Carbapenems versus other beta-lactams in treating severe infections in intensive care: a systematic review of randomised controlled trials

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CRD summary
This review concluded that the use of carbapenems, rather than antipseudomonal penicillins, could reduce mortality and the time taken before patients received appropriate antibiotic treatment for severe infections and febrile neutropenia. Evidence was insufficient for distinguishing between carbapenems and fourth-generation cephalosporins. The conclusions were likely to be reliable, but in practice local epidemiology would need to be assessed when choosing between antibiotics.

Authors' objectives
To compare carbapenems with fourth-generation cephalosporins (4GC) and antipseudomonal penicillins (APP) in the treatment of severe infections and febrile neutropenia.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and JICST-EPlus (Japan Science and Technology Corporation) were searched in November 2006; search terms were reported. Relevant journals and conference abstracts were handsearched. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) of adults with a severe lower respiratory tract infection, intra-abdominal infection, skin and soft structure infection, urinary tract infection or sepsis treated with 4GC, APP or carbapenems at an appropriate daily dose (based on clinical reviews, guidelines and licence) were eligible for inclusion, so long as any additional treatment was given equally in the two study groups.

The included studies assessed patients who were otherwise well, but had a severe infection or patients with a compromised immune system (febrile neutropenia) and severe infection. Carbapenems investigated were imipenem (daily dose of 2 g or 3 g), ertapenem (daily dose of 1 g) or meropenem (daily dose of 3 g). The 4GC investigated was cefepime (daily dose of 6 g) and the APP investigated was piperacillin (daily dose of 12 g).

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the quality of the included studies, based on the method of randomisation and concealment of allocation; disagreements were resolved by consensus. Trials that were deemed to be poor quality were excluded from the review.

Data extraction
Relative risks (RRs) with 95% confidence intervals (CIs) were extracted independently by two reviewers for the outcomes clinical response, bacteriologic response, all-cause mortality and adverse events. Data were extracted in an intention-to-treat format. Where data were presented in a per protocol format, they were recalculated where possible. Authors of primary studies were contacted for additional data when necessary.

Methods of synthesis
Studies were split into two categories depending on whether the patients had severe infection, but were otherwise well (called the severe infection group) or whether patients had a compromised immune system and severe infection (called the febrile neutropenia group). RRs were pooled for each group using the Mantel-Haenszel fixed-effect model. Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic. Subgroup analyses were planned based on different treatment regimens, different sites of infection, geographical location of the trial and other variables.
(depending on whether statistical heterogeneity was identified). Sensitivity analyses were planned by removing the quality assessment to include all trials, using a random-effects model and using all trials considered to be of adequate quality regardless of the antibiotic dose used.

Publication bias was assessed using funnel plots and by calculating a regression of normalised effect versus precision.

**Results of the review**

Twelve RCTs were included in the review (n=3,607).

**Severe infection**

Only one trial compared carbapenems with 4GC. There were no significant differences between carbapenems and 4GC for any of the positive or negative outcomes assessed.

Seven trials compared carbapenems with APP. There was no significant difference in clinical response, clinical cure, bacteriologic response, serious adverse events overall or gastrointestinal-related serious adverse events between carbapenems and APP. But, there was a significant reduction in all-cause mortality (RR 0.62, 95% CI: 0.41, 0.95; five RCTs) and serious adverse events leading to withdrawal (RR 0.65, 95% CI: 0.45, 0.96; six RCTs) with carbapenems compared with APP. There was no evidence of significant statistical heterogeneity. There was no clear evidence of publication bias.

**Febrile neutropenia**

Two trials compared carbapenems with 4GC. There were no significant differences between carbapenems and 4GC for any of the positive or negative outcomes assessed. Statistical heterogeneity was significant for the outcomes clinical response and bacteriologic response.

Two trials compared carbapenems with APP. There was no significant difference in clinical response, all-cause mortality and serious adverse events overall between carbapenems and APP. But, there was a significant improvement in clinical response (within 72 hours) (RR 1.37, 95% CI: 1.09, 1.74; two RCTs) and bacteriologic response (RR 1.73, 95% CI: 1.03, 2.89; one RCT) with carbapenems compared with APP. There was no evidence of significant statistical heterogeneity.

Results for subgroup analyses and sensitivity analyses were also presented.

**Authors’ conclusions**

The use of carbapenems, rather than APP, could reduce mortality and reduce the time before patients receive appropriate antibiotic treatment by simplifying treatment decisions. Current evidence is insufficient for distinguishing between carbapenems and 4GC.

**CRD commentary**

This review addressed a clear question and was supported by appropriate inclusion criteria. Adequate attempts were made to locate relevant studies, including searching sources of unpublished data, without using language restrictions, thus reducing the potential for publication bias and language bias. The quality of the included studies was assessed and studies deemed to be poor quality were excluded from the review. The authors stated that one trial was excluded based on quality assessment, but further results of the quality assessment were not reported. Few details of the included studies were provided. Two reviewers independently extracted data from the included studies and assessed study quality, thus reducing the potential for reviewer bias and error; it was unclear whether similar methods were used during study selection. Appropriate methods were used to pool the results of the trials and to investigate statistical heterogeneity.

Overall this was a reasonably well-conducted systematic review and the authors’ conclusions were likely to be reliable. However, the authors acknowledged that they did not assess the activity of individual antibiotics – a class-based approach was used – and that in clinical practice the local epidemiology would need to be assessed based on the known
resistance patterns when choosing between antibiotics (the review did not consider resistance as a modifying factor).

**Implications of the review for practice and research**

**Practice:** The authors stated that in clinical practice the local epidemiology would need to be assessed based on the known resistance patterns when choosing between antibiotics.

**Research:** The authors did not state any implications for further research.

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