-tazobactam: Intermittent dosing versus continuous infusion**	
Method	Prospective, single centre, open-labelled randomised clinical observational trial	
Participants	24 patients (17 male, age 32-76) with community or hospital-aquired infections were enrolled (specifically (late onset) hospital- acquired pneumonia, severe community-acquired pneumonia, severe urinary tract infection, cholangitis in patients with risk factors, complicated peritonitis, patients at risk with fever of unknown origin). Exclusion criteria were lack of informed consent, pregnancy or lactation in women, known hypersensitivity or intolerance to piperacillin–tazobactam, and epilepsy	
Interventions	Fixed combination of 4 g piperacillin and 0.5 g tazobactam every 8 h by intravenous intermittent bolus injection versus fixed combination of 2 g piperacillin and 0.5 g tazobactam loading dose by bolus injection over 1 h followed by 8 g piperacillin and 1 g tazobactam by constant rate infusion over 23 h (day 1) and 24 h from day 2. Dose was adjusted in patients with impaired renal function	
Outcomes	pharmacokinetic (serum concentration time profiles). Clinical or bacteriological success (based on clinical evaluation)	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear	patients randomised to therapy arms but method of randomisation not stated
Allocation concealment (selection bias)	Unclear	Randomised by envelope but opacity not stated
Blinding of participants and researchers (performance bias)	High risk	Open label, not blinded
Blinding of outcome assessment (detection bias)	High risk	Open label, not blinded
Incomplete outcome data (attrition bias)	Low risk	All patients enrolled in the study included in the results
Selective reporting (reporting bias)	Unclear risk	Clinical and bacteriological success was not a primary objective and not statistically assessed in the results "groups were comparable". Reported all pre-stated outcomes
Other bias	Unclear risk	Study sponsored by grants from Wyeth Lederle. Other antibiotics and renal replacement therapy were alllowed.

Chytra 2012	**Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial**	
Method	Prospective, single centre, open label, randomised trial	
Participants	240 patients (males 65% in the CI group and 69.2% in the control group, average age 44.9 in the CI group and 47.2 in the control group) "who suffered, at admission or during the ICU stay, from severe infection and received meropenem with predicted duration of treatment for at least four days were considered for inclusion", all enrolled patients fulfilled the criteria of sepsis. Exclusion criteria included <18 years old, pregnancy, acute or chronic renal failure and hypesensitivity/allergy to meropenem	
Interventions	Infusion group received a loading dose of 2 g of meropenem over 30 minutes followed immediately by continuous infusion of 4 g of meropenem over 24 hours. Bolus group received 2 g of meropenem over 30 minutes every 8 hours.	
Outcomes	Primary outcome measures - clinical and microbiological efficacy. Secondary outcomes - meropenem-related length of mechanical ventilation, meropenem-related length of ICU and hospital stay, ICU and in-hospital mortality, duration of meropenem treatment, the total dose of meropenem and the safety of both dosing regimens.	
Notes	Funded by Czech Ministry of Education	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	no mention of sequence generation, see below
Allocation concealment (selection bias)	Low risk	"randomized using sealed opaque envelopes in one-to-one proportion without stratification"
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Of the 240 patients enrolled only 198 made final analysis. None where lost to follow up and reasons were stated for other exclusions - 3 patients died within 4 days, antibiotic therapy was de-escalated/terminated in 21 and 2 patients were transferred to other hospitals
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported
Other bias	Low risk	approximately 50% of patients in each group received concomitant antibiotic therapy but use clearly documented and the groups were evenly matched. No conflicts of interest or industry funding

Cotrina-Luque 2015	**Continuous versus intermittent piperacillin/tazobactam infusion in infection due to or suspected pseudomonas aeruginosa**	
Method	Prospective, multi centre, double blinded, randomised trial	
Participants	78 patients (out of 400 patients "initially contemplated theoretically for enrolment", average age 64 years old, male 59%) with "complicated" or nosocomial infection due to suspected or proven P. aeruginosa infection. Aged 18 or over, 40kg or over and consent. The exclusion criteria were: more than one prior piperacillin–tazobactam dose administered before being enrolled; potential death within 72 h after enrollment; a declaration that the patient could not be resuscitated; central nervous system disease; pneumonia requiring mechanical ventilation; neutrophil count <500 cel/ mL; suspected infection by Acinetobacter baumannii or extended-spectrum beta lactamase (ESBL)-producing Enterobacteriaceae; cystic fibrosis; a need for haemodialysis, peritoneal dialysis, hemoperfusion, or plasmapheresis; state of shock (systolic arterial pressure <90 mmHg for >2 h); evidence of hypoperfusion despite adequate fluid support; high-dose sympathomimetic treatment (e.g., noradrenaline >1 mcg/Kg/h); or creatinine clearance <20 mL/ min	
Interventions	CI group were given an initial loading dose of piperacillin–tazobactam 2/0.25 g over 30 min., immediately followed by continuous infusion of piperacillin–tazobactam 8/1 g over 24 h plus 100 mL of placebo (saline solution) given for 30 min every 8 h. The II group received an initial loading dose of piperacillin–tazobactam 4/0.5 g by continuous infusion of placebo (saline solution) plus piperacillin–tazobactam 4/0.5 g in 100 mL of saline for 30 min every 8 h. The maximum duration of treatment in both groups was 14 days, which could be shortened depending on the patient's condition	
Outcomes	The primary efficacy endpoint was the percentage of patients having a satisfactory clinical response at completion of treatment, defined as clinical cure (complete resolution of the clinical signs and symptoms of infection) or clinical improvement (resolution or reduction of most clinical signs and symptoms). The secondary efficacy endpoints were microbiological response at completion of treatment; microbiological response at 3 days after starting treatment; time to microbiological cure; clinical response at 3 days after starting treatment; time to defervescence; percentage of patients who were switched to sequential oral therapy; antibiotic-free period	
Notes	Of the 11 participating hospitals 5 enrolled at least 1 patient but 83 of the final sample came from 1 centre. Funded by the Ministry of Health and Social Policy of Spain with no commercial interest. Patients were followed up until death or 60 days after start of treatment. 400 patient (200 in each arm) were required to show a difference in 14 day survival but only 78 patients were randomised. Lower total daily dose in the CI group (9g vs 13.5g). Data in Table 3 doesn't add up.	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	Allocated to one of the two study groups by the Pharmacy Department of each participating hospital, using the list of random numbers provided by the coordinator center at the start of the study. The randomization code for each patient consisted of three letters (corresponding to the hospital) and three numbers (corresponding to the randomization sequence). Randomization was carried out according to whether the indication for antibiotic treatment was empirical or targeted (with a positive culture of P. Aeruginosa); hence, there were two randomization lists for this purpose
Allocation concealment (selection bias)	Unclear risk	doesn't stat whether unblinded pharmacy staff were involved in any way in patient care. Pharmacy staff would be potentially aware which therapy was next "Patients were randomly assigned in a 1:1 ratio to receive piperacillin–tazobactam as either continuous infusion or standard intermittent infusion"
Blinding of participants and researchers (performance bias)	Unclear risk	double blinded but doesn't state if pharmacy staff involved in production were also involved in patient care
Blinding of outcome assessment (detection bias)	Unclear risk	double blinded but doesn't state if pharmacy staff involved in production were also involved in patient care
Incomplete outcome data (attrition bias)	Unclear risk	400 patients initially contemplated theoretically for enrolment (200 for each group), 152 were assessed for eligibility and 78 were ultimately included (19.5 %). No further mention of the 248 theoretical patients that weren't enrolled. Clear reasons were documented for the exclusion of the 74 that were assessed but uneligible.
Selective reporting (reporting bias)	Unclear risk	Reported on all prespecified outcomes but unable to assess as outcomes changed in view of power calculation and low enrollment
Other bias	Unclear risk	No comercial funding, no conflicts of interest. Use of Concomitant antibiotics not discussed

De Jongh 2007	Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection	
Method	Prospective, unblinded, randomised trial	
Participants	17 patients (mean age 57, males 75% (9 out of 12)) with a high probability of infection from nosocomial origin and no suspicion of an infection by Pseudomonas spp. or another temocillin-resistant bacteria. Exclusion criteria were (i) age <18 or >75 years; (ii) patient's weight <50 or >100 kg; (iii) renal insufficiency (estimated clearance ,45 mL/ min); (iv) haemodialysis; (v) estimated survival <5 days; (vi) documentation of temocillin-resistant organism; (vii) meningitis or other proven infections of the CNS; (viii) IgE-mediated allergy to penicillins; (ix) severe granulocytopenia (<500 poly-morphonuclear leucocytes/mm3); (x) pregnancy; (xi) patients having participated in another study <30 days before; and (xii) retrospectively, marked deterioration of the renal function during the study period	
Interventions	Continuous infusion group received a loading dose (2 g) administered over 30 min followed by infusion of 4 g over 24 hours; twice daily regemin was 2 g temocillin every 12 h injected over a 30 min period. All patients also received flucloxacillin (six times 1 g/day).	
Outcomes	Stability and compatibility; probability of target attainment probabilities; pharmacokinetic/pharmacodynamic (PK/PD) breakpoints.	
Notes	Clinical outcome and survival at 28 days were not predetermined but mentioned in the results	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Patients randomised but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	High risk	Unblinded
Blinding of outcome assessment (detection bias)	High risk	Unblinded
Incomplete outcome data (attrition bias)	High risk	4 out of 10 patients enrolled in the twice daily arm were excluded as there clinical records were not "evaluable", no further information is provided on their clinical outcome.
Selective reporting (reporting bias)	Unclear risk	The only relevant outcome (clinical outcome) was not a prespesified outcome but reported upon
Other bias	Unclear risk	Authors had various industry affiliactions "S. C. is working under contract with Eumedica s.a., Brussels, Belgium, and R. D. J. and P. M. T. are unpaid advisors to Eumedica s.a., Brussels, Belgium". "S. C. is supported by a First-Entreprise grant awarded by the Direction Generale de la Recherche et des Technologies of the Region Wallonne. This work was supported by the Belgian Fonds de la Recherche Scientifique Medicale (grant numbers 3.4549.00 and 3.4542.02) and by a grant-in-aid from Eumedica s.a., Brussels, Belgium to R. D. J.". unclear if open label antibiotic use allowed.

Dulhunty 2013	**Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial.**	
Method	Prospective, multi centre, double blinded, randomised controlled trial	
Participants	60 patients (males 76.7% in the intervention group and 63.3% in the control, average age 54 in the intervention group and 60 in the control) with (1) severe sepsis in the previous 48 hours (2) planned commencement or commencement within the previous 24 hours of ticarcillin-clavulanate, piperacillin-tazobactam or meropenem; and (3) an expected or actual ICU stay greater than 48 hours. Patients were excluded if they were <18 years of age, had an allergy to one or more of the study medications, were receiving palliative or supportive treatment only, were receiving continuous renal replacement therapy, did not have central venous catheter access with at least 3 lumens (a dedicated lumen was required for study drug administration), or had received the study drug for >24 hours.	
Interventions	either (1) active infusion and placebo bolus (intervention arm) or (2) placebo infusion and active bolus (control arm). The 24 hour dose was chosen by the clinician and unaffected by which arm the patient was randomised to.	
Outcomes	Primary endpoint was plasma antibiotic concentration above MIC. Secondary endpoints included clinical response. Time to clinical resolution. Vital status at ICU discharge. Vital status at hospital discharge. ICU- free days. Adverse events.	
Notes	sample size calculation and therefore target number of patients enrolled relate to the primary endpoint only	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by institution with 1:1 allocation to treatment arm
Allocation concealment (selection bias)	Unclear risk	"Following study enrollment, an unblinded research nurse or pharmacist responsible for preparation of the blinded medications determined allocation status by opening a sequentially numbered sealed envelope" opacity of envelopes not stated
Blinding of participants and researchers (performance bias)	Low risk	Double-blind, nurses and medical staff survey with regards to which therapy option they thought the patient was receiving
Blinding of outcome assessment (detection bias)	Low risk	Double-blind, nurses and medical staff survey with regards to which therapy option they thought the patient was receiving
Incomplete outcome data (attrition bias)	Low risk	Data for all 60 patients enrolled was analysed. No patients were lost to follow up. Only 22 patients in each arm (out of 30) had 4 or more days of randomised treatment and had samples taken for plasma antibiotic levels. Reasons for this clearly stated in CONSORT diagram.
Selective reporting (reporting bias)	Low risk	Al predetermined outcomes reported on (clinical response a secondary outcome but actually report clinical cure – both defined in the paper)
Other bias	Unclear risk	No industry financial support for the study but many potential conflicts of interest stated e.g. "J. A. R. has served as a consultant for AstraZeneca, Pfizer, Gilead and Janssen-Cilag. S. A. R. W. has attended Advisory Boards and acted as a consultant to Janssen-Cilag and AstraZeneca. C. G. has served as a consultant for Janssen-Cilag and Pfizer"

Dulhunty 2015	**A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis**	
Method	Prospective, multicenter, double-blind, double-dummy, randomized controlled trial	
Participants	422 patients (males 61.3 in CI group and 61.4 in II, average age 64 in CI and 65 in II) meeting the criteria for severe sepsis and commenced on piperacillin-tazobactam, ticarcillin-clavulanate or meropenem by the treating doctor were included patinets were excluded if the had received the prescribed β-lactam antibiotic for more than 24 hours prior to randomization, were less than 18 years of age, were pregnant or had an allergy or potential allergy to study medications	
Interventions	Participants were randomized to receive the β-lactam antibiotic by either continuous infusion or intermittent infusion over 30 minutes, in addition to an infusion of 0.9% sodium chloride administered as a double-dummy placebo	
Outcomes	Primary outcome measures - alive ICU-free days determined at Day 28 after randomization. Secondary outcome measures - Day-90 mortality, clinical cure assessed at Day 14 post antibiotic cessation, alive organ failure–free days at Day 14 and duration of bacteremia postrandomization. Adverse events recorded and assesssed for causality.	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	Quote "Permuted block randomization stratified by site allocated participants into treatment groups in a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	Quote "An unblinded staff member at each site used a consecutively labeled sealed opaque envelope to determine treatment allocation before study drug preparation". Not immediately clear how the unblinded member of staff was otherwise involved in the study/clinical care of the patients but elsewhere states "Participants, treating clinicians, and study investigators undertaking study assessments or data collection were masked to treatment allocation"
Blinding of participants and researchers (performance bias)	Low risk	Quote "Concealment was achieved by opaque labeling and double-dummy administration with adequacy of blinding reported previously. Participants, treating clinicians, and study investigators undertaking study assessments or data collection were masked to treatment allocation"
Blinding of outcome assessment (detection bias)	Low risk	Quote "Concealment was achieved by opaque labeling and double-dummy administration with adequacy of blinding reported previously. Participants, treating clinicians, and study investigators undertaking study assessments or data collection were masked to treatment allocation"
Incomplete outcome data (attrition bias)	Low risk	443 patients were randomised 11 then excluded, reasons stated in CONSORT diagram. 432 patients included in intention to treat analysis, 422 included in modified intention to treat analysis (excluded aptients accounted for). Per protocol analysis however only included 286 patient, not stated what happened to remaining patients
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported upon
Other bias	Unclear risk	Funding support in part from Baxter Healthcare Pty Ltd

Feld 1977	**A comparative trial of sisomicin therapy by intermittent versus continuous infusion**	
Method	Prospective, randomised controlled trial	
Participants	120 patients (aged 15 to 76; 52% male) with fever and a proven or presumed infection secondary to gram negative bacilli were first treated with a combination of carbenicillin and a cephalosporin antibiotic. If after 48 to 72 they didn't show signs of improvement then they received study drug. exclusion criteria not stated	
Interventions	Sisomicin loading dose of 30mg/m followed immediately via a continuous infusion of 120mg/m/24hours vs 30mg/m over 30 minutes 6 hourly	
Outcomes	complete response, superinfection	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	High risk	18 of 139 possible episodes deemed "inevaluable" for response. 11 where due to infections assumed not to respnd to aminogycosides. The other 7 patients were excluded for receiving other antibiotics but indication not clear. All episodes evaluated for toxicity (not a pre-specified outcome)
Selective reporting (reporting bias)	Low risk	All prestated outcomes reported on
Other bias	Unclear risk	Sisomicin supplied by Schering

Feld 1984	**Empiric therapy for infections in patients with granulocytopenia. Continuous v interrupted infusion of tobramycin plus cefamandole**	
Method	Prospective, randomised controlled trial	
Participants	78 febrile episodes in 70 patient (mean age 54 (range 19 to 83); 60% males in the "evaluable" episodes) with neutropenia and malignant neoplasms with presumed or proven infections due to gram-negative bacilli. Patients were ineligble if they had "poor veins", allergy to one or both study drugs, pregnant or lactating women, creatinine >2mg/dL	
Interventions	Tobramycin 60 mg/m2 (approx. 1.5mg/kg) loading dose over 30 minutes, followed by 300 mg/m2 (approx. 7.5mg/kg) daily as a continuous infusion (adjusted to maintain a serum concentration of approximately 4 to 5 mg/L) vs tobramycin 75 mg/m2 over 30 minutes every 6 hours (adjusted to a peak serum concentration of approximately 6 to 7 mg/L); minimum treatment duration of seven days or five days after the patient became afebrile	
Outcomes	Clinical cure/failure/partial response, mortality, superinfection, nephrotoxicity	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Method of administration determined by a series of random allocations (stratified by hospital) but how random allocations generated not stated
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes but opacity not stated
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	7 episodes were considered inevaluable for response, 5 had none suceptable organisms e.g. *candida spp*. 1 patient received aditional antibiotics for a proven staphylococcal infection. 1 died within "a few hours" of enrolment having received only one dose of study drug. all patients were considered evaluable for toxicity
Selective reporting (reporting bias)	Unclear risk	There were 3 superinfections but not stated in which study arm these occurred
Other bias	Unclear risk	outcomes stated as episodes rather than as participants with one or more episodes, other open label antibiotics allowed

Georges 2005	**Cefepime in critically ill patients: Continuous infusion vs. an intermittent dosing regimen**	
Method	Prospective, open-label, randomised trial with 2 "balanced" parallel groups	
Participants	50 participants receiving artificial ventilation (mean age 48, 82% males) with either probable/certain nosocomial pneumonopathy or bacteremia thought to be senaitive to cefepime. Exclusions: younger than 18 years old or older than 75. Life expectancy of less than 7 days. Allergy to Beta lactams. Resistance to cefepime and/or amikacin. CrCl less than 30mL/min. administration of antibiotics in the 3 preceding days except in cases of clinical failure or isolation of a resistant bacterium, septic shock. pregnancy. cystic fibrosis	
Interventions	2 g cefepime diluted in 50 ml of 0.9% NaCl continuously over 12 hours, twice daily versus 2 g cefepime diluted in 100 ml of 0.9% NaCl over 30 minutes, twice daily. No loading dose was given. Amikacin was given simultaneously with cefepime. In both groups, a single daily dose of 15 mg/kg/day was infused after a loading dose of 20 mg/kg/day and then adjusted according to serum levels	
Outcomes	Bacterial MIC. Pk/Pd parameters (AUCss, AUCss/MIC, AUICss, t>MIC, t>five-fold MIC, t>french breakpoint). Clinical, laboratory and bacteriological efficacy, tolerance and mortality.	
Notes	Prospective, open-label, randomised trial with 2 "balanced" parallel groups	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised with "two balanced groups". Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Blinding of participants and researchers (performance bias)	High risk	open label
Blinding of outcome assessment (detection bias)	High risk	open label
Incomplete outcome data (attrition bias)	Unclear risk	3 participants excluded from analysis for allergy, shock and death
Selective reporting (reporting bias)	High risk	Unclear when outcomes were decided (before or after study completion) "at the end of treatment, Clinical, laboratory and bacteriological efficacy, tolerance and mortality were analysed". Unclear how many patients data analysed. 3 patients were withdrawn from the study for "allergy, shock, and death independent of the infection"
Other bias	Unclear risk	Simultaneous amikacin in both groups and other "authorised antimicrobial treatment" (2 patients received glycopeptide, 1 antifungal). "Helpful" discussions with Bristol-Myers Squibb

Hanes 2000	**Intermittent and continuous ceftazidime infusion for critically ill trauma patients**	
Method	Randomised controlled trial	
Participants	32 critically ill trauma patients (aged 16-65, mean age 34, males 81%) with gram-negative nosocomial pneumonia. Exclusion: known sensetivity to cephalosporins, CrCl less than 30mL/min, resistant causative pathogen.	
Interventions	ceftazidime 2 g intravenouslyover 3o mins every 8 hours or ceftazidime 2g as an intravenous bolus followed by 60 mg/kg per day as a continuous intravenous infusion	
Outcomes	Pk parameters, clinical response	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned but randomisation method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Unclear risk	Quote "Fifteen and 17 patients were randomly assigned to receive intermittent and continuous ceftazidime therapy, respec- tively. One patient (continuous group) was excluded from outcome analysis secondary to an Acinetobacter calcoaceticus pneumonia intermediately sensitive to ceftazidime and another patient (intermittent group) was excluded from all analyses secondary to concomitant Enterococcus urinary tract infection from initial cultures"
Selective reporting (reporting bias)	High risk	Outcomes reported not specified *a priori.* Reporting of results unclear - unclear if reporting affect vs mean or actual MICs, outcomes discussed as percentages of each treatment not absolute numbers relatable to MICs/organisms
Other bias	Unclear risk	"supported by GlaxoWellcome"

Lagast 1983	**Treatment of Gram-Negative Bacillaty Septicemia with Cefoperazone**	
Method	Randomised controlled trial	
Participants	40 non-neutropenic and 5 neutropenic patients (age not stated, 44% (20/45) male) with proven aerobic gram-negative bacillary septicaemia. Exclusions: high likelyhood of death from non-infectios causes, history of allergy to penicillins or cephalosporins, hepatic impairment (bilirubin >2mg%) or renal impairment (creatinine >2mg%)	
Interventions	Both groups received 4g/day. Intermittent group received 2g over 15mins bd. Continuous group received a loading dose of 1g over 15mins followed by 3g over the remainder of the 24 hours on day 1 and the 4g/24hours thereafter	
Outcomes	Cure (defined as disappearance of clinical and laboratory evidence of infection), Failure (death or clinical deterioration requiring antibiotic change), super-infection, Bacterial colonisation, Bacteriological cure at 48 to 72 hours	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	Outcomes reported for all 45 patients
Selective reporting (reporting bias)	High risk	Focus on clinical failure - cure not reported. Adverse events reported but not stated *a priori* as an outcome. Failure not reported by intervention group
Other bias	Unclear risk	Patients age and severity of illness not stated. Funded by pfizer

Laterre 2015	**Temocillin (6g daily) in critically ill patients: continuous infusion versus three times a daily administration**	
Method	Prospective, two-centre, randomised, controlled trial	
Participants	32 patients (53% male, age range 54 to79) residing in adult ICU with clinical signs of abdominal or pulmonary infection likely to be sensitive to temocillin. Exclusions: potentially infected with a pathogen resistant to temocillin, allergy to any penicillin, pragnancy/lactation or participation in another investigational drug study in the preceeding 4 weeks	
Interventions	Patients received either continuous infusion (2g load over 30 mins followed by 6g over 24 hours) or intermittent infusion (2g over 30 mins every 8 hours). Dose was modified according to renal function using predetermined Creatinine clearance/dose banding. For patinets receiving CRRT (4 patients) temocillin was administered at a fixed dose by continuous infusion.	
Outcomes	Pk data, clinical cure, superinfection, overall ICU mortality, adverse events	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method not stated. Quote "divided into three groups"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Unclear risk	Not all patients followed up for pk data. "Thirty-two patients were included and analysed for clinical efficacy, and pharmacokinetics were measured in 29 of them"
Selective reporting (reporting bias)	High risk	Unclear when outcomes were decided (before or after study completion)
Other bias	Unclear risk	Quote "Temocillin and ticarcillin were obtained as Negaban (Eumedica s.a., Brussels, Belgium) and Timentin (GlaxoSmithKline Belgium, Rixensart, Belgium), respectively". "This work was supported in part by Eumedica s.a. Other support was obtained from the Belgian Fonds de la Recherche Scientifique Medicale and the Belgian Region Wallonne".

Lau 2006	**Randomized, Open-Label, Comparative Study of Piperacillin-Tazobactam Administered by Continuous Infusion versus Intermittent Infusion for Treatment of Hospitalized Patients with Complicated Intra-Abdominal Infection**	
Method	Multicenter, prospective, randomised, open-label comparative study	
Participants	262 Hospitalized male and nonpregnant, nonlac- tating female patients ≥18 years old (males 60%, age range 18 - 95) with peritonitis, an intra-abdominal or a periappendiceal abscess, and/or complicated perforated diverticulitis (but not uncomplicated appendicitis) were eligible for enrollment. Exclusions: underlying immunodeficiency or were receiving immunosuppressant medications, including >5 mg prednisone or equivalent per day; other infections requiring systemic antibiotic or antifungal treatment; infections caused by organisms resistant to piperacillin-tazobactam; active or treated leukemia or a systemic malignancy that required chemotherapy, immunotherapy, radiation therapy, or antineoplastic therapy within the past year; known hypersensitivity to β-lactams; infected pancreatic or peripancreatic necrosis in association with necrotizing pancreatitis; severe renal dysfunction (concurrent hemodialysis, peritoneal dialysis, or creatinine clearance <20 ml/ min after adequate hydration); neutropenia (white blood cell count, <1,000/mm3); thrombocytopenia (platelet count, <35,000/mm3); high levels of liver enzymes (aspartate aminotransferase, alanine aminotransferase, total bili- rubin, or alkaline phosphatase levels more than five times the upper limit of normal); an international normalized ratio two or more times the upper limit of normal; multiorgan system failure; irreversible shock; or an anticipated discharge from the hospital in less than 4 days.	
Interventions	Piperacillin-tazobactam was administered as either a one-time i.v. bolus of 2 g/0.250 g infused over 30 min, followed by 12 g/1.5 g infused continuously over 24 h, or an intermittent i.v. infusion of 3 g/0.375 g infused over 30 min every 6 h. Duration 4 - 14 days	
Outcomes	Clinical response at the test of cure, bacteriological response at the test of cure, time to defervescence, time to WBC normalisation, Safety	
Notes	on day 1 continuous infusion patients received a bigger dose (14g vs 12g Piperacillin)	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned but randomisation method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	High risk	262 patients were randomised and treated and then 4 excluded to make a "modified all-treated" of 258. Of this remaining group only 167 patients were "clinically evaluable" and only 114 "bacteriologically evaluable". Of those excluded after the modified all-treated step, 16 were excluded for undefined reasons.
Selective reporting (reporting bias)	High risk	Did not report outcomes for all treated patients
Other bias	High risk	Did not reach pre spesified sample size of 180 patients to assess clinical response (167 pts evaluated). Continuous infusion group potentially sicker (APACHE score >20 in 7 vs 0 patients although mean score 8.3 vs 7.6). Study supported by and authors affiliated to/employed by Wyeth Pharmaceuticals.

Lipman 1999	**Continuous infusion ceftazidime in intensive care: a randomized controlled trial**	
Method	Single site, randomised controlled trial	
Participants	18 adult patients (male/female split and age not stated) with normal renal function requiring ceftazidime according to usual clinical practice. Exclusions not independently stated.	
Interventions	Continuous infusion group received 12 mg/kg over 2 min followed immediately by 2 g over 478 min. They then received 2 g given as an infusion every 8 h. The bolus group received 12 mg/kg of ceftazidime over 2 min followed immediately by 2 g infused over 28 min. Subsequently they received 2 g infused over 30 min every 8 h. treatment duration not stated.	
Outcomes	Plasma ceftazidime concentrations for first 8 hours, adverse drug events	
Notes	Number of patients in each arm not stated. Only relevant outcome was adverse events but no absolute numbers stated therefore unable to include in meta analysis	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	Randomly assigned using "computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	High risk	Groups not evenly matched in age and severity of illness "the infusion group were older (64 vs 53 years; P <0.05) and had higher APACHE II scores (20.5 vs 15.5; P <0.05)". Funding not stated.

Lu 2013	**Treatment study of hospital acquired pneumonia by optimizing dosing regimen of piperacillin/tazobactam: prolonged vs. regular infusion (abstract only)**	
Method	Randomised controlled trial	
Participants	50 ICU patients (58% males, average age 67 and 69 years old) with hospital-aquired pneumonia. Other inclusion criteria and exclusion criteria unknown	
Interventions	Control group: Piperacillin/Tazobactam 4.5g 30 minute infusion every 6 hours. Treatment group: Piperacillin/Tazobactam 4.5g by prolonged infusion over 3 hours every 6 hours.	
Outcomes	Treatment success rate, remedial treatment rate, cost	
Notes	Unable to determine how this study's outcomes align with stated meta-analysis outcomes therefore results not included in data analysis	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomly divided but method not stated in abstract
Allocation concealment (selection bias)	Unclear risk	Not stated in abstract
Blinding of participants and researchers (performance bias)	High risk	Not stated in abstract
Blinding of outcome assessment (detection bias)	High risk	Not stated in abstract
Incomplete outcome data (attrition bias)	Low risk	All enrolled patients made it to final analysis
Selective reporting (reporting bias)	Unclear risk	Unable to determine if outcomes stated a priori
Other bias	Unclear risk	Unable to determine if there are any other sources of bias

Lubasch 2003	**Optimizing ceftazidime pharmacodynamics in patients with acute exacerbation of severe chronic bronchitis**	
Method	Multi-centred, open label, randomised controlled trial	
Participants	81 patients (56 males (69%), mean age 65.3 years old) with purulent exacerbations of severe chronic bronchitis (FEV1<50% predicted in stable phase). Inclusion criteria: age > 40 years; in females patients, a negative pregnancy test, or post-menopause; written informed consent; known chronic bronchitis with an FEV1 < 50% of predicted value; signs of acute exacerbation [at least two of the following symptoms: (i) dyspnoea or increased dyspnoea; (ii) increased sputum volume; (iii) increased cough; (iv) increased sputum purulence; (v) increased bronchial retention of secretion; and (vi) fever ≥37.8°C and/or chills]. Exclusion criteria were: pregnancy or lactation period; allergy or intolerance to β-lactams and/or aminoglycosides; radiological suspicion of pneumonia, asthma, cystic fibrosis, empyema, lung abscess, active tuberculosis or bronchial carcinoma; peak flow <150 L/min in males and <100 L/min in females; neuromuscular diseases; other infection requiring systemic antibiotic therapy; AIDS or HIV-positivity; systemic prednisolone long-term therapy (prednisolone >30 mg equivalent); antibiotic pre-treatment within last 72 h; progressive lethal disease, or life expectancy <1 month; alcohol or drug abuse; creatinine >2.5 mg/L or creatinine clearance <40 mL/min/1.73 m2; shock; mechanical ventilation; neutropenic patients (<2000 granulocytes/mm3); uncooperative patient; or participation in a clinical trial within the last 4 weeks.	
Interventions	For the extended infusion group ceftazidime 2 g iv as a loading dose, followed by ceftazidime 2 g iv over 7 h every 12 h, short infusion group ceftazidime 2 g intravenously over 30mins every 8 h	
Outcomes	Clinical assessment, lung function, and laboratory, sputum and bacteriological examinations were performed before treatment, between days 3 and 5, between days 8 and 9, and within 72 h of the end of treatment.	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Patients randomised but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Clinical outcomes reported for all patients. Bacteriological outcomes reported for all patients with pre-treatment pathogens
Selective reporting (reporting bias)	Low risk	Reported on all pre-specified outcomes of interest
Other bias	Unclear risk	Study sponsored by GlaxoSmithKline

McNabb 2001	**Cost-effectiveness of Ceftazidime by continuous infusion versus intermittent infusion for nosocomial pneumonia**	
Method	Prospective, open-labelled, randomised controlled trial	
Participants	41 adult patients (mean age 56 in II group and 46 in CI group; 56% males) in intensive care with nosocomial pneumonia clinically suspected to be bacterial in origin. Exclusions: AIDS, neutropenia, or had a documented allergy to Beta-lactam antibiotics, signs or symptoms of pneumonia at the time of admission, initial APACHE II >25, pregnancy, significant renal dysfunction (serum creatinine >2.5mg/dL or creatinine clearance <20mL/min, documented active tuberculosis, cystic fybrosis, viral pneumonia, infection with a microorganism known to be resistant to study medication, antimicrobial therapy with activity against suspected pathogens for more than 48 hours prior to enrolment without a persistently positive culture.	
Interventions	If creatinine clearance (CrCl) was >50mL/min then ceftazidime was administered either as an intermittent infusion (II) of 2g iv every 8 hours or as a continuous infusion (CI) of 3g over 24hours. The continuous infusion group received an initial dose of 1g at the start of therapy. For CrCl 31-50mL/min the dose was 2.5g CI over 24 hours vs 2g II every 12 hours, and CrCl 20-30mL/min 2g CI over 24 hours vs 2g II every 24 hours. All patients received once daily tobramycin at a dose of 7mg/kg according to a reference published protocol	
Outcomes	Cost analysis, adverse events, clinical outcome	
Notes	Clinical and microbiological outcomes reported in Nicolau 2001	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	High risk	forty one patients were randomised but six were subsequently declared non-evaluable due to their short duration of therapy (<5 days) (5 from CI and 1 from II)
Selective reporting (reporting bias)	Low risk	Reported on all pre-spesified outcomes of interest
Other bias	Unclear risk	Financial support was provided by Glaxo Wellcome

Nicolau 1999a	**Pharmacokinetics of continuous and intermittent ceftazidime in intensive care unit patients with nosocomial pneumonia**	
Method	Prospective, randomised controlled trial	
Participants	24 ICU patients (62 % males, age range 23 to 64 years old) who had been hospitalised for ≥72hours and then developed a suspected bacterial pneumonia. Exclusion criteria were not stated.	
Interventions	if creatinine clearance (CrCl) was >50mL/min then ceftazidime was administered either as an intermitent infusion (II) of 2g iv every 8 hours or as a continuous infusion (CI) of 3g over 24hours. The continuous infusion group received an initial dose of 1g at the start of therapy. For CrCl 31-50mL/min the dose was 2.5g CI over 24 hours vs 2g II every 12 hours, and CrCl 20-30mL/min 2g CI over 24 hours vs 2g II every 24 hours. All paients received once daily tobramycin at a dose of 7mg/kg according to a reference published protocol	
Outcomes	Pharmacokinetic parameters. Adverse events. No clinical outcomes	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Patients randomised but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	Only patients with normal renal function included in pk studies but all patients assessed for adverse events
Selective reporting (reporting bias)	High risk	Absolute number of adverse events not reported just that "No adverse events were attributed to the dosing regimen of ceftazidime"
Other bias	Unclear risk	Sponsored by a grant from Glaxo pharmaceuticals. Age mismatch between the groups (average age of 45 vs 36.5 in the intermittent and continuous groups respectively)

Nicolau 1999b	**Pharmacokinetic and pharmacodynamics of continuous and intermittent ceftazidime during the treatment of nosocomial pneumonia**	
Method	Prospective, single-centre, single blind, randomised controlled trial	
Participants	34 ICU patients with nosocomial pneumonia (61% males, age range 28 - 72). Patients aged 18 or over who had been hospitalised for at least 72 hours were considered eligible for the study whensuspected to have a bacterial pneumonia based on clinical evidence. No specific exclusion criteria stated.	
Interventions	if creatinine clearance (CrCl) was >50mL/min then ceftazidime was administered either as an intermitent infusion (II) of 2g iv every 8 hours over 30mins or as a continuous infusion (CI) of 3g over 24hours. The continuous infusion group received an initial dose of 1g over 30 mins at the start of therapy. For CrCl 31-50mL/min the dose was 2.5g CI over 24 hours vs 2g II every 12 hours, and CrCl 20-30mL/min 2g CI over 24 hours vs 2g II every 24 hours. Patients whose actual body weight was >100kg were given 1.5x the renally adjusted dose. All paients received once daily tobramycin at a dose of 7mg/kg according to a previously described protocol	
Outcomes	Pharmacokinetic outcomes, adverse events, no clinical outcomes	
Notes	very similar to Nicolau 1999b but appears to be a different group of patients (based on age range)	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	High risk	Single blinded but which group blinded not stated
Blinding of outcome assessment (detection bias)	High risk	Single blinded but which group blinded not stated
Incomplete outcome data (attrition bias)	High risk	41 patients participated but data only analysed for 34. Reasons for exclusion not stated
Selective reporting (reporting bias)	High risk	Outcomes not stated a priori. Adverse events not stated for intermittent group "all patients tolerated the continuous infusions with no infusion-related adverse events....."
Other bias	Unclear risk	Sponsored by a grant from Glaxo Pharaceuticals.

Nicolau 2001	**Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia**	
Method	Prospective, open-labelled, randomised, controlled pilot study	
Participants	41 adult patients (mean age 56 in II group and 46 in CI group; 56% males) in intensive care with nosocomial pneumonia clinically suspected to be bacterial in origin.Exclusions: AIDS, neutropenia, or had a documented allergy to Beta-lactam antibiotics, signs or symptoms of pneumonia at the time of admission, initial APACHE II >25, pregnancy, significant renal dysfunction (serum creatinine >2.5mg/dL or creatinine clearance <20mL/min, documented active tuberculosis, cystic fybrosis, viral pneumonia, infection with a microorganism known to be resistant to study medication, antimicrobial therapy with activity against suspected pathogens for more than 48 hours prior to enrollment without a persistently positive culture.	
Interventions	If creatinine clearance (CrCl) was >50mL/min then ceftazidime was administered either as an intermitent infusion (II) of 2g iv every 8 hours or as a continuous infusion (CI) of 3g over 24hours. The continuous infusion group received an initial dose of 1g at the start of therapy. For CrCl 31-50mL/min the dose was 2.5g CI over 24 hours vs 2g II every 12 hours, and CrCl 20-30mL/min 2g CI over 24 hours vs 2g II every 24 hours. All paients received once daily tobramycin at a dose of 7mg/kg according to a reference published protocol	
Outcomes	clinical and microbiological outcome at 14 and 21 days post-therapy or at the time of institutional discharge. Patients who received 5 or more days of therapy were considered for inclusion. Clinical outcomes defined as cure, improvement or failure, microbiological outcomes defined as eradication, presumed eradication or persistance	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Forty one patients were randomised but six were subsequently declared non-evaluable due to their short duration of therapy (<5 days) (5 from CI and 1 from II). Reasons not stated in this paper but documented in full in McNabb 2001
Selective reporting (reporting bias)	Low risk	Reported on all pre-specified outcomes of interest
Other bias	Unclear risk	Financial support was provided by Glaxo Wellcome

Okimoto 2009	**Clinical effects of continuous infusion and intermittent infusion of meropenem on bacterial pneumonia in the elderly (abstract only)**	
Method	Randomised controlled trial	
Participants	50 patients over 65 years old (60% males, age range 65 to 102) with moderate community-acquired pneumonia. Other inclusion and exclusion criteria unknown.	
Interventions	Control: 500mg meropenem intravenous twice daily, continuous: 1g intravenous over 24hours infused continuously	
Outcomes	Clinical efficacy on both the third day of treatment and the final day of treatment	
Notes	Unable to determine how this study's outcomes align with stated meta-analysis outcomes therefore results not included in data analysis	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomly divided but method not stated in abstract
Allocation concealment (selection bias)	Unclear risk	Not stated in abstract
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	All enrolled patients made it to final analysis
Selective reporting (reporting bias)	Unclear risk	Unable to determine if outcomes stated a priori
Other bias	Unclear risk	Unable to determine if there are any other sources of bias

Rafati 2006	**Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients**	
Method	Prospective, single site, randomised controlled trial	
Participants	40 ICU patients (67.5% male, mean age range 48 to 50) with sepsis with systemic inflammatory response syndrome due to a suspected or proven infection. Exclusion: under 18 years old, hypersensitivity or allergy to Beta lactam antibiotics, renal dysfunction (dialysis or creatinine clearance <40mL/min)	
Interventions	Piperacillin 2 g intravenously (i.v.) over 30 minutes as a loading dose followed by 8 g i.v daily over 24 h (continuous infusion (CI) group; n=20) or piperacillin 3 g i.v. every 6 h over 30 minutes (intermittent infusion (II) group; n=20). All patients received 15mg/kg amikacin daily.	
Outcomes	Clinical efficacy, pk/pd	
Notes	Groups received different total daily doses (10g day 1 then 8g (CI group) vs 12g/day (II group))	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	All patients enrolled included in analysis
Selective reporting (reporting bias)	Low risk	Mortality not stated *a priori* just "clinical efficacy"
Other bias	Unclear risk	Sponsored by grants from Tehran University of Medical Sciences research board. Conflicts of interest not stated. Unclear if open label antibiotic use permitted.

Roberts 2007	**Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study**	
Method	Prospective, single site, open label, randomised controlled trial	
Participants	57 ICU patients (58% male, mean age range 43 - 52 years old) aged 18-80 years old, infected site (as defined by clinical suspicion) and a clinical indication for ceftriaxone (with or without positive cultures), with normal renal function and SIRS, informed consent and treatment for 4 or more days with ceftriaxone. Exclusions: history of organ transplant or recent treatment with cytotoxic drugs	
Interventions	2g ceftriaxone intravenous (iv) bolus daily vs 2g iv over 24 hours. Day one bolus group received 2.5g bolus and continuous group a 500mg bolus then 2g/24hours. Mean duration of treatment 6.1 days (bolus) and 5.5 days (continuous)	
Outcomes	Clinical response and cure, bacteriological response/cure	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	"Patients were randomized into two groups….(sequence generated from a table of random numbers)"
Allocation concealment (selection bias)	Low risk	"using sequential opaque sealed envelopes"
Blinding of participants and researchers (performance bias)	High risk	Open label at point of administration of ceftriaxone
Blinding of outcome assessment (detection bias)	Low risk	"Clinical and bacteriological outcomes were assessed at the cessation of ceftriaxone treatment by a critical care physician blinded to the groupings and with no role in the management of the subjects"
Incomplete outcome data (attrition bias)	Low risk	"Analysis of data was primarily performed on an intention-to-treat (ITT) basis. However, as this was a pilot study, a priori, we also elected to analyse patients that received at least 4 days of antibiotic therapy." "Seven of the recruited patients did not receive at least 4 days of ceftriaxone therapy and were not included in the subgroup analysis."
Selective reporting (reporting bias)	Low risk	Reported all pre-specified outcomes of interest
Other bias	High risk	"Forty-three (of 57 enrolled) patients received concomitant antibiotics during ceftriaxone therapy of whom 19 patients received more than one additional antibiotic". Authors state there was no statistical difference in the number of antibiotics used between the infusion and bolus groups (P = 0.66) but no further details are given with regards to type of antibiotics

Roberts 2009a	Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution	
Method	Single site, randomised controlled study	
Participants	10 ICU patients (70% male, mean age range 55 to 57 years) with known or suspected sepsis and normal renal function	
Interventions	Continuous group received a 500mg bolus followed immediately by a continuous infusion of 3000mg over 24 hours. Bolus group received 1500mg bolus for the first dose then 1g 8 hourly thereafter.	
Outcomes	Stated objectives were comparison of observed plasma and tissue concentration-time profiles, pharmacokinetic variability (population pk model), pk/pd profile of dosing regimens and expected probability of target attainment	
Notes	Clinical outcome not stated as an outcome but mortality stated in results table 1 (survivors vs non-survivors). Timing of this assessment not stated.	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Patients were randomised using random numbers concealed in opaque sealed envelopes, method of random number generation not clear
Allocation concealment (selection bias)	Low risk	…."opaque sealed envelopes"
Blinding of participants and researchers (performance bias)	Unclear risk	Not stated
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	Outcome of interest reported for in all 10 patients
Selective reporting (reporting bias)	Unclear risk	Mortality not stated as an outcome but reported
Other bias	Unclear risk	use of other open label antibiotics not stated

Roberts 2009b	**Piperacillin penetration into the tissue of critically ill patients with sepsis - Bolus versus continuous administration?**	
Method	Prospective, single site, randomised controlled trial	
Participants	13 critically ill patients (77% male, mean age 42 years old in bolus group and 24.5 in continuous group) with known or suspected sepsis in whom piperacillin/tazobactam was deemed appropriate treatment. Exclusions: known/suspected allergy to penicillin or piperacillin/tazobactam. Renal impairment	
Interventions	Continuous group: day 1 4.5g intravenously (i.v.) over 20 minutes then 9g over 24 hours, day 2 onwards 13.5g over 24 hours. Bolus group 4.5g 6-8 hourly at prescribers discretion. Course length not stated.	
Outcomes	Clinical outcome, determination of unbound piperacillin fraction in plasma, drug assay	
Notes	Outcome data not included in meta-analysis and as this patient group and an additional 3 patients are reported again in Roberts 2010 (included)	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	"opaque sealed envolopes"
Blinding of participants and researchers (performance bias)	High risk	Open label, physicians allowed to select the dose used in bolus group (either 6 or 8 hourly)
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	"Cure" reported for all 13 patients (although cure is not defined, definitions provided for "resolution", "improvement" and "failure"
Selective reporting (reporting bias)	Low risk	All relevant prestated outcomes reported for all patients
Other bias	High risk	Continuous group younger. Young patient group with very good (augmented?) renal function and very little use of vassopressors - not typical sepsis/septic shock patients. Other antibiotic use not stated.

Roberts 2010	**First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis**	
Method	Prospective, single site, randomised controlled trial	
Participants	16 critically ill patients (69% male, mean age 41 years old in bolus group and 30 in continuous group) with known or suspected sepsis in whom piperacillin/tazobactam was deemed appropriate treatment. Exclusions: known/suspected allergy to penicillin or piperacillin/tazobactam. Renal impairment	
Interventions	In section 2.1 it is stated that patients received 16g/day in the bolus group versus 12g/day in the continuous group but then goes on to say in section 2.2 that the Continuous group: day 1 4.5g intravenously (i.v.) over 20 minutes then 9g over 24 hours, day 2 onwards 13.5g over 24 hours. Bolus group 4.5g 6-8 hourly at prescribers discretion. Course length not stated.	
Outcomes	(i) Comparison of the observed plasma concentration–time profiles for piperacillin administered by intermittent or continuous dosing to critically ill patients with sepsis at first dose and at steady state; (ii) to describe the pharmacokinetic variability of piperacillin in these patients with a population pharmacokinetic model; and (iii) to assess the pharmacokinetic/pharmacodynamic profile of various piperacillin dosing regimens and to assess the expected probability of target attainment (PTA) by MIC against bacterial pathogens commonly encountered in critical care units.	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Random numbers selected from an opaque sealed envelope. Method of number generation not stated
Allocation concealment (selection bias)	Low risk	"….Opaque sealed envelope"
Blinding of participants and researchers (performance bias)	High risk	Open label, prescriber selected dose (6 vs. 8 hourly) in the bolus group
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Clinical outcome reported for all 16 patients
Selective reporting (reporting bias)	Unclear risk	Mortality not stated a priori
Other bias	High risk	Open label use of other antibiotics not stated. Both groups untypical of the normal ICU septic patient - young and stable (good renal function and minimal vasopressor use)

Sakka 2007	**Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin in critically ill patients in a randomised, controlled trial**	
Method	Prospective, single site, randomised controlled trial	
Participants	20 surgical ICU patients (55% male, mean ages 59 (intermittent) to 62 (continuous) years old) with ICU-aquired pneumonia and normal renal function. Exclusions: renal replacement therapy	
Interventions	1g/1g imipenem/cilastatin i.v. over 40min then at 4 hours 2g/2g per 24 hours for 3 days versus 1g/1g i.v. over 40 mins 3 times daily for 3 days.	
Outcomes	Pharmacokinetic and pharmacodynamic analysis, which coveriates best predict patient survival and imipenem clearance	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	"….randomation code was provided to the clinical investigator in sealed envelopes" but opacity not stated.
Blinding of participants and researchers (performance bias)	High risk	No mention of blinding highly likely to be un-blinded
Blinding of outcome assessment (detection bias)	High risk	No mention of blinding highly likely to be un-blinded
Incomplete outcome data (attrition bias)	Low risk	Patients lost to follow up not explicitly stated but outcomes of interest reported for all 20 patients
Selective reporting (reporting bias)	Unclear risk	Reported on adverse events (not stated as an outcome *a priori)*
Other bias	Unclear risk	"Antibiotic pre-treatment was given to eight patients in the short-term-infusion group (four patients pre-treated with ceftriaxone, one with cefuroxime, two with piperacillin-tazobactam, and one with moxifloxacin). For comparison, nine patients in the continuous group received antibiotic therapy before administration of imipenem-cilastatin (four patients pre-treated with ceftriaxone, two with cefuroxime, two with piperacillin- tazobactam, and one with cefepime)." Study financially supported by MSD

Schmelzer 2013	**Vancomycin intermittent dosing versus continuous infusion for treatment of ventilator-associated pneumonia in trauma patients**	
Method	Prospective, randomised controlled trial	
Participants	73 adult (>18 years old) ICU patients (89% males, average age 41.3 years old (intermittent group) and 40.3 years old (continuous group)) stated on empiric vancomycin after bronchoalveolar lavage for suspected VAP. Exclusions: abnormal renal function (CrCl < 60mL/min), pregnancy, ascites or known allergy to vancomycin	
Interventions	Intermittent group started on 15mg/kg every 12 hours with a pre dose level checked before the fifth dose. Dose adjusted as per protocol and once level in range 15-20mg/L level checked every 7 days until end of therapy. Continuous group loaded with 20 mg/kg then dosed at 0.9-2.4 mg/kg/hour dependent on renal function, level checked after 48 hours and dose adjusted as per protocol until level in range 15-25mg/L. once in range level checked every 7 days until end of therapy. doses rounded to the nearest 200mg	
Outcomes	Attainment of a level in the appropriate range for each group at 48 hours. Number of levels draw after 48 hours. Number of dose changes required until discontinuation. Total cost. Incidence of nephrotoxicity. Clinical outcomes.	
Notes	Study not powered for clinical outcomes so although collected results not compared between groups. 12 patients enrolled in the study more than once.	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	"Patients were randomized to either the intermittent or the continuous dosing groups using computer-generated random number tables"
Allocation concealment (selection bias)	Unclear risk	not stated
Blinding of participants and researchers (performance bias)	High risk	Not stated but highly likely to be unblinded
Blinding of outcome assessment (detection bias)	High risk	Not stated but highly likely to be unblinded
Incomplete outcome data (attrition bias)	Unclear risk	18 patients were withdrawn from the study as a result of discontinuation of the drug before 48 hours or failure to draw levels at the correct time. This attrition was however allowed for in the original sample size calculation and the sample size in each group was still met
Selective reporting (reporting bias)	Unclear risk	All outcomes reported on except clinical outcome for which the data was collected but as the study was powered strictly as a pharmacokinetic study it wasn't compared between groups or reported in the paper
Other bias	High risk	Funding and affiliations not stated. Other open label antibiotic use not discussed

van Zanten 2007	Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/ pharmacodynamics, bacterial susceptibility and clinical efficacy	
Method	Prospective, open-label, randomised controlled study	
Participants	93 hospitalised patients (69% males, mean age 65.3 years (continuous) and 68.6 years (intermittent)) requiring antibiotic therapy for moderate to severe acute exacerbations of COPD (GOLD classes 2-4). Exclusions: included suspected or proven resistance to cefotaxime, administration of antibiotics in the preceding 48 hours, allergy to B-lactam antibiotics, bilirubin >20micromol/L, serum creatinine concentration >120micromol/L or WCC <3.0x109/L	
Interventions	"Continuous infusion of cefotaxime (2 g over 24 h) after an initial loading dose of 1 g given over 30 min (group 1), or cefotaxime 1 g intravenously in three dosages per day at intervals of 8 h infused over a period of 30 min (group 2)".	
Outcomes	Clinical assessment (success, failure, non-evaluable). Pharmacokinetic/pharmacodynamic parameters. Evaluation of antibiotic resistance	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	High risk	open label
Blinding of outcome assessment (detection bias)	High risk	open label
Incomplete outcome data (attrition bias)	High risk	10 patients excluded including 5 deaths "Of the 93 patients initially enrolled, 10 were excluded for the following reasons: death due to cardiac failure (n = 5); antibiotic treatment in the 48-h period before initiation of cefotaxime therapy (n = 2); final diagnosis of squamous cell carcinoma instead of infection (n = 1); and protocol violations (n = 2). These consisted of an unintended conversion from intermittent to continuous therapy (n = 1) and a switch to oral therapy after losing venous access (n = 1). Of the five patients who died after inclusion in the study, three died within 24 h of admission. The other two patients, one in group 1 and one in group 2, died on day 3 after admission. All patients died from cardiac causes [congestive heart failure (n = 4) or decompensated cor pulmonale (n = 1)]. None of these cases was thought to be related to a failure of antibiotic treatment."
Selective reporting (reporting bias)	Unclear risk	All *a priori* outcomes included but drug related adverse events also included in results
Other bias	Unclear risk	"The manufacturer of cefotaxime, Hoechst Marion Roussel, provided a restricted research grant for analysing serum cefotaxime concentrations and for assessing MIC values."

Wright 1979	**Gentamicin and penicillin in the treatment of severe respiratory infections**	
Method	Prospective, randomised controlled trial	
Participants	36 patients (male/female split not documented, age range 11 - 73 years old) mechanically ventilated on a respiratory ICU with either 1) severe pneumonia, 2) COPD with super infection or 3) "shock lung" or "adult respiratory distress syndrome". Exclusions not explicitly stated	
Interventions	"Group A received penicillin 5000000 units in 5% dextrose water by rapid intravenous bolus injection every 6 hours and gentamicin 60 mg/m' in 5% dextrose water every 8 hours by intravenous bolus administration over half an hour. Group B received the same penicillin regimen but the gentamicin was infused over 8 hours by a constant infusion pump after an initial loading dose calculated by the same formula" dose adjusted for renal dysfunction	
Outcomes	None stated	
Notes		
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and researchers (performance bias)	High risk	Not stated but assume not blinded
Blinding of outcome assessment (detection bias)	High risk	Not stated but assume not blinded
Incomplete outcome data (attrition bias)	Unclear risk	36 patients involved in trial and all followed up but levels only included in the results for 30 patients
Selective reporting (reporting bias)	Unclear risk	No outcomes stated *a priori*
Other bias	Unclear risk	use of other open label antibiotics not clear. Funding and conflicts of interest not stated. Groups markedly different sizes (bolus 13 patients, constant infusion 23 patients). ARDS/shock lung not necessarily caused by infection.

Wysocki 2001	**Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study**	
Method	Multicentre prospective randomised controlled study	
Participants	160 patients from 10 medico-surgical ICUs (Male 65%, mean age 63 years old) given vancomycin for MRSA infections (suspected or well established) acquired 72 h after admission. Exclusion: received vancomycin 72 h before current infection, beta-lactam allergy, previously included in the same protocol, or currently in another protocol	
Interventions	Vancomycin 15 mg/kg i.v. Infused over 60 minutes, followed by 30 mg/kg continuous infusion vs vancomycin 15 mg/kg i.v. Infused over 60 minutes q12h; mean treatment duration range 13 to 14 days	
Outcomes	Efficacy; safety; pharmacokinetics, treatment adjustments and monitoring; cost	
Notes	Multicentre prospective randomised controlled study	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	"Randomisation was stratified by centre using a random-number table and a block randomisation method with a block size of 8"
Allocation concealment (selection bias)	Low risk	"The infusion mode was contained in sealed opaque envelopes labelled consecutively with the randomisation numbers"
Blinding of participants and researchers (performance bias)	High risk	"Clinical failure was first evaluated by local investigators, and since the treatment was not administered in a blinded fashion, a committee blinded to the infusion mode reviewed the charts from patients with clinical failure, aswell as those of all of the study patients who died in the ICU" Patients and clinicians were not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	"Clinical failure was first evaluated by local investigators, and since the treatment was not administered in a blinded fashion, a committee blinded to the infusion mode reviewed the charts from patients with clinical failure, aswell as those of all of the study patients who died in the ICU" Patients and clinicians were not blinded
Incomplete outcome data (attrition bias)	High risk	160 patients randomly assigned but only 119 analysed
Selective reporting (reporting bias)	High risk	"After reviewing clinical, laboratory, radiological, and pathological findings, the committee decided by consensus if death could reasonably be attributed to the staphylococcal infection" stated analysis carried out on an intention to treat bases but this is not the case
Other bias	High risk	Administration of non-glycopeptide antibiotics in combination with vancomycin was permitted (and was only reported if > 5 d use). Author conflict of interest not stated.

Bao 2017	**Clinical outcomes of extended versus intermittent administration of piperacillin/tazobactam for the treatment of hospital-acquired pneumonia: a randomized controlled trial**	
Method	Single centre, prospective, single blinded, randomised controlled trial	
Participants	50 adult ICU patients (58% male, median age 71 (range 56 - 82)) with hospital-acquired pneumonia. Exclusions "severe pyemia with hypotension or/and evidences of failure of organ function (shock: systolic pressure <90 mmHg or diastolic pressure <60 mmHg, requiring more than 4 h of administration of vasopressor agents; renal impairment: urine volume <20 mL/h or <80 mL/4 h after excluding any other potentials; acute renal failure requiring dialysis; creatinine clearance (CLcr) <40 mL/min). Other exclusion criteria were: documented infection caused by pathogens beyond the antibacterial spectrum of piperacillin/tazobactam; previously diagnosed repeated lung infection (e.g., bronchial obstruction, ob- structive pneumonia, pulmonary abscess, empyema, and active tuberculosis); history of allergy to penicillins; pregnancy or breast-feeding women."	
Interventions	"Patients were randomized to receive piperacillin/tazobactam 4/0.5 g administered either over 30 min every 6 h as the II group or 3 h every 6 h as the EI group using a syringe pump via a central venous catheter" for a duration of 7 to 14 days. Use of placebo not mentioned. Requirement for additional open label antibiotics classed as clinical failure	
Outcomes	Clinical outcome (success or failure), pk/pd parameters, adverse events, cost	
Notes	Inclusion criteria state age range 18-70 years but median age in both groups 71 with a range of 56 to 80 in the II group and 82 in the EI group	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomized by the institution with 1:1 allocation to each arm but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Allocation status determined by opening sequentially numbered sealed envelopes but opacity not stated
Blinding of participants and researchers (performance bias)	High risk	Unblinded research nurse or pharmacist was responsible the preparation of the blinded drug but unclear if that person then had any further involvement in the care of the patient. Patients administered either a 30 min or 3 hour infusion without a placebo therefore at the very least the nursing staff would be unblinded
Blinding of outcome assessment (detection bias)	High risk	As above
Incomplete outcome data (attrition bias)	Unclear risk	52 patients originally enrolled but 2 were withdrawn, one withdrew informed consent, one creatinine clearance diminished severely after enrolment. Remaining 50 patients reported in final findings
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported
Other bias	Low risk	No conflicts of interest. Nationally funded. Concomitant antibiotic use documented and deemed as clinical failure

Fan 2017	**Clinical outcomes of extended versus intermittent infusion of piperacillin/tazobactam in critically ill patients: a prospective clinical trial**	
Method	single-centre, open-label, prospective, randomised clinical trial	
Participants	367 adults patients (67% males, mean age 69 in EI group and 70 in non-EI group) on a mixed medical/surgical ICU with bacterial infection or neutropenic fever. Excisions: "pregnancy; received more than 48 hours of treatment with effective antibiotics (defined by specimen culture and sensitivity results) within 5 days before the initiation of EI or Non-EI infusion piperacillin/tazobactam; or concomitant use of β-lactam antibiotics."	
Interventions	EI group, piperacillin/tazobactam was dosed according to renal function, at 4.5 g every 8–12 hours and infused over 4 hours. Non-EI group, dosed according to renal function, at 4.5 g every 6–8 hours for normal renal function, and infused over 30 minutes	
Outcomes	Primary clinical outcome was 14 day mortality. Secondary clinical outcomes included in-hospital mortality rate, time to defervescence (defined as the first day when oral, tympanic, or axillary temperature was < 38.0°C or when rectal or core temperature was < 38.5°C for the entire 24 hours in patients who had baseline temperatures above this range and who were considered a clinical success at the test of cure), duration of mechanical ventilatory support, length of ICU stay, and duration of hospital stay	
Notes	Single-centre, open-label, prospective, randomised clinical trial	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	A computer-generated unique hospital number was assigned to each patient on admission to the hospital. Patients whose hospital number ended with an even number (excluding the last checking digit) were assigned to the EI group, whereas those whose hospital number ended with an odd number were assigned to the non-EI group
Allocation concealment (selection bias)	High risk	intensivists and investigators could predict assignment as this was fixed and defined in the protocol i.e. even hospital numbers received EI
Blinding of participants and researchers (performance bias)	High risk	both intensitist and investigator unblinded
Blinding of outcome assessment (detection bias)	High risk	both intensitist and investigator unblinded
Incomplete outcome data (attrition bias)	Low risk	466 patients assessed for eligibility and those excluded clearly accounted for. 375 assigned to a group but 8 patients received the incorrect method of administration leaving the 367 patients for analysis therefore all patients accounted for.
Selective reporting (reporting bias)	Unclear risk	all outcomes stated a priori reported plus adverse events
Other bias	Unclear risk	Concomitant antibiotic use only discussed between survivor and nonsurvivors so split between treatment groups not described. No specific mention of funding.

Ram 2018	**Extended versus bolus infusion of broad spectrum β-lactams for febrile neutropenia: an un-blinded randomized trial**	
Method	Single-centre, open-label, un-blinded, prospective randomised controlled trial	
Participants	105 adults (72% (bolus) and 77% (EI) males, median age 60.1 (bolus) and 60.4 (EI)) undergoing hematopoietic cell transplantation or receiving induction or consolidation chemotherapy for acute leukaemia with febrile neutropenia. Exclusion: "....scheduled for outpatient follow-up during neutropenia, receiving maintenance chemotherapy for acute lymphoblastic leukemia, and if their calculated creatinine clearance was less than 40 ml/min. Patients infected or colonized with bacteria resistant to study antibiotics within 30 days prior to enrolment were also excluded from this study"	
Interventions	Piperacillin-tazobactam (4.5 g intravenously every 8 hours), or ceftazidime (2 g intravenously every 8 hours) in case of a documented history of penicillin allergy. Intermittent bolus infusion = 30-minute infusion, or extended infusion = administered over 4 hours. Patients in the extended infusion arm received a single loading dose of study medication over 30 minutes, followed 6 hours later by the first extended infusion of study medication. Vancomycin, amikacin and fluroquinolones were allow for specified indications as per local guidance.	
Outcomes	The primary study end-point was overall response on day 4 post symptom onset, defined as a composite of 4 criteria: 1. Resolution of fever for at least 24 hours; 2. Microbiological eradication (for microbiologically documented infection): sterile cultures on days 3 and 4; 3. Clinical response (for clinically documented infection): resolution of signs and symptoms of infection; and 4. No need for a change in the antibiotic regimen (addition of an aminoglycoside or a fluoroquinolone within 48 hours of initiating treatment was not considered treatment failure). Treatment was considered successful if all criteria were met. Secondary end points were: 1. Breakthrough bloodstream infection ≥5 days after initiation of treatment; 2. Recurrent fever ≥5 days after initiation of treatment; 3. Infection with Clostridium difficile. 4. Death within 30 days of enrolment into study; 5. Duration of hospitalization; 6. Acute kidney injury (doubling of serum creatinine level) within 4 days; and 7. Use of noradrenaline due to persistent hypotension.	
Notes	Adequately powered according to own calculation	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Low risk	"Enrolment and randomization were done prior to hospital admission for HCT patients and before starting chemotherapy for patients with acute leukemia. Patients were randomly assigned in advance at a 1:1 ratio using computerized random number generation to receive either bolus infusion or extended infusion of β-lactam in case of a febrile neutropenia."
Allocation concealment (selection bias)	Low risk	"Allocation was concealed in sequentially numbered sealed opaque envelopes which were opened by a study coordinator who marked the patient's file with the allocation arm"
Blinding of participants and researchers (performance bias)	High risk	Unblinded
Blinding of outcome assessment (detection bias)	Low risk	"Study endpoints were assessed by study investigators who were blinded to each participant's random assignment"
Incomplete outcome data (attrition bias)	Low risk	123 patients enrolled, 105 patients had febrile episodes so were included in ITT analysis, 91 patients were included in per-protocol analysis. All patient accounted for, no-one lost to follow up
Selective reporting (reporting bias)	Low risk	All primary outcomes reported in both ITT and per-protocol groups
Other bias	Unclear risk	Study funding not stated, "RB received consulting fees from Merck Ltd. and Pfizer pharmaceuticals."

Yang 2017	**Clinical effect and efficacy factors of modified piperacillin-tazobactam dosing regimens in abdominal tumor patients with post-operative pneumonia**	
Method	Prospective randomised controlled trial	
Participants	100 adults (58% males, average age 68.34 years) with pneumonia after abdominal tumor surgery who exhibited no pre-operative heart or lung disease or respiratory dysfunction during the operation or anaesthesia and they had no lung metastesis. The patients underwent radical excision of their tumor and had no post operative bleeding, fistula formation or cardiac dysfunction. Drug susceptibility testing showed an MIC of 4, 8, or 16 mcg/mL for TZP. Exclusions: infection or antibiotics for more than 48 before admission, kidney injury, infection with TZP-insensitive organism, recurrent pulmonary infection due to previously existing factors, penicillin allergy, pregnant/lactating females, "those with any factor likely to increase patients' risk or interfere with the clinical trial."	
Interventions	Patients were split into 4 groups of 25: simple pneumonia, pneumonia with pleural effusion, pneumonia and atelectasis, and severe pneumonia. These groups were then divided randomly into a control group (n=12) and a treatment group (n-13). Control group TZP 4.5g 6h by regular infusion over 30 minutes or treatment group same dose over 3 hours	
Outcomes	Cure/healing time	
Notes	Unable to extract relevant outcomes from the published data therefore not included in meta-analysis	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	randomised but method not stated
Allocation concealment (selection bias)	Unclear risk	randomised but method not stated
Blinding of participants and researchers (performance bias)	High risk	unblinded
Blinding of outcome assessment (detection bias)	Unclear risk	not stated if assessor were blinded
Incomplete outcome data (attrition bias)	Low risk	all patients reported on in the final results
Selective reporting (reporting bias)	Low risk	all outcomes stated a priori reported
Other bias	Low risk	No apparent conflicts of interest or problems with funding

Zhao 2017	**Pharmacokinetic and Pharmacodynamic Efficacies of Continuous versus Intermittent Administration of meropenem in Patients with Severe Sepsis and Septic Shock: A Prospective Randomized Pilot Study**	
Method	Single-centre, prospective, randomised, comparative study	
Participants	50 adults (42% males, average age 68 in continuous group and 67 in intermittent group) diagnosed with severe sepsis or septic shock and admitted to the ICU, received meropenem therapy, and provided informed consent were included in the study, concomitant antimicrobial therapy was permitted. Exclusion: age <18 years, pregnancy, acute or chronic renal failure with a glomerular filtration rate (GFR; calculated with the Cockcroft formula) <50 ml/min, immunodeficiency or taking immunosuppressant medication, allergy to meropenem, and previous application of meropenem in the past 2 weeks.	
Interventions	The patients in the continuous group received a loading dose of 0.5 g of meropenem in 100 ml of normal saline i.v. infused over 30 min followed immediately by continuous infusion of 3 g of meropenem over 24 h. The patients in the intermittent group received the first dose of 1.5 g of meropenem in 100 ml of normal saline infused over 30 min, and then 1 g in 100 ml of normal saline infused over 30 min for every 8 h. The dose for both groups on day 1 was 3.5 g and 3 g/day thereafter.	
Outcomes	Primary: clinical Success (complete or partial resolution)/failure, microbiological outcomes inc. eradication and superinfection. Secondary:ICU mortality, length of ICU stay, duration of meropenem therapy	
Notes	Single-centre, prospective, randomised, comparative study	
Risk of bias		
Bias	**Judgement**	**Support**
Random sequence generation (selection bias)	Unclear risk	Randomised but method not stated - "randomized into equally numbered groups using sealed opaque envelopes without stratification."
Allocation concealment (selection bias)	Low risk	"randomized into equally numbered groups using sealed opaque envelopes"
Blinding of participants and researchers (performance bias)	High risk	Not stated and researchers "not involved in clinical stratergy" but patient and staff would be aware of which group they had been allocated to
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated, reasearchers not involved in clinical stratergy
Incomplete outcome data (attrition bias)	Low risk	Outcomes of interest stated for all participants
Selective reporting (reporting bias)	Low risk	All prestated outcomes of interest reported
Other bias	Unclear risk	No conflicts of interest stated, funded by Chinese Medical Association, concomitant use of antibiotics not commented on

Appendix 9: Summary of the outcomes for each article

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Abdul-Aziz 2016	P/T, M, Cefepime	T	CI	Clincal Cure at 14/7 (1)	all ITT (mITT/PP in supp tables)	actual numbers	39	70	24	70				
				Pip/taz			22	38	15	47				
				Mero			14	21	8	21				
				Cefepime			3	11	1	2				
				ICU-free days (2)		Median					20		17	
				ventilator free days (2)		Median					22		14	
				Survival at 14/7 (2)		actual numbers	56	70	50	70				
				Survival at 30/7 (2)		actual numbers	52	70	44	70				
				AE (-)		actual numbers	0	70	0	70				
Adembri 2008	Linezolid	T	CI	Clinical Cure (1?)	PP	actual numbers	6	8	6	8				
				Microbiological Cure (1?)	PP	actual numbers	8	9	7	11				
Angus 2000	Ceftazidime	T	CI	All cause mortality (-)	*	actual numbers	3	10	9	11				
Bodey 1979	C/C	T	CI	Cure	data from episodes not patients therefore excluded from MA									
				Relapse										
				Superinfection										

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Buck 2005	P/T	T	CI	Response[a]	ITT	actual numbers	8	12	8	12				
Chytra 2012	M	T	CI	Clinical Cure (cured/improved)(1)	ITT	actual numbers	88	120	81	120				
				Clinical Cure (cured/improved)(1)	CE	actual numbers	88	106	81	108				
				Clinical Cure	ITT	actual numbers	30	120	24	120				
				Clinical Cure	CE	actual numbers	30	106	24	108				
				post hoc sub groups (1)	all PP	actual numbers								
				1a) cultures based			86	100	75	101				
				1b) Empirical			4	6	6	7				
				2)without conc. Abx tx against G-			80	95	76	102				
				3) APACHE II >20			37	49	42	53				
				4) MIC > or =1.5mg/L			10	14	12	21				
				Microbiological Cure (1)	PP	actual numbers	87	96	80	102				
				i) verified			67	96	62	102				
				ii) presumed			20	96	18	102				
				post hoc sub groups (1)	all PP	actual numbers								
				1a) cultures based			82	90	74	95				
				1b) Empirical			5	6	5	7				
				2)without conc. Abx tx against G-			77	85	75	96[b]				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Chytra 2012	M	T	CI	3) APACHE II >20			41	47	36	49				
				4) MIC > or =1.5mg/L			11	14	13	21				
				meropenem related length of	all ITTand PP									
				1) mechanical vent. (2)	ITT	Median					9		11	
					PP						9		12	
				2) ICU stay, LOS (2)	ITT	Median					10		12	
					PP						10		13	
				3) Hospital stay, LOS (2)	ITT	Median					26		22	
					PP						28		25	
				ICU mortality (2)	ITT	actual numbers	18	120	25	120				
					PP		14	106	17	108				
				in hospital mortality (2)	ITT	actual numbers	21	120	28	120				
					PP		17	106	19	108				
				duration of M tx (2)	ITT	Median (days)					7		8	
					PP						7		8	
				total M dose (2)	ITT	Median (dose in g)					24		48	
					PP						24		48	
				safety (2)	ITT (episodes)	actual numbers	10	120	12	120				
				withdrawal due to adverse events (-)	ITT	actual numbers	0	120	0	120				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Chytra 2012	M	T	CI	Superinfection (-)	PP	actual numbers	7	96	8	102				
Cotrina-Luque 2016	P/T	T	CI	Clinical response[c]; end of Tx(1)	ITT	actual numbers	26	40	32	38				
				Clinical Cure at end of Tx[w]	ITT	actual numbers	7	40	12	38				
				Microbiological response; end of Tx (2)	ITT	actual numbers	2	32	2	25				
				Microbiological response; day 3 (2)	ITT	actual numbers	2	32	2	25				
				Time to microbiological cure (2)	ITT	Median (days)					3		3	
				Clincal response[c]; day 3 (2)	ITT	actual numbers	18	33	17	29				
				Time to defervescence (2)	ITT	Median (days)					2		3	
				% patients switched to oral (2)	ITT	actual numbers	8	40	11	38				
				Antibiotic-free period[d] (2)	ITT									
De Jongh 2008	Temocillin	T	CI	Clinical outcome successful (-)	**	actual numbers	6	6	6	6				
				survival at 28 days (-)	**	actual numbers	6	6	6	6				
Dulhunty 2013	P/T, M, T/C	T	CI	Clinical response; 7-14/7 post abx stopped (2)	ITT	actual numbers	23	30	15	30				
				ICU mortality (2)[e]	ITT	actual numbers	2	30	4	30				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Dulhunty 2013	P/T, M, T/C	T	CI	in hospital mortality (2)[e]	ITT	actual numbers	3	30	6	30				
				ICU-free days (2)	ITT	Median (days)					19.5		17	
				Adverse events (2)	ITT	actual numbers	0	30	0	30				
Dulhunty 2015	P/T, M, T/C	T	CI	Alive ICU-free days (1)	all ITT (mITT/PP in supp tables)	Median (days)					18		20	
				Alive ICU-free days; ICU survivors (-)		Median (days)					21		22	
				Day 90 mortality (2)		actual numbers	156	212	158	220				
				ICU survival (-)		actual numbers	180	212	182	220				
				Hospital survival (-)		actual numbers	168	212	164	220				
				Clinical cure; 14/7 post abx cessation (2)		actual numbers	111	212	109	220				
				Alive organ failure free days (2)		Median (days)					6		6	
				Duration of bacteremia post randomisation (2)		Median (days)					0		0	
				ICU length of stay (-)		Median (days)					7		6	
				Hospital length of stay (-)		Median (days)					16		14	
				Adverse events (-)		actual numbers	20	212	28	220				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Dulhunty 2015	P/T, M, T/C	T	CI	Serious adverse events (-)		actual numbers	19	212	25	220				
Feld 1977	Sisomicin	C	CI	Clincal Cure (1?)	episodes (exclude)	actual numbers								
				Mortality (-)	ITT	actual numbers	8	63	6	57				
				Superinfection (1?)	can't find	actual numbers								
				Nephrotoxicity (-)	episodes (exclude)	actual numbers								
Feld 1984	Tobramycin	C	CI	Response (-)	episodes (exclude)	actual numbers	10	12	17	22				
				Mortality (-)	pts with proven infection	actual numbers	2	10	5	16				
				Nephrotoxicity (-)	evaluable patients	actual numbers	2	28	6	40				
				Superinfection (-)	ITT?	actual numbers	2	30	1	40				
Georges 2005	Cefepime	T	CI	Clinical cure (2?)	PP	actual numbers	22	26	16	24				
				days of ventilation (2?)	PP	Mean (days)					24		25	
				days on ICU (2?)	PP	Mean (days)					34		40	
				Clinical failure (2?)	PP	actual numbers	4	26	7	24				
				Bacteriological cure (2?)	PP	actual numbers	18	26	13	24				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Georges 2005	Cefepime	T	CI	No eradication (2?)[f]	PP	actual numbers	2	26	3	24				
				Failure (2?)	PP	actual numbers	1	26	2	24				
				Overinfection (2?)	PP	actual numbers	3	26	4	24				
				Mortality (2?)	PP	actual numbers	3	26	3	24				
Hanes 2000	Ceftazidime	T	CI	Clinical response (1?)[g]	PP	actual numbers	9	16	10	14				
				superinfection (-)	PP	actual numbers	7	16	3	14				
				days of ventilation (-)	PP	Mean (days)					13.3		22.9	
				days on ICU (-)	PP	Mean (days)					15.5		26.8	
				hospital stay (-)	PP	Mean (days)					28.7		41.7	
Lagast 1983	Cefoperazone	T	CI	Clinical cure (1?)	ITT	actual numbers	14	20	20	25				
				Bacteriological cure (1?)[h]	ITT	actual numbers	n/a	n/a	n/a	n/a				
				Superinfection (1?)	ITT	actual numbers	2	20	1	25				
				Death (1?)	ITT	actual numbers	5	20	4	25				
				withdrawal due to adverse events (-)	ITT	actual numbers	0	20	0	25				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Laterre 2015[i]	Temocillin	T	CI	Clinical cure (-)	ITT	actual numbers	13	14	11	14				
				Overall ICU mortality (-)	ITT	actual numbers	2	14	5	14				
				Adverse reaction (-)	ITT	actual numbers	1	14	0	14				
				Superinfection (-)	ITT	actual numbers	1	14	0	14				
Lau 2006	P/T	T	CI	Clincal success (1)[j]	mITT	actual numbers	96	128	104	130				
					CE	actual numbers	70	81	76	86				
					BE	actual numbers	46	56	49	58				
				Bacteriological response (2)[k]	BE	actual numbers	47	56	51	58				
				Time to defervescence (2)		median (days)					3	2 to 8	3	2 to 6
				Time to WBC normalisation (2)		Median (days)					3	2 to 11	3	2 to 11
				safety (2) (adverse events)[l]	mITT	actual numbers	22	130	18	132				
				as above but all	mITT	actual numbers	116	130	115	132				
				safety (2) (withdrawal due to adverse events)[l]	mITT	actual numbers	2	130	1	132				
				as above but all	mITT	actual numbers	6	130	3	132				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Lipman 1999		T	CI	no relevant outcomes										
Lu 2013	P/T	T	EII	treatment success	ITT	actual numbers	22	25	20	25				
				Relapse	ITT	actual numbers	1	25	2	25				
Lubasch 2003	Ceftazidime	T	EII	Clinical outcome (1)[m]	ITT	actual numbers	37	41	36	40				
				bacteriological efficacy (1)	BE	actual numbers	37	41	35	40				
				safety (-)	patients not separated out									
McNabb 2001[u]	Ceftazidime	T	CI	adverse events (-)	ITT	actual numbers	11	17	13	18				
				Superinfection (-)	ITT	actual numbers	3	17	3	18				
Nicolau 1999b	Ceftazidime	T	CI	adverse events (-)	ITT	actual numbers	0	11	0	13				
Nicolau 2001	Ceftazidime	T	CI	clinical cure at day 14-21 (1)	CE	actual numbers	7	17	6	18				
				clinical cure and improvement at 14-21/7 (1)	CE	actual numbers	16	17	15	18				
				microbiological erad at day 14-21 (1)[n]	BE	actual numbers		20		31				
				microbiological erad and presumed erad 14-21/7[n]	BE	actual numbers		20		31				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Nicolau 2001	Ceftazidime	T	CI	microbiological response	BE	actual numbers	10	13	12	15				
				bacterial eradication (-)	BE	Average (days)					6	2 to 10	3.9	0.1 to 7.7
				safety (-)	ITT	actual numbers	patients not separated out (but reported in McNabb 2001)							
				Superinfection	ITT	actual numbers	patients not separated out (but reported in McNabb 2001)							
				ICU length of stay (-)	CE	Average (days)					8.5	5.2 to 11.9	9.3	5.3 to 13.3
Okimoto 2009	M	T	CI	Efficacy rate (-)	?	actual numbers	20	25	19	25				
				bacterial eradication (-)	?[o]	actual numbers	11	12	15	17				
Pedeboscq 2001	P/T	T	CI	no relevant outcomes										
Rafati 2006	Piperacillin	T	CI	WCC normalisation (-)	pts with abnormal WCC	actual numbers	12	16	10	12				
				Mortality (-)	mITT	actual numbers	5	20	6	20				
Roberts 2007	Ceftriaxone	T	CI	Clinical response (1)[p]	ITT	actual numbers	25	29	23	28				
				Clinical cure (1)	ITT	actual numbers	13	29	5	28				
				Bacteriological cure (1)[q]	ITT	actual numbers	18	29	14	28				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Roberts 2007	Ceftriaxone	T	CI	Superinfection (1)	ITT	actual numbers	1	29	2	28				
				Secondary infection (1)	ITT	actual numbers	1	29	0	28				
				Clinical response (1)[p]	PP	actual numbers	24	25	22	25				
				Clinical cure (1)	PP	actual numbers	13	25	5	25				
				Bacteriological cure (1)[q]	PP	actual numbers	18	25	14	25				
				Superinfection (1)	PP	actual numbers	1	25	2	25				
				Secondary infection (1)	PP	actual numbers	1	25	0	25				
				mortality (-)	ITT	actual numbers	3	29	0	28				
				adverse events			"neither was associated with an increased incidence of AE"							
Roberts 2009a	M	T	CI	mortality (outcome) (-)	ITT	actual numbers	2	5	0	5				
Roberts 2009b	P/T	T	CI	Clinical outcome[r]	ITT	actual numbers	6	6	7	7				
Roberts 2010	P/T	T	CI	mortality (outcome) (-)	ITT	actual numbers	0	8	0	8				
Sakka 2007	I/C	T	CI	mortality (outcome) (-)	ITT	actual numbers	1	10	2	10				
				ICU LOS (-)	ITT	Average (days)					14	6 to 22	12	5 to 19

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Sakka 2007	I/C	T	CI	Adverse events (-)	ITT	actual numbers	0	10	0	11				
Schmelzer 2013	Vancomycin	MIC:AUC	CI	Nephrotoxicity (2) (defined AE in MA(1))	PP	actual numbers	1	28	3	27				
van Zanten 2006	Cefotaxime	T	CI	Clinical outcome (1)[s]	NE	actual numbers	37	40	40	43				
				Microbiological analysis (1)	NE	actual numbers	not relevant to this study							
				AE (-)	NE	actual numbers	0	40	0	43				
				Mortality (-)	ITT	actual numbers	4	47	1	46				
Wright 1979	Gentamicin	C	CI	Mortality (-)	ITT	actual numbers	5	23	3	13				
Wysocki 2001	Vancomycin	MIC:AUC	CI	Efficacy (1)[t]	PP	actual numbers	48	61	47	58				
				Safety (1)	PP	actual numbers	12	n/a	12	n/a				
				Nephrotoxicity (defined AE in MA(1))	PP	actual numbers	10	61	11	58				
				mortality (-)[v]	PP	actual numbers	21	61	19	58				
Bao 2017	P/T	T	EII	Clinical outcome (1)[x]	PP	actual numbers	22	25	20	25				
				AE (1)	PP	actual numbers	23	25	19	25				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Bao 2017	P/T	T	EII	SAE (-)	PP	actual numbers	5	25	4	25				
				WAE (-)	PP	actual numbers	2	25	3	25				
Fan 2017	P/T	T	EII	Mortality 14/7 (1)	PP	actual numbers	21	182	29	185				
				Mortality in hospital (2)	PP	actual numbers	52	182	59	185				
				Time to defervescence (2)	PP	mean (days)					4		6	
				Duration of mechanical support (2)	PP	mean (days)					5		5	
				ICU length of stay (2)	PP	median (days)					3		4	
				Hosptial length of stay (2)	PP	median (days)					20		21	
				AE (-)	PP	actual numbers	0	182	0	185				
Ram 2018	P/T, ceftazidime	T	EII	Overall response (1)[y]	ITT	actual numbers	35	47	32	58				
					PP	actual numbers	35	43	30	48				
				Clincal failure (1)[z]	ITT	actual numbers	3	47	11	58				
					PP	actual numbers	1	43	5	48				
				Fever (2)	ITT	median (days)					2		2	

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Ram 2018	P/T, ceftazidime	T	EII		PP	median (days)					2		2	
				Noradrenaline (2)	ITT	actual numbers	4	47	10	58				
					PP	actual numbers	2	43	4	48				
				AKI (2)	ITT	actual numbers	3	47	6	58				
					PP	actual numbers	3	43	4	48				
				C. diff (2)	ITT	actual numbers	0	47	2	58				
					PP	actual numbers	0	43	2	48				
				breakthrough BSI (2)	ITT	actual numbers	2	47	7	58				
					PP	actual numbers	2	43	7	48				
				Breakthrough fever after day 4 (2)	ITT	actual numbers	6	47	10	58				
					PP	actual numbers	5	43	9	48				
				LoS	ITT	median (days)					23		24	
					PP	median (days)					22		23	
				Death, 30 days	ITT	actual numbers	1	47	2	58				

Study Name	Antibiotic	T vs C vs MIC:AUC	EII or CI	Outcome	Sample Tested	Form?	EI Event	EI total	Standard Event	Standard Total	EI	conf. int.	Standard	conf. int.
Ram 2018	P/T, ceftazidime	T	EII		PP	actual numbers	1	43	2	48				
Yang 2017	P/T	T	EII	no relevant outcomes										
Zhao 2017	M	T	CI	Clinical success (1)[aa]	ITT	actual numbers	16	25	14	25				
				Superinfection (1)	ITT	actual numbers	1	25	4	25				
				ICU length of stay (2)	ITT	average (days)					10		10	
				ICU mortality (2)	ITT	actual numbers	7	25	8	25				
				Duration of meropenem treatment (2)	ITT	average (days)					7.6		9.4	

Key

ITT	Intention To Treat
mITT	modified Intention To Treat
PP	per-protocol
CE	Clinically evaluable
BE	Bacteriologically evaluable
NE	Number of evaluable patients
*	those included in PK/PD analysis
**	limited to pts with evaluable samples
1	stated primary outcome
2	stated secondary outcome
-	outcome not stated a priori
?	stated a priori but not clear if 1 or 2
P/T	Piperacillin/tazobactam
M	Meropenem
C/C	Carbenicillin/cefamandole
T/C	Ticarcillin/clavulanate
I/C	Imipenem/cilistatin
EI	Extended infusion
EII	Extended intermittent infusion
CI	Continuous infusion
T	Time dependent kill
C	Concentration dependent kill
MIC:AUC	Ratio dependent kill

Notes

a	resolution or improvement of clinical and laboratory signs of infection
b	deduced from percentage stated
c	clinical cure and clinical improvement
d	time between the end of the 1st treatment and the beginning of a 2nd for the same focus of infection
e	expressed in the paper as survival
f	no eradication: clinical recovery but pathogen persistent
g	"cure" and "improvement" classified as successful clinical response
h	stated in method but then not reported on as CI vs II
i	I've not included the pts on CVVH as they all received CI
j	"cure" and "improvement" classified as successful clinical response
k	success = eradication/presumed eradication, failure = persistence/presumed persistence
l	limited to treatment-related rather than all
m	"cure" and "improvement" classified as successful clinical response
n	primary outcomes not reported in the body of the paper
o	sample those patient that grew a microorganism
p	"resolution" and "improvement" regard as clinical response for the purpose of this MA
q	success = eradication/presumed eradication, failure = everything else
r	clinical outcome cure in the table and resolution/improvement/failure in definition
s	"cure", "improvement" or no requirement for antibiotic treatment within 48hrs of discontinuation classified as successful clinical response
t	efficacy defined as clinical failure (death or clinically unchanged/worsening)
u	reported in both McNabb 2001 and Nicolau 2001
v	in ICU mortality
w	numbers in table don't add up
x	"cure" and "improvement" classified as successful clinical response and no additional antibiotic therapy required
y	composite of 4 elements inc. clinical failure
z	clinical failure reversed to give clinical response
aa	clinical success defined as complete or partial resolution