Ribavirin for respiratory syncytial virus lower respiratory tract infection: a systematic review

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Authors' objectives
To review the evidence regarding the efficacy of aerosolised ribavirin in the treatment of infants with respiratory syncytial virus (RSV) lower respiratory tract infection.

Searching
MEDLINE was searched from January 1975 to April 1995; the search terms are given. Additional published and unpublished studies were identified by examining reference lists of review articles and primary studies, and by contacting three experts in the field.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) comparing ribavirin with a placebo control, where the population consisted of infants with documented RSV infection and lower respiratory tract infection.

Specific interventions included in the review
Ribavarin at a 20 mg/ml concentration mixed in normal saline or water, continuously aerosolised with the use of a collision generator for 12 to 24 hours a day for a variable number of days.

Participants included in the review
Infants with documented RSV lower respiratory tract infection were included.

Outcomes assessed in the review
Mortality; respiratory deterioration leading to withdrawal from the study; length of hospitalisation; and length of ventilation and oxygen dependence.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
A methodological assessment of each study was carried out. A scale was used which examined the following criteria: how patients were selected, the baseline comparability of the patient groups, the quality of randomisation, the control of confounders, whether outcomes were explicitly defined, whether drop-outs were analysed, and the details of blinding of outcome assessment. The papers were assessed for validity by two authors, with agreement assessed using the Kappa statistic and any disagreements resolved by consensus.

Data extraction
The data were extracted by two independent reviewers.

Methods of synthesis
How were the studies combined?
Fixed-effect meta-analyses (Mantel-Haenszel method) were carried out to analyse data on mortality and treatment failure (respiratory deterioration).
How were differences between studies investigated?
A test of homogeneity, the Breslow-Day test, was performed to ensure that the study outcomes were qualitatively similar across studies.

Results of the review
Eight studies in total were identified (n=121 patients): 6 in nonventilated patients (n=88) and 2 in ventilated patients (n=33). Data on mortality secondary to respiratory were summarised from 3 studies (total n=56); data on lengths of hospitalisation, ventilation and oxygen dependence were summarised from 4 studies (total n=33); and data on respiratory deterioration were pooled from 3 studies (total n=56).

Ribavirin does not significantly reduce mortality rate (relative risk, RR 0.42, 95% confidence interval, CI: 0.13, 1.44) or lower the probability of respiratory deterioration (RR 0.42, 95% CI: 0.16, 1.34) when meta-analysis is used to pool the outcomes of 3 trials, although trends in the direction of benefit were observed. The tests for homogeneity relating to these meta-analyses were not significant. No study found ribavirin to shorten length of hospitalisation, while results on length of ventilation were conflicting. Rate of improvement in the severity of illness was examined in 5 studies though variability in the reporting of this outcome prevented pooling of the data. No significant differences in improvement in respiratory rate, wheezing, fever, or upper respiratory tract changes were found.

Subjective global assessment of improvement in severity of illness was found to be significant in 5 studies, with the differences in improvement between groups ranging from 11 to 37.5; all differences were statistically significant.

Improvement in oxygenation was assessed in 6 studies and results were found to be conflicting.

One study assessed pulmonary function and found no significant improvement in dynamic lung compliance at 24 or 48 hours or 7 days.

Toxicity and side-effects: ribavirin did not alter laboratory indicators of hematopoietic, hepatic or renal function in 3 studies. No episodes of ventilator malfunction occurred and the drug was well tolerated in all studies of nonventilated patients.

Authors' conclusions
Use of ribavirin in infants with RSV lower respiratory tract infection is not supported by evidence of significant benefit. However, previous studies lack sufficient power to rule out a potential reduction in mortality rate or respiratory deterioration. A large RCT of ribavirin for ventilated and other high-risk patients is needed.

CRD commentary
The review is well-conducted and methodologically sound, and the authors’ conclusions are well-founded. Any future update of the review might usefully examine databases other than MEDLINE. There is little else to add except to emphasise the need for a large good quality RCT of treatment with ribavirin.

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