A pilot randomised controlled trial in intensive care patients comparing 7 days’ treatment with empirical antibiotics with 2 days’ treatment for hospital-acquired infection of unknown origin

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Executive summary

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Background


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 ICUs that have a high proportion of patients following major surgery as the surgery alone may precipitate a SIRS episode. A good example of this is the cardiac surgical ICU, as 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 in which there are no compelling positive microbiological results.


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 count and heart rate, even if no radiographic changes are apparent. We hypothesise that prolonged treatment 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 of unknown and unproven origin 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 for whom 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 ICUs. However, at the landmark time points in the trial we collected samples for the biphasic activated partial thromboplastin time (APTT) waveform and procalcitonin concentration and these data are presented.

**Method**

This study was carried out in the intensive care and postoperative critical care units at Liverpool Heart and Chest NHS Foundation Trust between May 2010 and July 2011. Institutional and national ethical approvals were obtained before commencing recruitment.

Patients being treated within the ICU were recruited into the trial if they were being commenced on 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°C or < 36°C, tachycardia (≥ 90 beats per minute), tachypnoea (≥ 20 breaths per minute) and a white blood count > 12 × 10⁹/l or < 4 × 10⁹/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 there was 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 Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score were recorded [Vincent J, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis Related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707–10], 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 and serum and plasma separated and frozen for analysis at a later stage. This was followed by the administration of the study antibiotics. The study antibiotics were a combination of teicoplanin (Targocid®, Sanofi-Aventis) given 12-hourly for the first 24 hours and then once daily and meropenem (Meronem®, AstraZeneca) given three times daily. The dose of teicoplanin was weight adjusted and the dose of meropenem was 1 g.
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 (CRFs). 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, radiography 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 by the research team for a period of 10 days. SOFA scores were calculated and documented in CRFs. Blood samples were taken at baseline, at 48 hours and on initiation of additional antibiotics beyond the randomised schedule for measurement of prospective biomarkers of sepsis: biphasic APTT and procalcitonin. 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 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 methicillin-resistant Staphylococcus aureus (MRSA) (B. S. Weeks & E. Alcamo) Jones & Bartlett International Publishers, 2008 and Clostridium difficile (B. S. Weeks & E. Alcamo) Jones & Bartlett International Publishers, 2008.

Results

Recruitment took place over 14 months with 46 patients randomised into the trial; this compares with the planned target of 60 patients within 12 months. A total of 103 patients were assessed for eligibility. The majority of patients recruited were postcardiothoracic surgical patients.

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

Although there was a preponderance of male patients, they were equally spread between the two trial groups. There was no significant difference between the groups regarding age, ethnicity or weight. Diabetes was less prevalent in the 7-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 an abnormal white blood cell count was present in >75% of patients in both groups. Only 10% 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 postoperative 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 scores decreased over the trial period in both groups, with the suggestion (not significant) of lower SOFA scores at 2 days in the 48-hour antibiotics group. This difference was significant at 10 days but data were missing for some patients. Inotrope
requirements were unchanged following antibiotic use in either group. Length of stay in the ICU was shorter for those who received only 2 days of antibiotics and mortality was comparable between groups. There was a suggestion of longer periods of invasive ventilation for those patients in the 7-day group, although this was not statistically significant.

Less than 20% of patients receiving only 2 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 7-day group was on long-term steroids. This patient did not require a longer course of antibiotics but was started on antifungal therapy for yeasts (tracheal aspirate) on day 6. Of those receiving 7 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 C. difficile infection in either group.

The median baseline procalcitonin concentration (interquartile range) for patients who restarted antibiotics was 2.4 (0.8–7.0) compared with 0.6 (0.3–1.8) for those who did not receive further antibiotics in excess of their trial drugs (p = 0.06). Logistic regression analysis of baseline procalcitonin showed that it was a predictor of restarting antibiotics, with an odds ratio of 1.45. [95% confidence interval (CI) 1.04 to 2.02; p = 0.01]. Similarly, procalcitonin was also a strong predictor for the composite outcome measure (death and needing further antibiotics), with an odds ratio of 1.79 (95% CI 1.20 to 2.67; p = 0.005).

Results from the economic analysis showed a potential antibiotic cost saving of £200 per patient, which would extrapolate to a saving of > £100,000 per annum for our ICU alone assuming that, in patients in whom 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 are suggestive that there are likely significant benefits of reducing broad-spectrum antibiotic use in the ICU without undermining patient safety. In cost terms alone there would be a potential saving in our unit of > £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, further investigation is warranted using a large randomised trial with greater patient numbers to explore 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 a reduced course of antibiotics. Invariably, some patients will be experiencing true infective episodes and will require longer periods of antibiotics. From our trial we would predict that these patients are those who have a high baseline procalcitonin concentration. This pilot study 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 (Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis 2007;7:210–17). Clinical reassessment of the need for antimicrobial therapy at 48 hours allows those patients experiencing a SIRS response to be exposed to broad-spectrum antimicrobials for as short a time as possible.
The results of this pilot study are very encouraging and suggest that it is feasible to design a binary non-inferiority trial with the need for further antibiotic use above that allocated at randomisation as the primary outcome measure. (In this pilot study we observed that the need for further antibiotic use in the 2-day treatment was 17% compared with 13% in the standard 7-day treatment.) Secondary outcome measures could include death, duration of mechanical ventilation, duration of ICU stay and health economic outcomes.

**Trial registration**

This trial is registered as ISRCTN82694288.

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**Publication**

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