A Pilot Randomised Control Trial, in Intensive Care Patients, Comparing Seven Days Versus Two Days Treatment With Empirical Antibiotics to Treat Hospital Acquired Infection of Unknown Origin

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List of Abbreviations

AE	Adverse Event
APACHE II	Acute Physiological and Chronic Health Evaluation II
APTT	Activated Partial Thromboplastin Time
BSIs	Blood Stream Infections
CABG	Coronary Artery Bypass Graft
CCA	Critical Care Area
eGFR	Estimated Glomular Filtration Rate
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
MI	Myocardial Infarction
NHS	National health Service
OG	Oesophagogastrectomy
PCI	Percutaneous Coronary Intervention
POCCU	Post-op Critical Care Unit
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIRS	Severe Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment score
UTI	Urinary Tract Infection
VAP	Ventilator Acquired Pneumonia

EXECUTIVE SUMMARY

Background:

Patients in intensive care units (ICUs) are at higher risk of hospital-acquired infections and sepsis than those in non-critical care areas [(1)]. Hospital-acquired sepsis is reported to occur in 10% to 70% of patients undergoing invasive mechanical ventilation, the rate varying with the patient population studied and diagnostic criteria used [(2)]. Despite the major advances in intensive care management, sepsis and its complications remain the leading cause of mortality in ICUs [(3)].

Management of ICU sepsis is also complicated by the high incidence of Systemic Inflammatory Response Syndrome (SIRS), which mimics many of the signs of sepsis but often without an infective cause. This is particularly true in ICU's that have a high proportion

of patients following major surgery since the surgery alone may precipitate a SIRS episode. A good example of this is cardiac surgical ITU since cardiopulmonary bypass is a strong trigger for SIRS generating; for example, pyrexia and a raised white cell count in the absence of an infective cause.

The potential difficulty in differentiating sepsis from SIRS in these high-risk patients makes it inevitable that intensivists often have a low threshold for commencing antibiotics to 'cover' the potential of an infection - even though a definite infective cause has not been proven. Indeed, many patients with suspected sepsis in ICU may be given antibiotics for a significant proportion of their stay to reduce the risk of septic complications, even in cases where there are no compelling positive microbiological results.

To date most studies have focused either on optimising antibiotic treatment for ventilator acquired pneumonia (VAP), which accounts for approximately 50% of antibiotics use in ICU [4-6] or for treatment of suspected sepsis often of unknown origin.

In the group of patients with apparent sepsis of unknown origin, clinical decisions for empirical antibiotic treatment are usually based on fever, excessive tracheal aspirates, increased white cell counts and heart rate, even if no x-ray changes are apparent. We hypothesise that prolonged treatments with antibiotics in these patients is unnecessary particularly if there are no confirmed organisms grown in blood cultures.

Objectives:

Evidence from randomised trials about the duration of antibiotic use is absent. In this pilot randomised trial we investigated whether, in the ICU, 48 hours of antibiotic treatment is adequate to safely treat suspected sepsis when it is of unknown and unproven origin, when compared with a more traditional week-long course.

In addition, we planned to explore the role of the newer biomarkers for sepsis in predicting the patients in which 48 hours of antibiotics might be inadequate. We did not use these biomarkers as part of the entry criteria for the trial, as this is not currently routine practice in most UK intensive care units. However, at the land-mark time points in the trial, we collected samples for the biphasic APTT waveform and the procalcitonin concentration and this data is presented.

Method:

This study was carried out in the intensive care and post-operative critical care units at Liverpool Heart and Chest NHS Foundation Trust between May 2010 and July 2011. Institutional and National ethical approvals were obtained prior to recruitment commencing.

Patients being treated within the intensive care were recruited into the trial if they were being commenced upon the 'Surviving Sepsis' Care Bundle antibiotics by the intensivist in the absence of an actual known cause for that potential sepsis. To trigger the bundle, patients needed to have at least two of the four markers of SIRS (i.e. temperature $>38^0$C or $<36^0$C, tachycardia (>90beats per minute), tachypnoea ($\geq$20 breaths per minute) and white blood count > $12\times 10^{9/}$L or < 4×10^9/L) and a suspected but not proven infection. In other words, patients were recruited if the intensivist was planning to commence antibiotics because of evidence of SIRS and a strong suspicion of infection – but no actual known source for that infection. Patients were therefore excluded if they had positive microbiological cultures before randomisation

Eligible patients were randomised in equal proportions between the two trial groups:

- Antibiotic treatment administered for **48 hours**
- Antibiotic treatment administered for **7 days**

After randomisation, a baseline Acute Physiological and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment score (SOFA score) [(7)] was recorded, two sets of blood culture, at least 15 minutes apart were taken and blood samples were sent for baseline biphasic APTT waveform and procalcitonin analysis. These samples were centrifuged; serum was separated and frozen for analysis at a later stage. This was followed by the administration of the study antibiotics.

Table 1: Antibiotic prescribing method

Patient Weight	Teicoplanin	Meropenem
< 85kg	400mg twice a day on day 1 400mg once a day thereafter.	1g 3 times a day
>= 85kg	6mg/kg rounded to nearest 50mg twice a day on day1 6mg/kg rounded to nearest 50mg once a day thereafter.	1g 3 times a day

After completion of the treatment regime allocated at randomisation, additional antibiotic use constituted an outcome measure. The reason for the initiation of further antibiotics was documented in the trial case record forms. Similarly, if the antibiotics were stopped or changed before the scheduled completion of the course, the reason was recorded. Decisions to change, restart or stop antibiotics were made by consultant intensivists or microbiologists who were guided by evidence of positive cultures, X-ray and other imaging diagnostic information or poor physiological status believed to be related to infection. The reasons for any deviation from the protocol were also documented.

The trial patients were followed up for a period of 10 days by the research team. SOFA scores were calculated and documented in case record forms. Blood samples were taken at baseline, 48 hours and on initiation of additional antibiotics beyond the randomised schedule for measurement of prospective biomarkers of sepsis: biphasic APTT and procalcitonin (8-10). Trial antibiotics were prepared, packaged, stored and dispensed in accordance with Good Manufacturing Practice for Investigational Medicinal Products.

Primary outcome measures were defined by either initiation of antibiotic therapy after the completion of the treatment schedule allocated at randomisation or in trial mortality. Secondary outcome measures were defined in terms of duration of ICU stay, duration of mechanical ventilation, duration of hospital stay, and incidence of infection with MRSA and Clostridium Difficile.

Results:

Forty-six patients were randomised into the trial out of a total of 103 patients assessed for eligibility. The majority of patients recruited were post –cardiothoracic surgical.

Recruited patients were evenly split between the trial groups with 23 patients in each. Of the 57 patients accessed for eligibility but excluded for the trial the majority (44) were excluded because they did not meet the full inclusion criteria.

Although there was a preponderance of male patients this was equally spread between both trial groups. There was no significant difference between the groups regarding age, ethnicity or weight. Diabetes was less prevalent in the seven-day group but the small number of patients prevented statistical analysis. Renal function and APACHE II scoring were comparable in both sets of patients.

Presenting signs of systemic inflammatory response were equally common in both groups and that an abnormal white blood cell count was present in greater than seventy-five percent

of patients in both groups. Only ten percent of patients in either group had positive microbiological isolates during the trial period.

Adverse events were few in both groups and not in excess of expected post-operative complications following major cardiac and thoracic surgery in the study population. There was no statistical difference in adverse events between the two groups.

Sequential Organ Failure (SOFA) scores decreased over the trial period in both groups with the suggestion (not significant) of lower SOFA scores at two days in the forty-eight hour antibiotics group. This difference was significant at ten days but data was missing in some patients. Inotrope requirements were unchanged following antibiotic use in either group. Length of stay on ITU was shorter for those who received only two days of antibiotics and mortality was comparable between groups. There was a suggestion of longer periods of invasive ventilation for those patients in the seven day group although this was not statistically significant.

Less than twenty percent of patients receiving only two days of antibiotics required further antibiotics during the trial period. Only three of these had positive microbiological culture results with two patients receiving an extended course of antibiotics for reasons based on clinician preference alone and one having antifungal therapy added based on clinician suspicion alone. One patient in the seven day group was on long-term steroids. They did not require a longer course of antibiotics but were started on antifungal therapy for yeasts (tracheal aspirate) on day six. Of those receiving seven days of antibiotics, three had additions made to their antimicrobial regime based on positive microbiological results with two patients receiving further doses of Teicoplanin based on a clinician decision. There were no documented incidences of MRSA or Clostridium Difficile infection in either group.

Results from the economic analysis showed a potential antibiotic cost saving of £200 per patient and this would extrapolate to a saving of over £100,000 per annum for our ITU alone assuming, in patients in which there are signs of potential sepsis but in whom cultures for bacteria are negative, antibiotics are stopped after 48 hours.

Conclusions:

The preliminary data from this study is suggestive that there are likely significant benefits of reducing broad spectrum antibiotics use in the ICU without undermining the patient's safety. In cost terms alone, there would be a potential cost saving in our unit of over £100,000 per year which would potentially extrapolate to a massive national overall health economy

saving. However, evidence from this pilot trial is not definitive hence it warrants further investigation in a large randomised trial with greater patient numbers to explore further efficacy and cost implications of reduced antibiotic use in critical care units (general and cardiothoracic) both nationally and internationally.

It must be clarified that we are not of the opinion that all patients can be treated with reduced courses of antibiotics. Invariably, some patients will be experiencing true infective episodes and will require longer periods of antibiotics. This pilot merely highlights that the distinction between infective and inflammatory processes in critically ill patients is a difficult one. Even the use of procalcitonin and biphasic waveform APTT to identify those patients who truly have sepsis has been questioned by analysis of available studies [(11)]. Clinical reassessment of antimicrobial therapy at forty-eight hours allows those patients experiencing a SIRS response to be exposed to broad spectrum antimicrobials for as short a time as possible.

The outcomes of this pilot study are very encouraging and suggest that it is feasible to design a binary non-inferiority trial with need for further antibiotics outcome above that allocated at randomisation as the primary outcome measure. (In this pilot study we observed that the need for further antibiotic use in two day treatment (group 1) was 17% as compared with 13% in the standard seven day treatment (group 2)). Secondary outcome measures could include death, duration of mechanical ventilation, ICU stay, and health economics outcomes

INTRODUCTION

Patients in intensive care units (ICUs) are at higher risk of hospital-acquired infections and sepsis than those in non-critical care areas [(1)]. Hospital-acquired sepsis is reported to occur in 10% to 70% of patients undergoing invasive mechanical ventilation, the rate varying with the patient population studied and diagnostic criteria used [(2)]. Despite the major advances in intensive care management, sepsis and its complications remain the leading cause of mortality in ICUs [(3)].

Bloodstream infections (BSIs), pneumonias and urinary tract infections (UTIs) are the most common hospital-acquired infections and are most often associated with the use of invasive devices [(12)]. Coagulase-negative staphylococcus BSIs have recently increased in frequency, and enterococci such as staphylococcus aureus have also been reported as causing BSIs in increasing numbers of ICUs. Recently, gram-negative bacilli have been reported more frequently than gram-positives in this setting. Fungal urinary tract sepsis has also increased [(13)].

Management of ICU sepsis is also complicated by the high incidence of Systemic Inflammatory Response Syndrome (SIRS), which mimics many of the signs of sepsis but often without an infective cause. This is particularly true in ICU's that have a high proportion of patients following major surgery since the surgery alone may precipitate a SIRS episode. A good example of this is cardiac surgical ITU since cardiopulmonary bypass is a strong trigger for SIRS generating, for example, pyrexia and a neutrophilia in the absence of an infective cause.

The potential difficulty in differentiating sepsis from SIRS in these high risk patients makes it inevitable that intensivists often have a low threshold for commencing antibiotics to 'cover' the potential of an infection - even though a definite infective cause has not been proven. Indeed, many patients with suspected sepsis in ICU may be given antibiotics for a significant proportion of their stay to reduce the risk of septic complications, even in cases where there are no compelling positive microbiological results.

To date most studies have focused either on optimising antibiotic treatment for ventilator acquired pneumonia (VAP), which accounts for approximately 50% of antibiotics use in ICU [4-6] or for treatment of suspected sepsis often of unknown origin.

In these patients with apparent sepsis of unknown origin, clinical decisions for empirical antibiotic treatment are usually based on fever, excessive tracheal aspirates, increased white cell counts and heart rate, even if no x-ray changes are apparent. We hypothesise that prolonged treatments with antibiotics in these patients is unnecessary particularly if there are no confirmed organisms grown in blood cultures.

Other markers of sepsis may guide early diagnosis and decision making on necessity and duration of antibiotic treatment. Existing evidence, from a recent retrospective study by Aarts et al 2007 [4], suggests that patients without proof of nosocomial infection receiving empirical antibiotics for longer than 4-days had higher 28-day mortality (32.1%) than those whose antibiotics were discontinued (7.7%). We hypothesize that, in fact, a 2-day regime with broad spectrum antibiotic is sufficiently potent to eliminate any potential microbial threat in these patients.

This is consistent with current international recommendations and guidelines that there is a need for continuous reassessment of antibiotic therapy with microbiology and clinical data to reduce duration when appropriate from the traditional 7-10 days of antibiotic therapy.

Although early identification and treatment of sepsis can have a major impact on the outcome of these patients [14], diagnosis of sepsis is generally difficult particularly in cases where there is no positive isolated microbiological growth.

Whilst there has been no shortage of proposed markers of sepsis [15], two assays have emerged as increasingly relevant in recent years. These are the biphasic activated partial thromboplastin test (APTT) waveform and procalcitonin (PCT). The APTT waveform reflects light transmittance changes in plasma. Septic patients have been found by several investigators to show an abnormal biphasic pattern. Increasing abnormality of this waveform correlates with real time clinical progression and its molecular mechanism is due to calcium dependent complexes between C-reactive protein (CRP) and very low density lipoprotein [16]. This has also been shown to be superior to CRP in the diagnosis of sepsis and the risk of mortality [14].

In a previous small trial, authors have reported that APTT waveform analysis may be of benefit in differentiating between SIRS and sepsis in the difficult post cardiopulmonary bypass group of patient[25].However, whilst it remains a relatively novel technique we did not use the results as a basis for recruitment into the trial which was based on an intention to treat base.

For PCT, the degree of rise in concentration can help differentiate between infectious and non-infectious triggers for elevations in apparent sepsis markers. For example, PCT has been shown to be effective in differentiating infectious from non-infectious causes of acute respiratory distress syndrome [17]. Most recent work has shown that the use of PCT tests in combination with the biphasic APTT waveform can increase the specificity of the latter test in identifying sepsis [18]. Indeed, it has recently been shown that serial measurement of PCT may allow monitoring of a reduction in antibiotic treatment duration and exposure in patients with severe sepsis and septic shock without apparent harm [19].

Evidence from randomised trials about the duration of antibiotic use is absent. In this pilot randomised trial we investigated whether, in the ICU, 48 hours of antibiotic treatment is adequate to safely treat suspected sepsis when it is of unknown and unproven origin, when compared with a more traditional week-long course. In this pilot study, we did not use biomarkers of sepsis as part of the entry criteria as this is not currently routine practice in most UK intensive care units. However, in the study we had the opportunity to collect samples for the APTT waveform and the procalcitonin concentration and this data is presented.

METHODS

This study was carried out in the intensive care and post-operative critical care units at Liverpool Heart and Chest NHS Foundation Trust between May 2010 and July 2011. Institutional and local ethical approvals were obtained prior to recruitment commencing.

In this feasibility, pilot randomised trial the impact on safety and efficacy of a reduced course of antibiotics for the treatment of ICU infections of unknown origin (48 hours versus 7 days) were investigated. The secondary feasibility outcomes of the pilot trial included the assessment of the ratio of patients screened as eligible compared to the number randomised; the incidence of cross-over between the randomised treatment groups and the accuracy of data collection assessed by a 20% source data verification check. In addition, this pilot study wished to identify the likely barriers to an effective recruitment into a main definitive trial, and whether the outcome measures and data collection methods were appropriate and reliable.

Patients being treated within the intensive care unit were recruited into the trial if they were being commenced upon the 'Surviving Sepsis' Care Bundle antibiotics by the intensivist in the absence of an actual known cause for that potential sepsis. To trigger the bundle, patients needed to have at least two of the four markers of SIRS (i.e. temperature $>38^0$C or $<36^0$C, tachycardia (>90beats per minute), tachypnoea ($\geq$20 breaths per minute) and white blood count > $12\times 10^{9/}$L or < 4×10^9/L) and a suspected but not proven infection. In other words, patients were recruited if the intensivist was planning to commence antibiotics because of evidence of SIRS and a strong suspicion of infection – but no actual known source for that infection.

Patients were excluded if they had positive microbiological cultures before randomisation, were <18 years of age, enrolled in another study such that randomisation in the trial would result in deviation from either protocol. They were also excluded if they had an allergy to trial antibiotics or if consent/assent was declined or could not be obtained.

Once the decision to start antibiotics treatment was made by the intensivist, a referral was made to the study team who would assess the patient's eligibility for recruitment. If the intensivist making the decision to start the antibiotics was one of the investigators, a second opinion was required from an independent consultant colleague to assess eligibility. Once the patient was considered as a suitable candidate for recruitment, consent or assent was

taken depending on the clinical state of the patients. If the next of kin was not present for the assent process, they were contacted by telephone to discuss their participation in the study. In the case where telephone assent was taken, the next of kin was asked to sign the assent form on their earliest visit to the hospital. In all the cases of assent, a formal consent was taken from the patient once they had sufficiently regained capacity to give consent. Patients that declined consent were withdrawn from the study and data was only used for analysis after consent had been given.

Eligible patients were randomised in equal proportions between the two trial groups:

- Antibiotic treatment administered for **48 hours**
- Antibiotic treatment administered for **7 days**

Treatment assignment was based on the block randomisation method using randomly varying block sizes of 2, 4 and 6 to ensure numerical balance between the groups. An independent statistician provided the randomisation tables. Only trial staff with a unique user ID and password were able to log onto the bespoke, encrypted database. The allocation was revealed after entering unique patient data and access to any list of previously randomised patients was not permitted.

After randomisation, a baseline Acute Physiological and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment score (SOFA score) [7] (Appendix 1) was recorded, two sets of blood culture, at least 15 minutes apart were taken and blood samples were sent for baseline biphasic APTT waveform and procalcitonin analysis. These samples were centrifuged; serum was separated and frozen for analysis at a later stage. This was followed by the administration of the study antibiotics.

Table 1: Antibiotic prescribing method

Patient Weight	Teicoplanin	Meropenem
< 85kg	400mg twice a day 1 400mg Once a day thereafter	1g 3 times a day
>= 85kg	6mg/kg rounded to nearest 50mg twice a day 1 6mg/kg rounded to nearest 50mg once a day thereafter	1g 3 times a day

After completion of the treatment regime allocated at randomisation, additional antibiotic use constituted an outcome measure and the reason for the initiation was documented in the trial

case record forms. Similarly, if the antibiotics were stopped or changed before the scheduled completion of the course, the reason was recorded. Decisions to change or restart or stop antibiotics were made by consultant intensivists or microbiologists who were guided by evidence of positive cultures, X-ray and other imaging diagnostic information or poor physiological status believed to be related to infection. The reasons for any deviation from the protocol were also documented.

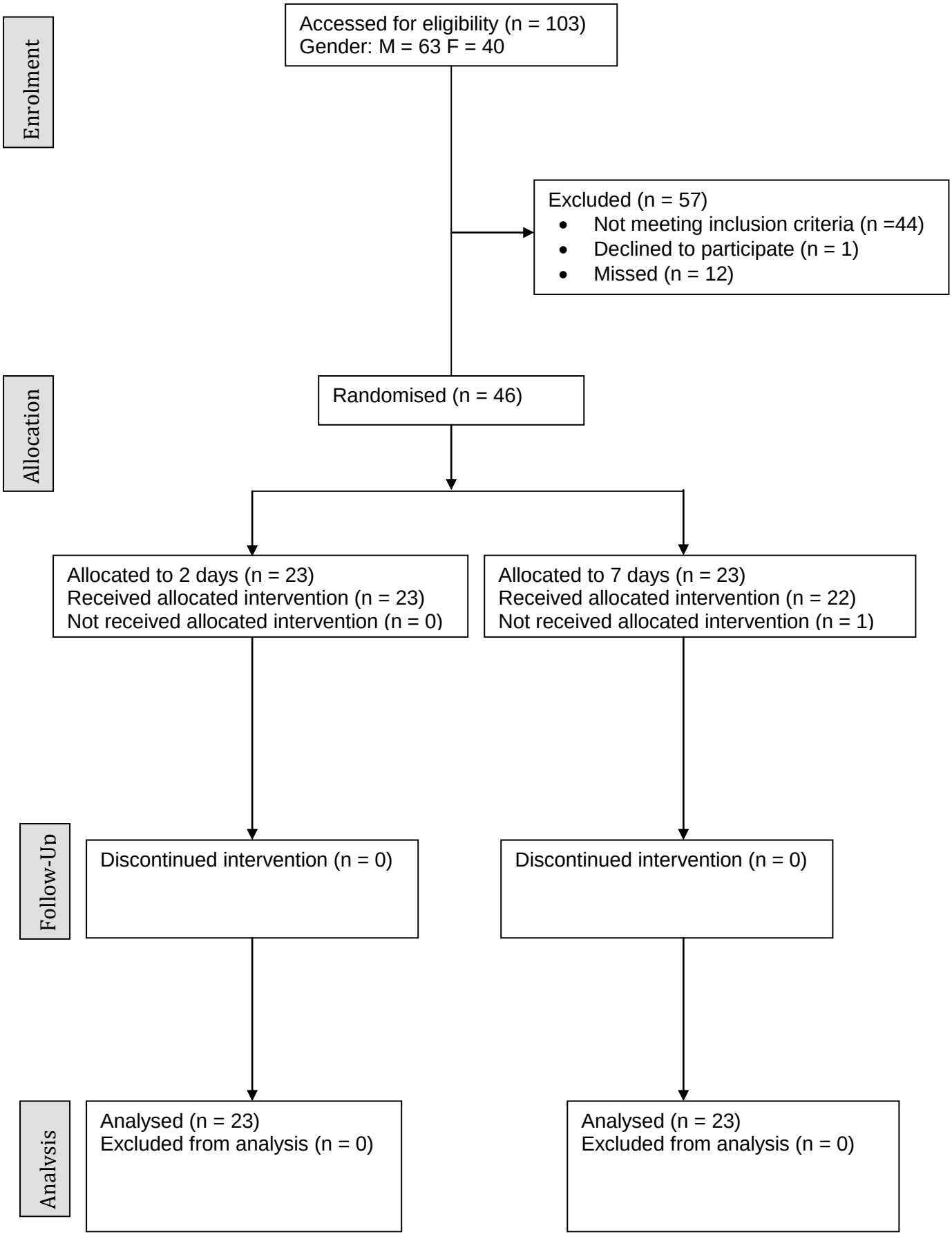
The trial patients were followed up for a period of 10 days by the research team. SOFA scores were calculated and documented in case record forms. Blood samples were taken at baseline, 48 hours, on initiation of additional antibiotics beyond the randomised schedule for measurement of prospective biomarkers of sepsis: biphasic APTT and procalcitonin (Appendix 2) [8-10]. Trial antibiotics were prepared, packaged, stored and dispensed in accordance with Good Manufacturing Practice for Investigational Medicinal Products.

Biphasic APTT waveform and procalcitonin concentrations were used as markers for sepsis. A biphasic profile occurs when light transmission decreases before clot formation in the first part of the curve. Slope = -0.05% T/sec was considered as biphasic waveform and the value of transmittance at 18 sec (TL18) was measured. To quantify this abnormality, light transmission at time 0 was set to 100%, and the value recorded 18 seconds later (TL18) was taken as the index of the abnormality [20-23] TL18 of 100% was considered as normal and <99% when biphasic waveform occurred.

Primary outcome measures were defined by either initiation of antibiotic therapy after the completion of the treatment schedule allocated at randomisation or in trial mortality. Secondary outcome measures were defined in terms of duration of ICU stay, duration of hospital stay, duration of mechanical ventilation and incidence of infection with MRSA and Clostridium difficile.

A small proportion of post-cardiac surgery patients do return to theatre, usually for bleeding. It is common to use haemofiltration on patients who have a pre-surgery low eGFR. Arrhythmia is also common, especially in heart-valve patients, usually atrial fibrillation, which may be treated with Amiodarone infusion, or in some cases by cardio-version shock.
The statistical analysis was performed by Chi-square, Mann Whitney U and Fisher's exact test. The adverse events were analysed using Chi square and Fisher's exact test and outcome measures were analysed using Mann Whitney U test.

Results – Participant Flow Chart



As shown on Table 2, the majority of the patients recruited into the trial were post-surgical (mostly cardiac bypass or aortic/mitral valve surgery). All patients in the two day groups received the allocated antibiotics for at least two days.

Table 2: Reason for hospital admission

Reason	No of Pts	Group 1	Group 2	p Value
CABG	15	6	9	NS
CABG + Valves	9	3	6	NS
Valves	10	8	2	NA
Great vessels	3	1	2	NS
MI and or PCI	5	2	3	NS
OG	2	2	0	NS
Thoracic	2	1	1	NS

CABG = Coronary Artery Bypass graft, Valves = heart valves, Great vessels means any part of the aorta, MI = Myocardial Infarction, PCI = Percutaneous Coronary Intervention, OG = Oesophagogastrectomy Thoracic = lung surgery for cancer, NA = expected cell frequencies too low, NS = not significant

Recruitment took placed over 14 months. The actual recruitment was 46 patients compared with the planned target of 60 patients within 12 months.

Table 3: Demographic and baseline data

Variable		Group 1 2 days	Group 2 7 days	Significance
		n=23	n=23	
Gender	n (%)			
	Female	9 (39.1)	7 (30.4)	
	Male	14 (60.9)	16 (69.6)	NS[1]
Age Mean(SD)		68.5(9.8)	65.3(11.5)	
	Min Age	53	39	
	Max Age	86	81	
Ethnicity	n(%)			
	White British	23 (100)	22 (95.7)	
	Asian/Asian	0	1 (4.3)	NS[1]

	British			
Smoking Status	n(%)			
	Never	6 (26.1)	3 (13.3)[b]	
	Ex-smoker	15 (65.2)	13 (61.9)	
	Current	2 (8.7)	5 (23.8)	NA
Weight	Median(IQR)	78 (28)[a]	80.5 (28)[a]	NS[2]
Diabetes	n(%)			
	None	14 (60.9)	18 (81.8)[a]	
	Type I	1 (4.3)	1 (4.5)	
	Type 2	8 (34.8)	3 (13.6)	NA
Pre Op White Blood Count	Median(IQR)	8.9 (8)	9.8 (5)	NS[2]
Urea	Median(IQR)	7.5 (6.3)	8.6 (7.7)	NS[2]
Creatinine	Median(IQR)	102 (64)	104 (75)	NS[2]
eGFR	Median(IQR)	58 (53)	58 (38)	NS[2]
Hb	Median(IQR)	11.8 (4)	11.25 (3.3)	NS[2]

NS – not significant, 1 - Chi-squared test, 2 – Mann Whitney U test, 3 – Fisher's exact test NA – not applicable – expected cell frequency < 5 for some cells, a – One missing value, b – Two missing values

Table 4: Numbers analysed

Variable		Group 1	Group 2	Significance
n		23	23	
APACHE II Score	Median(IQR)	13(6)	14(8)[a]	NS[2]
Baseline SOFA	Median(IQR)	8(7)	11(6)[a]	NS[2]
48 hr SOFA	Median(IQR)	5(7)[c]	11(7)[b]	p=0.08[2]
Total time vented (hrs)	Median(IQR)	28 (155)[a]	108 (218)[b]	p=0.08[2]
Inotropes required (hrs)	n(%)			
Adrenaline and/or	No	13 (56.5)	10 (43.5)	
Noradrenaline	Yes	10 (43.5)	13 (56.5)	NS[1]
Teicoplanin doses given	Median(IQR)	3(17)	8(12)	p = < 0.001[2]
Meropenem doses given	Median	6	21	
	n(%)			
Positive Cultures	No	20 (87)	20 (87)	
	Yes	3 (13)	3(13)	NS[3]
Days on ITU	n(%)			

	< 3 Days	2 (10)[c]	3 (15.8)[d]	
	3-10 days	12 (60)	4 (21.1)	
	> 10 days	6 (30)	12 (63.3)	NA
	n(%)			
Days on ITU	< = 10days	14(70)[c]	7 (36.8)[d]	
	>10 days	6(30)	12 (63.2)	P=0.04[1]
	n(%)			
Death	No	20 (87)	22 (95.7)	
	Yes	3 (13)	1 (4.3)	NS[3]

1-Chi-squared test, 2 – Mann Whitney U test, 3- Fisher's exact test, a – one missing value, b – Two missing values, c – Three missing values, d – Four missing values, NA-expected cell frequencies too-low

The primary analysis was intention to treat and involved all patients who were randomised. One patient was randomised inappropriately and no data collected, but was counted in the numbers. Twenty-three patients were randomised in each of the two groups. There were no significant differences between the two groups for APACHE II, SOFA time on ventilator, inotropes required, positive cultures and days on ITU or death.

One patient in the control arm (7 days group) whose Meropenem were stopped on the third day in view of isolated positive cultures from a drain site for Staphylococcus aureus and was instead treated with Rifampicin 600mg antibiotics for the remainder of the time. For patients in group one (2 days antibiotics) four (17.4%) required further antibiotics, and three in group two (13%). All patients had blood cultures taken at the time of randomisation and some patients were swabbed and had samples of tracheal aspirate taken. Of these 6 (13%) returned positive, three in each arm of the trial. These were: staphylococcus aureus (1, two day group), Escherichia coli (1, two day group), Non-lactose fermenting coli form (1, seven day group), Coagulase negative staphylococci (1, seven day group) and yeasts (2, both seven day group).

A total of 4 patients died within the ten-day trial period. The trial events adjudication panel confirmed that none of the deaths were due to the trial intervention. The causes of death were: a) sepsis and gastrointestinal bleed, pulmonary abscess, oesophageal carcinoma b) multi-organ failure, sepsis, ischaemic bowel, ischaemic heart disease c) CVA, thoracic aneurysm d) multi-organ failure and coronary artery disease.

No patients who died during the trial period had received further antibiotics in addition to the trial antibiotics.

Table 5: Trial outcomes

Outcome		Group 1	Group 2	Significance
Need for further antibiotics above that allocated at randomisation:	n(%)			
	No	19 (82.6)	20 (87)	
	Yes	4 (17.4)	3 (13)	NS[3]
Composite outcome of death and need for further antibiotics above that allocated at randomisation	n(%)			
	No	16 (69.6)	19 (82.6)	
	Yes	7 (30.4)	4 (17.4)	NS[1]

1- Chi-squared test, 3- Fisher's exact test

The risk difference between the two groups for the composite outcome was 0.12 (95% confidence interval: -0.11, 0.13) with a p value 0.3

Table 6: Adverse Events

Variable		Group 1	Group 2	Significance
		n=23	n=23	
Re-Explore in Theatre	n(%))			
	No	22 (95.7)	21 (91.3)	
	Yes	1 (5.9)	2 (8.7)	NS[3]
Other Adverse Events	n(%))			
	No	23 (100)	20 (87)	
	Yes		3 (13)	NS[3]
Haemofiltration (HF)	n(%))			
	No	18 (78.3)	17 (73.9)	
	Yes	5 (21.7)	6 (26.1)	NS[1]
HF due to Anuria or oliguria	n(%))			
	No	20 (87)	18 (78.3)	

	Yes	3 (13)	5 (21.7)	NS[3]
HF due to Abnormal	n(%)			
Electrolytes	No	21 (91.3)	22 (95.7)	
	Yes	2 (8.7)	1 (4.3)	NS[3]
Other Arrhythmias	n(%))			
	No	21 (91.3)	23 (100)	
	Yes	2 (8.7)		NS[3]
Anaemia	n(%))			
defined as Hb <8 g/dL	No	15 (65.2)	15 (65.2)	
	Yes	8 (34.8)	8 (34.8)	NS[1]
Standard	n(%))			
Tracheotomy	No	23 (100)	20 (87)	
	Yes		3 (13)	NS[3]
Other Adverse Events	n(%))			
	No	23 (100)[e]	22 (95.7)	
	Yes		1 (4.3)	NS[3]

1-Chi squared test, 3- Fisher's exact test

Tracheotomy was performed on three patients who required a respiratory wean from the ventilator.

There was a single Serious Adverse Reaction reported. This was a patient whose liver function tests became abnormal after commencement of antibiotic therapy. The Alanine transaminase **(**ALT) was 506 U/L (normal range 3-35 u/L), Gamma glutamyl transferase (γGT) was 449 U/L (normal range < 50) and Alkaline Phosphatase (ALK) 627 U/L (normal range 35 to 125U/L). These values began to return to normal in the days following cessation of antibiotics.

Biomarkers

Two biomarker blood tests were used as an indication of sepsis. These were taken at baseline (after randomisation), at forty-eight hours and at ten days or discharge. These were Procalcitonin and Biphasic activated Partial Thromboplastin Time (aPTT).

Unfortunately, there is a lack of consensus as to whether there is a strong relationship between abnormal APTT waveforms and the underlying pathology of sepsis. Matsumoto et al (2006) [(24)] pointed out that in patients with disseminated intravascular coagulation (DIC)

and sepsis the test was effective in patients who did not have solid cancers. They used a 'cut-off' of any waveform slope below -0.25%T/sec to indicate Biphasic waveform.

We decided to use two values as a cut-off as discussed previously by Delannoy et al 2009 who had used a comparable study population as ourselves[25], The values that Delannoy used were -0.25 and -0.465. Are results are shown in the table below:

Table 7: Groups and Timeline for various values of cut-off for Biphasic aPTT

Group and Time	-0.25%T/sec	-0.465% T/sec
Group 1 (48 hours) Baseline	**11**	**9**
Group 2 (7 days) Baseline	**8**	**6**
Group 1 (48 Hours) at 48 hours	**2**	**2**
Group 2 (7 days) at 48 hours	**4**	**3**

The results of the procalcitonin analysis are not available at the time of writing of this report.

The results of the analysis of the abnormality APTT waveforms indicated a lack of significant difference between the two groups at baseline. As a measure of validity of the APTT waveform tests we compared the APTT results in patients who had known positive blood cultures and then we performed tests for sensitivity and specificity looking for the level of agreement. At the two different cut-off points of slope (-0.25, -0.465) of APTT waveform data there was a very poor agreement with 'blood culture positive sepsis' [Kappa values (with 95%CI) of -0.048(-0.26, 0.17), -0.465(-0.24, 0.25) respectively]. To test whether an abnormal APTT waveform has the ability to identify people with sepsis as correctly positive blood culture, a sensitivity analysis was performed. The results at the two different cut-off points of slope (-025, -0.465) of APTT waveform data indicated that sensitivity (with 95% CI) was also very poor [0.105(0.00, 0.24), 0.13(0.00, 0.30) respectively.

To test whether an abnormal APTT waveform has the ability to recognise people without sepsis, a specificity analysis was performed. The results at the two different cut-off points of slope (-025, -0.465) of APTT waveform data indicated that specificity (with 95% CI) was quite reasonable [0.85(0.72, 0.98), 0.87(0.75, 0.99). With a likelihood ratio for positive test ranging from 0.5 to1.0, we can interpret the findings as that there is an equal or slightly less chance of finding a positive abnormal APTT waveform test in someone with 'blood culture positive' sepsis as compared to the one without sepsis.

Economic Analysis

For the full economic analysis see the attached addendum by Haycox and Houten.

The major findings were as follows:

1. Cost Minimisation Technique (CMA) was used as there were no significant differences between the trial and control groups.
2. The mean antibiotic cost per patient for the two day group was £168.97, and for the seven day group £375.86. The average cost difference was therefore over £200 per patient.
3. We obtained data detailing the number of patients seen in our ICU department for nine months, and the number of these patients who had blood cultures taken and the number that returned a positive result. This data was then extrapolated for a full year.
4. Interestingly, of all the patients who had cultures taken over the nine month period, only 10.4% returned positive.
5. The potential per annum cost saving for the ICU was estimated to be in the range £108,140 to £126,060, assuming that at 48 hours if the cultures were negative the antibiotics were stopped in all cases.

Key Findings

Although there was a preponderance of male patients this was equally spread between both trial groups. There was no significant difference between the groups regarding age, ethnicity or weight. Diabetes was less prevalent in the seven day group but the small number of patients prevented statistical analysis. Renal function and APACHE II scoring were comparable in both sets of patients. Relatively few patients were missed for potential enrolment. It is accepted however that patients who were informally discussed between clinicians or in whose case the individual clinician did not deem them to be eligible were probably missed from the screening log. A relatively high number (nearly fifty percent) did not meet the full inclusion criteria but the collected data does not allow us to ascertain why this was.

Presenting signs of systemic inflammatory response were equally common in both groups and that an abnormal white blood cell count was present in greater than seventy-five percent of patients in both groups. Only ten percent of patients in either group had positive microbiological isolates during the trial period.

Adverse events were few in both groups and not in excess of expected post-operative complications following major cardiac and thoracic surgery in the study population. There was no statistical difference in adverse events between the two groups.

Sequential Organ Failure Assessment (SOFA) scores decreased over the trial period in both groups with the suggestion (not significant) of lower SOFA scores at two days in the forty-eight hour antibiotics group. This difference was significant at ten days but data was missing in some patients. Inotrope requirements were unchanged following antibiotic use in either group. Length of stay on ITU was shorter for those who received only two days of antibiotics and mortality was comparable between groups. There was a suggestion of longer periods of invasive ventilation for those patients in the seven day group although this was not statistically significant.

Less than twenty percent of patients receiving only two days of antibiotics required further antibiotics during the trial period. Only three of these had positive microbiological culture results with two patients receiving an extended course of antibiotics for reasons based on clinician preference alone and one having antifungal therapy added based on clinician suspicion alone. One patient in the seven day group was on long-term steroids. They did not require a longer course of antibiotics but were started on antifungal therapy for yeasts (tracheal aspirate) on day six. Of those receiving seven days of antibiotics, three had additions made to their antimicrobial regime based on positive microbiological results with two patients receiving further doses of Teicoplanin based on a clinician decision. No patients who died required antibiotics in excess of those they received as part of the trial. There were no documented incidences of MRSA or Clostridium Difficile infection in either group.

Discussion

Sepsis is a potentially serious medical condition that is characterized by an inflammatory response to an infective agent that may affect the whole body [1;27]. The patient may develop an inflammatory response to microbes in their blood, urine, lungs, skin, or other tissues [1;27]. If left untreated sepsis may progress to severe sepsis and septic shock which is associated with a high mortality.

Most patients who develop suspected sepsis either requiring ICU admission or during an ICU admission are given antibiotics [1;3;12;13;27]. In cardiothoracic intensive care units (CICU) clinical decisions are often taken to treat patients with suspected sepsis of unknown origin for a week or longer with broad spectrum antibiotics usually on the basis of onset of fever, increased tracheal aspirates, increased white cell counts and heart rate, even if no x-ray changes are apparent. However, there is increasing concern that this practice may be detrimental to patients, as several observers have highlighted in the medical literature over the last thirty years [4;28-30]. In particular, the rise in reported clostridium difficile cases linked

to mortality [31] and the increasing levels of antibiotic resistance bacterial strains is of concern.

Indeed, current evidence from a recent retrospective study by Arts et al 2007 [4]has suggested that patients without proof of nosocomial infection receiving empirical antibiotics for longer than 4-days had higher 28-day mortality (32.1%) than those whose antibiotics were discontinued (7.7%). International recommendations and guidelines have suggested that there should be continuous reassessment of antibiotic therapy guided by clinical response, microbiology and clinical data and also a reduction in the duration when it is appropriate (from the usual 7-10 days of antibiotic therapy) [32]. However, in the absence of strong evidence for optimal duration of antibiotics use in the ICU from randomised trials, these recommendations and guidelines have had little impact on current practice. Other evidence in the literature, also from small studies, is suggestive that reduction in antibiotics use may be cost-saving and may reduce the rates of antibiotics resistance [21].

The primary outcome measures for this pilot trial showed no significant difference in the need for additional antimicrobial therapy or an increased risk of mortality for patients treated with only two days of empirical antibiotics. This suggests that further investigation by means of a multi-centre trial would be safe and advantageous for our approach to treatment of suspected nosocomial infections in critical care areas.

Prolonged ITU stay in those patients receiving antibiotics for seven days may suggest that the seven day patients were sicker. This was not borne out however by the APACHE and the initial or 48 hour SOFA scores. Alternatively, the continuation of potent, broad-spectrum antibiotics may have led clinicians to perceive these patients as being ‘critically unwell’ for longer periods of time. Continuing antibiotics may have delayed decisions to remove central access catheters and arterial pressure lines. All these factors may have contributed to prolonged ITU stay.

Although not clinically significant, the difference in total time invasively ventilated is intriguing (although there is significant crossover between the IQR). Again, if these values did represent a significant difference one might question if the seven day group were a ‘sicker’ cohort of patients despite the illness severity scores suggesting otherwise. It is difficult to hypothesise why patients on longer courses of antibiotics might need longer periods of ventilation other than a clinician perception of patients being ‘critically unwell’ while still on broad-spectrum antibiotics. This may have led clinicians to prolong advanced organ support in these patients for fear of them relapsing should that support be withdrawn too quickly.

Additionally, the effect of individual clinicians' weaning strategies on this result cannot be accounted for from this data.

In the case of both ITU length of stay and length of invasive ventilation both groups had spent similar time in ITU prior to being enrolled. This again refutes the suggestion that those patients who received seven days of antibiotics were sicker because they had spent more time on ITU before they were involved in the trial.

Interestingly, the comparison of secondary health economic outcomes -determined by assessing resource utilisation and costs associated with each of the two pilot arms - indicated that there was a significant cost saving in the 2-days arm of antibiotics treatment group up to £126,060 per annum, ranging from £191.06 to £222.72 per patient, a finding that is in agreement with a previous small study [21]. If this cost-saving is extrapolated nationally in England alone it represents a substantial savings to the NHS healthcare budget.

The main obstacles to recruitment in this pilot trial were factors related to the strategy for obtaining consent. The need for expedited initiation of antibiotic treatment once a patient is suspected of having sepsis significantly limited the amount of time that patients or their next of kin would have to decide whether to participate in the trial or not. In some cases this was the basis for several patients or their legal representatives declining permission for enrolment in the trial since they had insufficient time to consider their decisions. In addition, difficulties in contacting patient's legal representatives meant that this could result in delay for commencement of antibiotic treatment. Outcomes have been shown to be worse in septic patients where antibiotics were delayed [15;33;34] and so in most instances these patients were excluded.

Although uncommon in our sample group, the onset of possible sepsis during antisocial hours meant that it was inappropriate to contact next of kin for these patients to discuss enrolment. In a few cases, attending clinicians were of the opinion that the illness was too severe and that it would be unethical to delay antibiotics while assent was being sought. It could have been inappropriate to approach relatives/legal representatives in such a situation where objective decisions regarding involvement in a clinical trial would have been difficult. For these reasons some of these patients were not recruited into the trial and therefore may potentially be a source of bias. It is suggested that these recruitment issues could be addressed by the use of preoperative consent of patients in the outpatient setting.

Other barriers to recruitment identified included differences in interpretation of what constituted a 'probable' chest infection, particularly when patients had 'increased sputum production' where they would be considered ineligible for recruitment (because this would constitute sepsis of known origin). In addition, the appearance of basal or lobar collapse on chest x-ray was interpreted by some clinicians as evidence of a probable source of infection. The nature of cardiothoracic surgery (thoracic wall incisions, lung collapse intra-operatively, high incidence of chronic lung disease in patient population) meant that the appearance of abnormalities on chest x-ray were more frequent but did not necessarily constitute a pneumonic process. In the future it is recommended that these patients should be considered for inclusion into the trial.

A significant change was seen in clinician behaviour towards antibiotic use during the later part of the pilot period. Closer scrutiny of antibiotic use brought about by the trial led to clinicians increasing their threshold for starting antibiotics in post-operative patients. Although commendable in reducing antibiotic exposure for patients, this approach led to reduced recruitment to the trial and may have exposed truly 'septic' individuals to a delay in treatment.

Another difficulty with the trial in our particular unit is that we are not a "closed' unit. For many patients developing signs of sepsis, their first medical review was by a cardiac surgical registrar. Despite a great deal of publicity and attempts at education there remained several patients who were either simply commenced on antibiotics by their 'team' doctors before being given a chance to be recruited into the trial.

An additional obstacle to recruitment during the trial period was a six week closure of the ICU for H1N1 epidemic national planning purposes.

Another area that needs further consideration when designing the larger definitive trial is the dispensing of trial antibiotics which would in the future require unique packaging with specific tracking numbers different from existing medications intended for routine use. This would avoid confusion between stock drugs used in the unit for non-trial patients. In addition, careful consideration of the choice of antibiotic regime when involving general and cardiothoracic intensive care units is required. Some units may routinely use third generation cephalosporins or beta-lactam/beta lactamase inhibitor drugs as apposed to carbapenams. The choice of a regime for a future trial may also be hindered by varying local susceptibility patterns. Finally, although the use of a glycopeptide drug is becoming routinely a part of

empirical sepsis cover, having an outcome measure for MRSA infections where one of the treatment options is the trial drug may not be logical.

The small size of this pilot study prevents any kind of definitive answers being derived or even suggested with any degree of certainty. It is important to note that these were all post-operative patients and that the incidence of pure sepsis episodes as opposed to SIRS in medical critically unwell patients may not be as pronounced. This calls into question the external validity of future trial results for general ITU patients.

Measurement of height to allow calculation of basal metabolic index (BMI) would allow for better matching of patient demographics and should be included in future trial data collection. Future trial data would also benefit from a more detail being collected around why apparently suitable patients were not included in the trial.

Although the trial protocol took into account the effect of patient weight on antibiotic dosage, it did not address potential changes in dose necessitated by renal and hepatic impairment or the effect of haemofiltration and potential disruptions in this therapy. In practice this only affected one patient who transferred from haemofiltration to haemodialysis. The use of steroids in sepsis was not addressed as a possible confounding factor due to potential immuno-compromise increasing the risk of on-going infection.

CONCUSION

The preliminary data from this study is suggestive that there are likely significant benefits of reducing broad spectrum antibiotics use in the ICU without undermining the patient's safety. In cost terms alone, there would be a potential cost saving in our unit of over £100, 000 per year which would potentially extrapolate to a massive national overall health economy saving. However, evidence from this pilot trial is not definitive hence it warrants further investigation in a large randomised trial with greater patient numbers to explore further efficacy and cost implications of reduced antibiotic use in critical care units (general and cardiothoracic) both nationally and internationally.

It must be clarified that we are not of the opinion that all patients can be treated with reduced courses of antibiotics. Invariably, some patients will be experiencing true infective episodes and will require longer periods of antibiotics. This pilot merely highlights that the distinction between infective and inflammatory processes in critically ill patients is a difficult one. Even the use of procalcitonin and biphasic waveform APTT to identify those patients who truly have sepsis has been questioned by analysis of available studies [(11)]. Clinical reassessment

of antimicrobial therapy at forty-eight hours allows those patients experiencing a SIRS response to be exposed to broad spectrum antimicrobials for as short a time as possible.

The outcomes of this pilot study are very encouraging and suggest that it is feasible to design a binary non-inferiority trial with need for further antibiotics outcome above that allocated at randomisation as the primary outcome measure. In this pilot study we observed that the need for further antibiotic use in two day treatment (group 1) was 17% as compared with 13% in the standard seven day treatment (group 2). The null hypothesis is that the percentage of patients requiring further antibiotics use for those in group 2 is better than the percentage for those in group 1 by an amount *d (non-inferiority limit)*. Assuming different values of *d*, we estimate sample sizes at the following alpha and power levels of:

Table 8: Sample size calculations for multicentre trial

Alpha	Power (%)	*d (%)*	Sample size
0.05	80	5	31500
0.05	80	10	880
0.05	80	12.5	436
0.05	80	15	260
0.05	90	10	1204
0.05	90	12.5	604
0.05	90	15	360

Secondary outcome measures could include death, duration of mechanical ventilation, ICU stay, and health economics outcomes.

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Appendix 1: The SOFA Score

SOFA Score	1	2	3	4
Respiration PaO_2/FiO_2 mmHg	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $\times 10^3/mm^3$	,150	<100	<50	<20
Liver Bilirubin, mg/dl (μmol/l)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovascular Hypotension	MAP<70mm Hg	Dopamine $\leq$5 or dobutamine (any dose)[a]	Dopamine >5 Or epiniephrine $\leq$0.01 Or norepinephrine $\leq$ 0.1	Dopamine >15 Or epiniephrine>0.01 Or norepinephrine

				> 0.1
Central Nervous System (Glasgow Coma Score)	13-14	10-12	6-9	<6
Renal Creatinine, mg/dl (μmol/l) or urine output	1.2-1.9 (110-170)	2.0-3.4 171-299	3.5-4.9 300-440 or < 500ml/day	>5.0 (>440) or <200ml/day

[a] Adrenergic agents administered for at least 1 hr (dose in μg/kg/min)

Appendix 2: Interpretation of procalcitonin levels

PCT ng/ml	Interpretation
<0.05	Normal values • Local inflammation or infection is possible: systemic inflammatory response unlikely
<0.5	On first day of ICU admission this indicates a low risk for progression to severe sepsis and/or septic shock • Local inflammation or infection is possible: systemic inflammatory response unlikely
≥ 0.5 and <2	Systemic inflammatory response present due to infection, severe trauma, major surgery or cardiogenic shock • If the patient has a proven infection it could be sepsis
≥ 2 and < 10	Likely to be sepsis (systemic inflammatory response associated with infection) • On first day of ICU admission this indicates a high risk for progression to severe sepsis and/or septic shock
≥ 10	Severe sepsis or septic shock • Organ dysfunction • High risk of death