Authors' objectives
To determine whether administering recombinant granulocyte colony-stimulating factor (rG-CSF) to neonates with bacterial septicemia reduces mortality.

Searching
MEDLINE was searched from January 1990 to May 2000 using the search terms 'rG-CSF', 'recombinant human G-CSF', 'recombinant human methionyl G-CSF', 'infection', 'septicemia' and 'infant-newborn'. In addition, personal files and the references of the retrieved articles were checked for additional references. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
All studies with a control group (either placebo recipients or historic controls) were included in the review.

Specific interventions included in the review
Studies that assessed the utility of rG-CSF were included in the review. All of the included studies used a commercially available rG-CSF preparation. The doses varied from 1.0 to 10.0 microg/kg and were administered over 3 to 14 days. The control groups received placebo or were historic controls.

Participants included in the review
Studies that examined human neonates with proven or suspected septicaemia were eligible for inclusion in the review. Of the five studies ultimately included, two enrolled only patients weighing 2,000 g or less, whilst the remaining three had no birth weight criterion. The definition of early-onset septicaemia was less than 72 hours (3 studies) or less than 96 hours (2 studies). Positive blood cultures were not required in any of the studies. The mean age of the patients ranged from 21 to 30 weeks.

Outcomes assessed in the review
The primary outcome measure was death.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the articles in a non-blinded fashion to assess their relevance for inclusion in the review. The authors did not state whether this was undertaken independently, or how any disagreements regarding inclusion were resolved.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers extracted the data in a non-blinded fashion. Data on the study and year, study design, the number of patients, mean weight, mean age, the number of patients with neutropenia and the number of deaths were extracted and tabulated.

Outcome was dichotomised into 'died' and 'lived', and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each study.
Methods of synthesis

How were the studies combined?
The summary measure of effect across studies was calculated as the exact common OR and 95% CI. All statistical tests were performed as 2-sided comparisons.

How were differences between studies investigated?
The Breslow and Day homogeneity test was also undertaken; a P-value of less than 0.10 was used to reject the null hypothesis of homogeneity. This test was performed as a prerequisite screen to determine whether it was valid to estimate a summary measure of effect. In addition, an a priori planned subgroup analysis was undertaken to examine the effects of:

- study with a randomised placebo-controlled design versus a historical control design;
- study patients with a birth weight of less than 2,000 g versus greater than 2,000 g; and
- study patients with neutropenia versus those without neutropenia. The definition used for neutropenia was that set by the authors of the individual studies.

Results of the review

Five studies (n=155) were included: 3 randomised controlled trials (n=92) and 2 historically controlled trials (n=63). The analysis involved 73 rG-CSF recipients and 82 controls.

In the aggregate, death was less likely among the rG-CSF recipients than among the controls (OR 0.17, 95% CI: 0.13, 0.70, P<0.05). When the two studies in which historical controls were used were excluded from the analysis, the OR for death was 0.43 (95% CI: 0.14, 1.23, P=0.13). For the subgroup of patients with birth weights of less than 2,000 g, the OR was 0.32 (95% CI: 0.11, 0.83, P<0.02), while for patients with neutropenia, the OR was 0.20 (95% CI: 0.06, 0.56, P<0.001).

The test for heterogeneity was acceptable (P=0.31).

Authors' conclusions

The efficacy of rG-CSF use among neonates with suspected septicaemia is unproven, but it has merit and warrants further study. Since it was the lower birth weight neonates and those with neutropenia who appeared more likely to benefit, these two items should be considered when designing future studies.

CRD commentary

The authors stated a clear review question, which was addressed by inclusion criteria for the type of intervention, population, outcome measures and study designs that were to be assessed in the review. However, the literature search was restricted to one database, which means that other studies may have been missed. Two of the authors independently screened the studies for relevance for inclusion in the review; this means that selection bias is likely to have been minimised. A method for assessing the validity of the studies was not reported, so it is difficult to assess the quality of the primary studies included. The statistical analysis was appropriate, with heterogeneity between the results of different studies being examined. Furthermore, the authors explored how the results of the studies differed according to study design.

Overall, this was a reasonable review, although further steps should have been taken to reduce bias in the review process. The authors' conclusions appear to have been consistent with the evidence base reviewed, but other relevant studies may have been missed due to the limited literature search.

Implications of the review for practice and research

Practice: The authors stated that the routine use of rG-CSF cannot be recommended for all neonates with sepsis.
Research: The authors stated that further research is warranted to assess the efficacy of rG-CSF, particularly in lower birth weight neonates with suspected septicaemia and those with neutropenia.

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