Efficacy and safety of cefepime in pediatric patients: a systematic review and meta-analysis
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CRD summary
The results of this review suggested that treatment with cefepime in paediatric patients was not associated with an increased risk of adverse outcomes, although the included studies were very small and of low quality. The review was well conducted and the authors’ cautious conclusions are likely to be reliable.

Authors’ objectives
To assess the efficacy and safety of cefepime compared with other conventionally used antibiotic regimens in child and adolescent patients.

Searching
MEDLINE and EMBASE were searched from inception for January 2009 for relevant studies; search terms were reported. References of the included trials were checked for additional studies. Cochrane Central Registry of Controlled Trials (CENTRAL), regulatory reviews, new drug applications to the Food and Drug Administration (FDA) and abstracts of relevant conferences were searched for unpublished trials. The reviewers contacted clinical trials investigators, the FDA and pharmaceutical companies to identify additional studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that compared cefepime to other medication in patients under 19 years of age were eligible for inclusion. Trials that included adults were eligible if the results for paediatric patients were reported separately. The primary outcomes were overall mortality and clinical failure (defined as incomplete resolution of the infection without treatment modification). Secondary outcomes were microbiologic failure and adverse events.

Included patients’ age ranged from 0.1 years to 18 years. The clinical indications for which the patients received treatment were febrile neutropenia, pneumonia, meningitis and serious bacterial infections. Most studies compared cefepime to a single agent (included ceftazidime, cefotaxime, cefuroxime, meropenem and piperacillin). Other medications used with and compared with cefepime were netilmicin, ceftazidime, amikacin, tazobactam, sulbactam, meropenem and ceftriaxone. Addition of antimicrobial agents such as aminoglycosides and glycopeptides were allowed where this was consistent with accepted clinical practice.

Two reviewers independently performed study selection; any disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed methodological quality using a three-item Jadad scale of randomisation, allocation concealment, and patient attrition and a nine-item Delphi scale of methods of enrolment, randomisation, allocation concealment, blinding, similarity of baseline characteristics and data analyses. Any disagreements between reviewers were resolved by consensus.

Data extraction
Data were extracted independently by two reviewers to enable calculation of risk differences (RD) and 95% confidence intervals (CI) for the primary outcomes. The reviewers used intention-to-treat data where possible. Any disagreements between reviewers were resolved by consensus.

Methods of synthesis
Pooled risk differences and 95% CIs were calculated using a Mantel-Haenszel model. Statistical heterogeneity was assessed using $X^2$ and $I^2$ tests. Sensitivity analyses were undertaken to assess the impact of patient characteristics on outcomes and compare per-protocol data with data derived from intention-to-treat analyses. Subgroup analyses were conducted to identify differences in febrile neutropenia outcomes.

Results of the review
Sixteen RCTs (1,827 patients) were included in the review. None of the RCTs adequately described randomisation processes. One RCT reported the method of allocation concealment. Nine trials described withdrawals and patients lost to follow-up. Intention-to-treat analyses were utilised in 10 trials.

There were no significant differences observed between cefepime and the comparators in all-cause mortality (16 trials, 1,827 patients) and in clinical failure rates (16 trials, 1,770 patients). Microbiological failure was confirmed in nine trials of 682 patients and failure rates were similar for cefepime and the comparators.

There was a non-significant trend for patients with febrile neutropenia who received cefepime to have lower rates of treatment failure than patients who received comparators (RR 0.70, 95% CI 0.46 to 1.07).

Rates of adverse events were similar for cefepime and comparators across the studies, although in one study 10 adverse events were reported in the cefepime group (n=20) and no events were reported in a group of eight patients who received cefuroxime.

There was no statistically significant heterogeneity reported across the studies for any of the outcomes assessed.

Authors' conclusions
The results of the review suggested that treatment with cefepime in paediatric patients was not associated with an increased risk of adverse outcomes. The conclusions were limited because of the poor quality of the included studies in the review.

CRD commentary
The review addressed a clear question. Criteria for the inclusion of studies were clearly stipulated. Appropriate electronic databases were searched without language restrictions. The searches included attempts to identify unpublished literature and ongoing trials. Steps were taken by the authors throughout the review process to minimise errors and bias by the reviewers. The authors' decision to pool the study results appeared justified, as shown by the statistical homogeneity across the results. The limitations of the review, particularly the low quality and small sample sizes of the included trials, were correctly acknowledged by the authors.

This was a well-conducted review and the authors' cautious conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for research
Research: The authors stated that well-designed clinical trials were required to establish the safety and efficacy of cefepime in children and adolescents. Important subgroups should be considered, particularly any differences between children and adults in treatment effects and adverse events

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