Aerosolized ribavirin in the treatment of respiratory syncytial viral infection in children: a meta-analysis

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Authors' objectives
The efficacy of aerosolised ribavirin in the treatment of respiratory syncytial viral (RSV) infection in children.

Searching
MEDLINE, Excerpta Medica and the Science Citation Index were searched from 1981 through May 1995 using the search terms provided. The New England Journal of Medicine, Journal of Paediatrics, Paediatric Infectious Diseases Journal, the Journal of the American Medical Association and Critical Care Medicine were handsearched for the same time period. Conference Proceedings of the Society for Paediatric Research, Interscience Conference of Antimicrobial Agents and Chemotherapy, and the American Thoracic Society were reviewed for abstracts on ribavirin in RSV infection. The reference lists from published RCTs and review articles were examined for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Ribavirin (20 mg/mL in normal saline or water) aerosolised with a collision generator was administered continuously for 12 to 20 hours for at least three days. The placebo was saline or water.

Participants included in the review
Infants and children with RSV lower tract respiratory infection, with or without underlying diseases. RSV infection was diagnosed using an indirect immunofluorescent antibody test on nasal wash, nasopharyngeal swab or aspirate. Studies enrolling both spontaneous breathing and ventilated infants were included.

Outcomes assessed in the review
The outcomes were respiratory deterioration, mortality, the duration of hospital stay, the duration of oxygen therapy, and the duration of ventilation. The secondary outcomes selected after reviewing the articles included severity of illness, as determined by the illness severity score, and the improvement in oxygenation, as determined by pulse oximetry or arterial oxygen tensions.

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
Two validity scoring systems were used to assess the quality of the included studies. The first scoring system assessed the control of bias within a trial at entry, after entry (follow-up), and in assessing the outcome(s). The second system was used to assess three components related to study design: randomisation, blinding, and description of the withdrawals and drop-outs. Two independent assessors reviewed all of the trials. The inter-rater reliability in assessing study quality was tested by using inter-class correlation. The Spearman rank correlation coefficient was used to test for correlation between the two quality study scales.

Data extraction
The data were abstracted by two assessors independently. Dichotomous outcomes were expressed as events in treated
and control groups. Continuous variables were expressed as means for each group. The primary authors were contacted for missing data, identified after reviewing the papers.

Methods of synthesis
How were the studies combined?
For the continuous variables (illness severity score, days on ventilator, days on oxygen, and days of hospitalisation), the effect of treatment was determined by the estimate of the effect size and its 95% confidence interval (CI). A weighted mean differences method was also applied in estimating the treatment effect for continuous variables.

For dichotomous outcomes (e.g. mortality and respiratory deterioration), the Mantel-Haenszel relative risk (RR) with its 95% CI were used to summarise the treatment effect.

How were differences between studies investigated?
The Breslow-Day chi-squared test (see Other Publications of Related Interest no.1) was used to determine statistical homogeneity of the RR among the studies. The Q statistic was used to determine statistical homogeneity of the effect size and weighted mean differences. A test result of greater than 0.05 indicated that the observed difference between studies was not greater than what one would expect by chance. Both fixed-effect and random-effects models were conducted for the analysis.

Results of the review
Eight RCTs with a total of 269 participants (138 treated and 131 in the control group) were included.

Mortality was described in 5 studies, where the overall RR was 0.6 (95% CI: 0.22, 1.75). Respiratory deterioration was reported in 3 studies, where the overall RR was 0.4 (95% CI: 0.16, 1.13).

Two studies of ventilated patients compared length of hospitalisation, days of oxygen dependence and the duration of ventilation. A third study compared days on oxygen supplementation with days on a ventilator. In this study, there were 5 ventilated patients. Two studies showed a significant reduction in the length of ventilation while the other did not. The pooled 'effect size' was -0.59 (95% CI: -1.09, -0.10) which implied a significant reduction in the duration of ventilation (p=0.01). Using the weighted mean difference method, the ribavirin-treated group had an average of 5.25 days less on mechanical ventilation (95% CI: -2.74, -7.74). These results were significant in both the fixed- and random-effects models.

The duration of oxygen-dependence was also significantly shorter in the treated group in 2 of these studies. The pooled effect size was -0.522, which was statistically significant (p=0.005). The treatment group had an average of 3.6 fewer days (95% CI: -5.56, -1.28) of oxygen-dependence.

The duration of hospitalisation favoured ribavirin with an effect size of -0.22 (95% CI: -0.7, 0.27) and a weighted mean difference of -2.48 days (95% CI: -7.49, 2.97).

Clinical improvement was the main outcome in 5 studies of non-ventilated babies. The pooled standardised effect size was 1.44 (95% CI: 1.08, 1.79), which was significant (p<0.001).

Four studies in non-ventilated patients used improvements in oxygenation as an outcome measure. However, because the measures of oxygenation were different, pooling was not possible. These studies supported findings of a shortened duration of oxygen supplementation in ribavirin recipients.

Authors' conclusions
This overview does not justify the use of ribavirin in most children hospitalised with RSV lower tract respiratory infection. Ribavirin did not significantly reduce the frequency of death or respiratory deterioration, although there was a trend for these outcomes to be reduced with ribavirin. However, the study numbers may not have provided enough power to detect important differences in these rare events.
Ribavirin treatment reduced the duration of ventilation and oxygen supplementation in ventilated patients. These findings were a good incentive to use the agent, but this benefit was threatened by the exclusion of one study published as an abstract. Furthermore, one study used aerosolised water as a placebo, which may have produced bronchospasm and worsened the condition in the control group, thus exaggerating the effectiveness of ribavirin. These concerns render the observed benefit of using ribavirin inconclusive. In addition, the high costs of ribavirin and the difficulty in its administration remain significant problems.

**CRD commentary**
This was a well-conducted thorough review in terms of the search strategy conducted, the inclusion criteria used, the validity assessment of the included studies, and the synthesis of the results. However, there was no information given on how decisions on whether to include or exclude the individual studies were made. In addition, while it was reported that two reviewers conducted the data extraction there was no information on how any differences between them were resolved.

The authors’ conclusions that the results are hampered by limited power, and therefore do not have a clear clinical implication, seems justified given the small number of included trials which also have a limited number of patients.

**Implications of the review for practice and research**
The authors note that these findings provide evidence that the drug has some efficacy which warrants further study. An RCT which addresses costs in addition to other outcome measures is needed. Such a study would be targeted towards high-risk or ventilated patients who stay in hospital longer than previously healthy children.

The question of ribavirin efficacy was unanswered by the meta-analysis. However, the results provided the justification for a new RCT, and are important in this regard. The results also provided support for those clinicians who withhold the use of the agent in patients meeting the criteria described by the American Academy of Pediatrics.

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Record Status
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