A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics

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CRD summary
The review concluded that the limited data available suggested continuous infusion of β-lactam antibiotics led to the same clinical results as higher dosed bolus administration in hospitalised patients. The authors' conclusions were suitably cautious in reflecting the limited data available and their conclusions are likely to be reliable.

Authors' objectives
To compare the effectiveness of continuous and extended infusion of β-lactam antibiotics.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to November 2007. Search terms were reported. The authors' own files were searched. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) where the randomisation technique was clearly stated or observational studies that compared continuous or extended infusion (administered over at least three hours) with bolus administration of β-lactam antibiotics in hospitalised adults with acute infections were eligible for inclusion. Mortality and clinical cure were the outcomes of interest.

Piperacillin and ceftazidime were the main antibiotics studied. Patients had a range of illnesses (commonly sepsis or hospital-acquired pneumonia). Regimens used for both bolus and continuous administration groups varied between studies. Some studies used concomitant antibiotics.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Study quality was assessed by evaluating allocation concealment, blinding and use of intention-to-treat analyses.

The authors did not state how many reviewers assessed study quality.

Data extraction
Data were extracted to calculate odds ratios (OR) and 95% confidence intervals (CI). Study authors were contacted for missing data when necessary.

Two reviewers independently extracted data. Disagreements were resolved through a third reviewer.

Methods of synthesis
For RCTs, a random-effects model was used to pool odds ratios with 95% CIs. Heterogeneity was assessed using $\chi^2$ and $I^2$. Observational studies were described narratively. Publication bias was assessed with a funnel plot.

Results of the review
Fourteen RCTs (n=846) and two observational studies (n=283) were included in the review. Four RCTs reported use of adequate allocation concealment, seven used an intention-to-treat analysis and none reported use of blinding.

Continuous or extended infusion was associated with neither improvement in clinical cure (OR 1.04, 95% CI 0.74 to 1.46, $I^2=0$%; nine studies) nor improvement in mortality (OR 1.00, 95% CI 0.48 to 2.06, $I^2=15$%; nine studies).

A funnel plot indicated a possibility of publication bias. Two observational studies indicated extended or continuous infusion was associated with improvement in clinical cure.
Authors' conclusions
The limited data available suggested that continuous infusion of β-lactam antibiotics led to the same clinical results as higher dosed bolus administration in hospitalised patients.

CRD commentary
The review addressed a clear question supported by appropriate eligibility criteria. Three electronic databases were searched to identify relevant studies in any language. It appeared that the authors did not search for unpublished studies. Independent duplicate procedures were used to minimise risks of reviewer error and bias for the processes of study selection and data extraction; no details were reported for methods used in the quality assessment. Appropriate methods were used to pool data and assess heterogeneity. The authors noted a general difference in doses between the bolus administration groups (which received a higher overall dose) and continuous infusion groups. The results of the quality assessment were tabulated, but other than the issue of blinding were not discussed in relation to the review results.

The authors' conclusions were suitably cautious in reflecting the limited data available and their conclusions appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that large well-designed RCTs were necessary. Such studies should be of patients with a high acuity of illness (with illnesses being homogenous) and should use equal total dose of antibiotic in both bolus and infusion groups. Length of hospital stay and pharmacoeconomic analysis should be reported.

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