A pilot randomised controlled trial in intensive care patients

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

N Scawn,[1]* D Saul,[1] D Pathak,[1] B Matata,[1] I Kemp,[1] R Stables,[1] S Lane,[2] A Haycox[3] and R Houten[3]

[1]Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, UK
[2]Department of Biostatistics, University of Liverpool, Liverpool, UK
[3]Liverpool School of Management, University of Liverpool, Liverpool, UK

*Corresponding author

Executive summary

Health Technology Assessment 2012; Vol. 16: No. 36
DOI: 10.3310/hta16360

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

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 (Bochud PA, Calandra T. Pathogenesis of sepsis: new concepts and implications for future treatment. *BMJ* 2003;**326**:262–6). Hospital-acquired sepsis is reported to occur in 10–70% of patients undergoing invasive mechanical ventilation, the rate varying with the patient population studied and diagnostic criteria used (Rello J, Diaz E. Pneumonia in the intensive care unit. *Crit Care Med* 2003;**31**:2544–51). Despite the major advances in intensive care management, sepsis and its complications remain the leading cause of mortality in ICUs (Gross PA, Neu HC, Aswapokee P, Van Antwerpen C, Aswapokee N. Deaths from nosocomial infections: experience in a university hospital and a community hospital. *Am J Med* 1980;**68**:219–23).

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.

To date, most studies have focused on optimising antibiotic treatment either for ventilator-acquired pneumonia, which accounts for approximately 50% of antibiotic use in ICUs (Aarts MA, Brun-Buisson C, Cook DJ, Kumar A, Opal S, Rocker G, *et al*. Antibiotic management of suspected nosocomial ICU-acquired infection: does prolonged empiric therapy improve outcome? *Intensive Care Med* 2007;**33**:1369–78; Micek ST, Ward S, Fraser VJ, Kollef MH. A randomised controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004;**125**:1791–9; Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. *Am J Respir Crit Care Med* 2000;**162**:505–11), 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 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 $> 12 \times 10^9$/l or $< 4 \times 10^9$/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 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.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Publication

Scawn N, Saul D, Pathak D, Matata B, Kemp I, Stables R, *et al*. 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. *Health Technol Assess* 2012;**16**(36).

How to obtain copies of this and other HTA programme reports

An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

– fax (with **credit card details**)
– post (with **credit card details** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services' (out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card
You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of *HTA on DVD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/13/38. The contractual start date was in February 2010. The draft report began editorial review in November 2011 and was accepted for publication in March 2012. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Charlesworth Press.