

# In the Literature

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## Administration of Antibiotic Therapy for 2 Days to Treat Possible Sepsis of Unknown Origin: A Pilot Study

Scawn N, Saul D, Pathak D, 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:i–xiii, 1–70. Available at: [http://www.journalslibrary.nihr.ac.uk:83/\\_\\_data/assets/pdf\\_file/](http://www.journalslibrary.nihr.ac.uk:83/__data/assets/pdf_file/) and [http://www.journalslibrary.nihr.ac.uk/\\_\\_data/assets/pdf\\_file/0007/63970/ExecutiveSummary-hta16360.pdf](http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0007/63970/ExecutiveSummary-hta16360.pdf) (executive summary).

Investigators at the Liverpool Heart and Chest NHS Foundation Trust performed a prospective, randomized, pilot feasibility trial to examine the hypothesis that prolonged antibiotic administration is unnecessary in patients with apparent sepsis of unknown origin. Patients who met at least 2 of 4 systemic inflammatory response syndrome (SIRS) criteria in the absence of a documented infection and for whom the “surviving sepsis” management bundle was being started by their intensivist were eligible for study entry. The patients were randomly assigned to receive antibiotic therapy in the form of dose-adjusted teicoplanin (once every 12 hours for the first 24 hours and then every 24 hours thereafter) plus meropenem (1 g 3 times daily) for either 48 hours or 7 days.

Of the 103 patients assessed for eligibility, 46 patients, most of whom had undergone cardiothoracic surgery, were randomly assigned to a treatment group. Most exclusions were for failure to meet all of the entry criteria. The 23 patients in each treatment group were reasonably well matched. Three patients, all in the 7-day group, did not complete their assigned duration of therapy, one because of a drug-related adverse event, one because of hospital discharge at day 4, and one because of death.

The primary outcome of the study was a composite of death and initiation of antibiotic therapy after the completion of the randomly assigned treatment regimen. The risk difference between the 2 groups for the occurrence of the composite outcome was 0.12 (95% confidence interval, .11–.13;  $P = .3$ ). Four of 23 patients (17.3%) who were assigned to receive antibiotics for 2 days and 3 of 23 (13.0%) assigned to receive antibiotics for 7 days received further antibiotic therapy. Three patients in each group had positive culture results during the treatment period, but their specimen sources (blood, swab, and tracheal aspirate) cannot be determined from the report. Four patients died during the trial (3 in the 48-hour group and 1 in the 7-day group), none as the result of trial conditions. The individual causes of death were (1) sepsis and gastrointestinal bleed, pulmonary abscess, and esophageal carcinoma; (2) multiorgan failure, sepsis, ischemic bowel, and ischemic heart disease; (3) cerebrovascular accidents and thoracic aneurysm; and (4) multiorgan failure and coronary artery disease.

The length of intensive care unit (ICU) stay was shorter in the 48-hour group, and there was a nonsignificant trend toward a shorter duration of mechanical ventilation. Administration of antibiotics for only 48 hours was associated with significant cost savings.

The serum procalcitonin (PCT) concentration was measured at randomization and, in most patients, at intervals thereafter, and analysis suggested that the baseline PCT level appeared to be a possible predictor of antibiotic therapy being restarted and of the occurrence of the composite outcome measure.

The finding that baseline PCT levels were strongly predictive of both a perceived need for restarting antibiotics and the composite outcome of death and need for further antibiotics deserves further study. In contrast, a large randomized clinical trial, found that ongoing monitoring of the PCT level beyond the baseline value was not useful in the decision to escalate antibiotic therapy [1, 2]. Other data, however, indicate that PCT monitoring may be useful in assisting in the decision to discontinue antibiotic administration.

Consistent with the trial's purpose of being only a pilot and feasibility study, it was underpowered relative to its end points. Its results are nonetheless consistent with clinical experience, as well as with some clinical trial data. Studies dealing with presumed pneumonia in the ICU, as well as with the use of rapid diagnostic techniques to avoid the need for coverage of a specific pathogen, such as *Staphylococcus aureus*, also point the way toward shortened durations of empirical antibiotic therapy [3–6]. These results also strongly support the implementation of the Centers for Disease Control and Prevention's recommendation for a formal “antibiotic time-out” after 48–72 hours of empirical therapy.

Entry into this study required, in addition to suspected but not proven infection, the presence of only 2 of the 4 SIRS criteria: a temperature of  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , a heart rate of  $>90$  beats/minute, a respiratory rate of  $>20$  breaths/minute, and a white blood cell count of  $>12\,000$  cells/mm<sup>3</sup> or  $<4000$  cells/mm<sup>3</sup>. In addition, the patients entered into the study had median Acute Physiology and Chronic Health Evaluation II scores of only 13–14 and Sequential Organ Failure Assessment scores of 8–11. Thus, the applicability to patients with a greater severity of illness is uncertain. Also, most patients had undergone cardiothoracic surgery, so the applicability of these findings to other patient types is also uncertain.

The biggest drawback is, of course, the small sample size, although the population was appropriate for the purposes of the study. The investigators actively examined practical aspects of the trial, including barriers to patient acquisition, such as a reliance on ICU personnel for case referral. As a result, the full study, the results of which we all anxiously await, will have a better chance of providing definitive results.

## References

1. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin And Survival Study (PASS) Group. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med* 2011;39:2048-58.
2. Deresinski S. In the literature. Procalcitonin and antibiotic escalation in critical care patients—not a good idea. *Clin Infect Dis* 2012;54. iii-iv.
3. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004;125:1791-9.
4. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit—a proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000;162:505-11.

5. Boyce JM, Pop OF, Abreu-Lanfranco O, et al. A trial of discontinuation of empiric vancomycin therapy in patients with suspected methicillin-resistant *Staphylococcus aureus* health care-associated pneumonia. *Antimicrob Agents Chemother* 2013;57:1163-8.
6. Leone M, Malavieille F, Papazian L, et al. Routine use of *Staphylococcus aureus* rapid diagnostic test in patients with suspected ventilator-associated pneumonia. *Crit Care* 2013;17:R170.