Antibiotics for sepsis: comparison of short and prolonged duration intravenous infusions

A meta-analysis of RCTs found prolonged infusions of broad-spectrum beta-lactam antibiotics (carbapenems, penicillins and cephalosporins) significantly reduced all-cause mortality in adults with sepsis compared with short-term infusions. There was no significant difference in clinical cure or improvement, adverse events and antimicrobial resistance between prolonged and short-term antibiotic infusions. For people presenting with sepsis, timely management with antibiotics is essential, as discussed in the NICE guideline on sepsis.

Overview and current advice

Sepsis is a life-threatening condition occurring in people of all ages. The NICE guideline on sepsis: recognition, diagnosis and early management recommends that adults, children and young people aged 12 years and over who have suspected sepsis and 1 or more high risk criteria should be given a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting [see risk stratification tools in the NICE guideline]).

Intravenous antibiotics can be administered at different rates. A bolus injection delivers the dose in less than 30 minutes, a short-term infusion in less than 1 hour, and a prolonged infusion delivers the dose over a number of hours or continuously.

The NICE guideline makes recommendations on specific antibiotics depending on the cause of the infection and the age of the person, and advises using local antimicrobial guidance, but does not describe how the antibiotics are to be administered, such as the duration of an infusion.

The NICE interactive flowchart on sepsis brings together all related NICE guidance and associated products on this topic in a set of topic-based diagrams.

New evidence

A systematic review and meta-analysis assessed the effect of prolonged infusions (administered continuously or over 3 hours or more) of broad-spectrum beta-lactam antibiotics compared with short-term intravenous infusions (1 hour or less, Vardakas et al. 2017).

The systematic review included randomised controlled trials (RCTs) in adults with sepsis that compared infusion rates for the same antibiotic and reported mortality or clinical efficacy data. The
systematic review excluded non-RCTs, studies reporting only pharmacokinetic or pharmacodynamic data, studies involving 10 or fewer participants, cross-over RCTs and cluster RCTs.

The meta-analysis included 22 studies (1,876 participants). Three studies were double-blind, 9 studies were open-label and in 10 studies blinding was not reported. Studies were conducted in Asia-Pacific (10 studies), Europe (9 studies) and the US (3 studies). The definition of sepsis varied between studies. Carbapenems and penicillins were each studied in 9 RCTs, and cephalosporins in 8 RCTs. Allocation concealment was adequate in 7 studies, inadequate in 2 studies and not assessable in 13 studies. The quality of the evidence on mortality, assessed using GRADE, was high. The average (mean or median) age of participants was less than 45 years in 5 studies, 45 to 65 years in 12 studies and over 65 years in 1 study. Four studies did not provide data on age. In most studies, the cause of sepsis was not documented in a large number of participants (up to 81%). In 15 studies only people in intensive care units were enrolled.

All-cause mortality was reported in 17/22 studies (1,597 participants). The review found that prolonged antibiotic infusions of broad-spectrum beta-lactams were associated with lower all-cause mortality compared with short-term infusions (relative risk 0.70, 95% confidence interval [CI] 0.56 to 0.87). Heterogeneity between studies was not observed and there was no evidence of publication bias.

Clinical cure or improvement was reported in 18/22 RCTs. There was no statistically significant difference between prolonged and short-term infusions for both the intention to treat (11 RCTs, 1,219 participants, RR 1.06, 95% CI 0.96 to 1.17) and per-protocol analyses (10 RCTs, 1,091 participants, RR 1.13, 95% CI 1.00 to 1.28).

Adverse events and emergence of resistance were generally poorly reported across the studies. Across 7 RCTs (980 participants), there was no difference in adverse events between the prolonged and short-term infusion groups (RR 0.88, 95% CI 0.71 to 1.09). Emergence of antimicrobial resistance was reported in 4 RCTs. In 2 of these studies, resistant strains were not isolated in either treatment group and no significant difference in resistance was observed in the other 2 studies (RR 0.60, 95% CI 0.15 to 2.38).

Although the same antibiotic was used in each treatment arm, the total daily dose varied both within and between studies. People treated with prolonged infusions either received antibiotics continuously over 24 hours or over an extended period of time (3 to 7 hours). In 13/22 studies, participants in the prolonged infusion group received a lower total antibiotic dose (50% to 67% lower) compared with the short-term infusion group. When reported, the course length for the antibiotics was also variable.

Commentary

Commentary provided by Dr Timothy Felton, Consultant and Senior Lecturer in Critical Care and Respiratory Medicine, Manchester University NHS Foundation Trust and The University of Manchester

Intravenous broad-spectrum beta-lactam antibiotics, such as piperacillin-tazobactam and meropenem, may be administered to patients with sepsis as a bolus, over a short amount of time (typically less than thirty minutes), or as a prolonged infusion (over many hours). Examples of prolonged infusions include extended infusion where the antibiotic is administered over half the dosing interval (for example, an antibiotic that can be given as a bolus every 8 hours is given as a 4 hour infusion every 8 hours) or as a continuous infusion.

A global survey of practice published in 2015 (Tabah et al.) showed approximately one-third of intensive care units were administering broad-spectrum beta-lactam antibiotics via prolonged infusions rather than as a bolus dose.
This new meta-analysis by Vardakas and colleagues shows prolonged infusion of intravenous broad-spectrum beta-lactam antibiotics to patients with sepsis is associated with lower mortality. Less than half the studies included in the meta-analysis (7 studies, 980 patients) reported adverse events. This meta-analysis suggests that prolonged infusions and bolus dosing associated with the same rate of adverse events. No difference in the rate of emergence of antimicrobial resistance was reported in the 2 included studies which is a weakness in the trial design of the available studies.

Generalisability of the results to the NHS may be limited due to a lack of studies including UK patients and the inclusion of studies involving a younger population of critically ill patients than typically is found in UK intensive care units. A randomised clinical trial (Beta-Lactam InfusioN Group Study, BLING III), led by the Australian and New Zealand Intensive Care Society Clinical Trial Group, of continuous versus bolus infusions of antibiotics is currently underway and will include a limited number of UK centres.

Declaration of interests:
Dr Tim Felton declared no interests.

Study sponsorship
No funding was obtained for this systematic review and meta-analysis.

References

About this Medicines Evidence Commentary
Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.