

AEROSOLIZED RIBAVIRIN IN THE TREATMENT OF RESPIRATORY SYNCYTIAL VIRAL INFECTION IN CHILDREN: A META-ANALYSIS

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Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRI) in infants and young children,^{1,2} accounting for 60%-90% of cases of bronchiolitis and 5%-40% of cases of pneumonia. Ribavirin is the only specific antiviral agent available for the treatment of RSV infection. The drug was approved by the Food and Drug Administration in 1985 for use in non-ventilated babies with RSV infection. The Committee on Infectious Diseases of the American Academy of Pediatrics recommended that the use of nebulized ribavirin therapy for three to seven days may be considered for all infants with RSV LRI who are severely ill or mechanically ventilated, and for all infants with underlying disease who are at high risk of RSV-associated complication.³

Despite these guidelines, the drug is still not used widely by physicians. In the United States, most pediatric intensivists disagree with the published guidelines.⁴ In Canada, there are regional differences in the use of ribavirin, but overall, it is prescribed in fewer than 30% of patients meeting the published guidelines.⁵ The reason for lack of compliance with the guidelines includes questions regarding efficacy,⁶⁻¹⁰ complexity of administration and high cost. A systematic review of randomized trials may provide insight into the role of this agent.

Methodology

Search Strategy

Randomized clinical trials (RCTs) published from 1981 through May 1995 were identified, using various search strategies. Three computerized databases were searched. Medline was searched independently by two people. The search terms were "ribavirin" and explode "respiratory

Computer printouts, including title and abstracts, if available, were examined independently by two individuals to identify potential controlled clinical trials. Copies of the complete text of all articles likely to be controlled clinical trials were obtained.

The Excerpta Medica Database was searched from 1981 through May 1995 by one person using the search terms "ribavirin" and "respiratory syncytial virus" or "bronchiolitis." These terms were searched individually and in combination. Computer printouts were reviewed to identify relevant articles. Science citation index (SCI) was also searched. Printouts of citations quoting the chosen articles were examined for relevant articles which might be clinical trials.

In addition to the search of databases, the *New England Journal of Medicine*, *Journal of Pediatrics*, *Pediatric Infectious Diseases Journal*, the *Journal of the American Medical Association* and *Critical Care Medicine* were searched manually by screening the tables of contents of each issue of these journals from 1981 through May 1995 for relevant titles. These journals were searched because at least one trial had been published in them. Conference Proceedings of the Society for Pediatric Research, Interscience Conference on Antimicrobial Agents and Chemotherapy and The American Thoracic Society were reviewed for abstracts on ribavirin in RSV infection. Reference lists from published RCTs and review articles were examined for additional studies.

Study Inclusion and Exclusion Criteria

All RCTs conducted in infants and children with RSV LRI were included irrespective of whether the children had underlying diseases. Similarly, studies enrolling both spontaneous breathing and ventilated infants were included. Studies published in abstract form were included if enough information could be obtained from the abstract, or from the author. Studies comparing short duration ribavirin therapy with standard duration ribavirin therapy were excluded.

Outcome Measures

Primary outcomes were selected in advance, and were thought to have major clinical importance impacting on the decision to use ribavirin. These included respiratory

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syncytial viruses," explode "bronchiolitis" or "all virus or viruses or viral" and explode "clinical trials" and "human."

deterioration, mortality, duration of hospital stay, duration of oxygen therapy and duration of ventilation. Secondary outcomes were selected after reviewing the articles, and were thought to have less clinical importance. They included severity of illness as determined by illness severity score, and improvement in oxygenation, determined by pulse oximetry or arterial oxygen tensions.

Study Quality Assessment

Two independent assessors reviewed all trials using two instruments.^{11,12} The method assessing three dimensions of trial methodology felt to be the most important sources of bias was described by Chalmers et al.¹¹ These dimensions are control of bias at entry, after entry (follow-up), and in assessing outcome(s). The maximum possible score was 10.

Another scoring system developed and validated by Jadad¹² was also used in quality assessment. Three components related to study design determine a composite score of 5. These included randomization, blinding and description of withdrawals and dropouts.

Data Abstraction

Data was 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. Missing data identified after reviewing the papers was sought from the primary authors.

Statistical Analysis

For the continuous variables of illness severity score, days on ventilator, days on oxygen and days of hospitalization, the effect of treatment was determined by the estimate of the effect size and its 95% confidence interval.^{13,14} A weighted mean differences method was also applied in estimating the treatment effect for continuous variables.^{13,15} The inter-rater reliability in assessing study quality was tested by using inter-class correlation. Spearman rank correlation coefficient was used to test for correlation between the two quality of study scales.

For dichotomous outcomes, such as mortality and respiratory deterioration, the Mantel-Haenszel relative risk, with its 95% confidence interval, was used to summarize treatment effect. The Breslow-Day chi-squared test¹⁶ was used to determine statistical homogeneity of relative risk among studies. Q-statistic¹³ test was used to determine statistical homogeneity of effect size and weighted mean differences. A test result of >0.05 indicates that the observed differences between studies is not greater than what one would expect by chance. Both fixed and random effect models were conducted for this analysis.¹⁶ The Cochrane Collaboration Review Manager (Revman) and SAS Software were used for statistical analysis.

Results

After reviewing the results of all search strategies, twenty studies were identified through at least one strategy, and of these, fourteen were RCTs. Eight out of fourteen identified clinical trials were included in the analysis.^{17-19,20-24} One of the trials included was an abstract.²⁴ Six studies were excluded for the following reasons: absence of a placebo group,²⁵ inadequate reporting of data,²⁶ pulmonary function results being the only outcome,²⁷ IgA and IgE responses being the only outcome,²⁸ inclusion of only adult patients,²⁹ outcome measured was different from those of other studies, and inclusion of patients who were RSV negative.³⁰ The characteristics of the included trials are summarized in Table 1. An overall quality score was assigned to each study by averaging each rater's score. One abstract²⁴ was not assigned a quality score because of incomplete information. The average score ranged from 3 to 5 on Jadad's scale and from 6 to 10 on Chalmer's scale, which was an indication of good quality.

The inter-rater reliability in the two scales was good. The interclass correlation was 0.6 and 0.7 for the first and second method respectively. Mean scores for the two scales correlated well with a Spearman correlation coefficient of 0.8.

All studies included only confirmed cases of RSV. RSV infection was diagnosed with indirect immunofluorescent antibody test on a nasal wash, nasopharyngeal swab or aspirate.

Aerosolized ribavirin was administered to patients in a similar fashion in all studies. Ribavirin at a concentration of 20 mg/mL in normal saline or water aerosolized with a collision generator was administered continuously for 12 to 20 hours a day for at least three days. In all studies of non-ventilated babies, the treatment was given until there was a clinical improvement; the duration ranging from three to six days. In ventilated patients, the treatment was given for five days in one study²³ and for seven days in the other study,²² or until extubation if that occurred first. Two studies used aerosolized normal saline^{18,23} and six studies^{17,19-24} used aerosolized water as placebo.

Three trials in non-ventilated patients¹⁷⁻¹⁹ did not state the method used to ensure blinding of the outcome assessor(s). In one study,²¹ a blinded physician used observations by therapists to assign clinical scores during the period of home therapy for a sub-group treated at home, but this may also have been biased. In studies on ventilated patients,^{22,23} the respiratory therapists cleaned the ventilation circuits before the clinical assessment by a physician.

TABLE 1. Characteristics of the included studies.

Study	Population	Ribavirin / control	Placebo	Outcome measures
Taber 1983	Previously healthy term infants	12/14	Saline	Illness severity score; viral shedding

Hall 1983	Previously healthy infants; pre-term infants	17/16	Water	Illness severity score; improvement in oxygenation; viral shedding
Hall 1985	50% previously healthy; 50% with underlying congenital heart or lung diseases	14/12	Water	Illness severity score
Rodriguez 1987	Previously healthy infants or infants with broncho-pulmonary dysplasia	20/10	Water	Mortality; illness severity score; viral shedding
Groothuis 1990	Infants with underlying congenital heart or lung diseases	20/27	Water	Respiratory deterioration; illness severity score; improvement in oxygen
Edelson 1990	Previously healthy patients and patients with underlying diseases	19/19	Water	Days on oxygen; duration of ventilation
Smith 1991	Ventilated infants 75% previously healthy; 25% with underlying diseases	14/14	Water	Mortality; respiratory deterioration; duration of hospitalization and ventilation; duration of oxygen supplementation; improvement of oxygenation
Meert 1995	Ventilated infants: 22% previously healthy; 65% with underlying diseases	22/19	Saline	Mortality; respiratory deterioration; duration of hospitalization and ventilation; duration of oxygen supplementation; improvement of oxygenation

In all the studies, randomization resulted in groups that were similar in terms of age, race and gender, as well as presence of underlying diseases and disease severity.

All studies on non-ventilated patients evaluated clinical condition using clinical analogue scales. Scales ranged from 0-3,⁴¹ 0-4,^{40,44} and 0-10,^{42,46} with the highest number representing the most severe condition. For each patient, the follow-up assessments and score assignments were made by the same physician. The physician assessed the severity of the illness by making a mark on a continuous ruler between baseline and severe or life-threatening. The positions of the marks on the scale were measured, and the fractional improvement from day to day was calculated. No statement was made as to the clinical relevance of differences in the clinical score. Validity or reproducibility were not described. Improvement in oxygenation was measured using change in blood gas oxygen tension^{17,19} or transcutaneous oxygen saturation. Days of oxygen dependence or days of hospital stay were not used as

outcome measures. Treatment failure, defined as respiratory deterioration, was reported in three studies.²¹⁻²³

Drug toxicity was monitored in all the studies. No hematological or liver function abnormalities were noted.

Results of Meta-Analysis

Mortality

Mortality was described in five studies. Some missing data were obtained directly from the authors. The overall relative risk was 0.6 (95% CI: 0.22, 1.75). This difference did not reach statistical significance with the confidence intervals crossing 1 (see Figure 1), (Cochrane-Mantel-Haenszel test, $P=0.357$). The Breslow-Day test for heterogeneity was not significant ($P=0.689$).

Respiratory Deterioration

Worsening of the respiratory condition on aerosol therapy was reported in three studies. Fifteen patients (out of 116) failed therapy, four received ribavirin and 11 received placebo. The overall relative risk was 0.4 (95% CI: 0.16, 1.13), and with all of the confidence intervals crossing 1 (Figure 2), the data were not heterogeneous ($P=0.62$). Cochrane-Mantel-Haenszel test showed no significant difference between treated and control groups ($P=0.08$).

Duration of Ventilation, Days of Oxygen Dependence and Days of Hospitalization

Two studies of ventilated patients^{22,23} compared length of hospitalization, days of oxygen dependence and duration of ventilation. A third study²⁴ compared days on oxygen supplementation and days on a ventilator. In this study there were five ventilated patients. Two studies^{22,24} showed a significant reduction in length of ventilation while the other²³ did not. Despite one negative trial, a significant reduction in duration of ventilation was observed in the pooled estimate.

The test of heterogeneity was not significant ($P=0.147$). The pooled "effect size" was -0.59 (95% CI: $-1.09, -0.10$), which implied significant reduction in days of ventilation ($P=0.01$).

Using the weighted mean differences method, the ribavirin-treated group had an average of 5.25 days less on mechanical ventilation (95% CI: -2.74 to -7.74) (Figure 3). These results were significant in both fixed and random effects models.

Days of oxygen-dependence were also significantly shorter in the treated group in two of these studies.^{22,24} There was no evidence of heterogeneity ($P=0.32$). Pooled effect size was -0.522 , which was statistically significant ($P=0.005$). The treated group had an average of 3.6 fewer days (95% CI: -5.56 to -1.28) of oxygen-dependence.

Days of hospitalization favored ribavirin with an effect size of -0.22 (95% CI: -0.7 to 0.27) and weighted mean

difference of -2.48 days (95% CI: -7.49 to 2.97), but the difference did not reach statistical significance ($P=0.12$).

Sensitivity Analysis

Excluding the data from an abstract²⁴ decreased the treatment effect. The number of days of ventilation were shorter in the ribavirin group, with an effect size of -0.53 ($-1.03, -0.015$) and a weighted mean difference of -4 days ($-7.12, -0.93$). Days of oxygen dependence were less in the ribavirin group, with an effect size of -0.4 ($-0.9, 0.09$) and a weighted mean difference of -3.78 days ($-7.32, 0.24$) with P -value= 0.054 , which just borders on conventional levels of significance.

Illness Severity Score

Clinical improvement was the main outcome in five studies of non-ventilated babies. All studies consistently showed significant improvement in the clinical score in treated versus placebo groups (Figure 3). The difference in improvement between the ribavirin and placebo group ranged from 11% to 37%. The effect size of individual studies favored treatment and the 95% confidence interval did not include 0. (Inclusion of 0 in the confidence interval indicates lack of statistical significance). Heterogeneity testing (Q-statistic) was not significant ($P=0.10$). The pooled standardized effect size was 1.44 (95% CI: 1.08, 1.79), which was also significant ($P<0.001$).

Improvement in Oxygenation

Four studies^{17,19-21} in non-ventilated patients used improvement in oxygenation as an outcome measure. However, because measures of oxygenation were different, pooling was not possible. Two studies^{20,21} using differences in oxygen saturation on pulse oximetry demonstrated 1.5% to 4% improvement in oxygen saturation in the ribavirin group compared with -2% to 1.3% in placebo. In those studies measuring arterial blood gases, the increment in arterial oxygen tension ranged from 1.4 to 4 mm Hg for placebo compared with an increment ranging from 13 to 21 mm Hg for ribavirin.^{17,19} These studies support findings of a shortened duration of oxygen supplementation in ribavirin recipients.

Discussion

In this meta-analysis, attempts were made to include data from all controlled trials examining ribavirin efficacy. This overview does not justify the use of ribavirin in most children hospitalized with RSV LRI. Ribavirin did not significantly reduce the frequency of death or respiratory deterioration, but trends were that these outcomes were reduced due to ribavirin. However, study numbers may not have provided enough power to detect important differences in these rare events. If trends to reduction in mortality are borne out in further studies, the use of this agent would have greater justification. Another recent

meta-analysis came to a similar conclusion.³¹ However, in that overview, only data on mortality and respiratory deterioration were pooled. Here, we also attempted to combine results of studies examining ribavirin effect on days of ventilation, oxygen days, duration of hospitalization and illness severity score. Ribavirin treatment reduced days of ventilation and oxygen supplementation in ventilated patients. These findings are good incentives to use the agent, however, this benefit was threatened by exclusion of one study published as an abstract. Furthermore, one study²² used aerosolized water as a placebo, which may have produced bronchospasm and worsened the condition in the control group, exaggerating the effectiveness of ribavirin.^{32,33} These concerns render the observed benefit of using ribavirin inconclusive. In addition, high cost of using ribavirin and the difficulty in its



FIGURE 1. Effect on mortality: ribavirin versus control. Between trials test for heterogeneity (B-D chi-square test at 3 degree of freedom) is 1.95, $P=0.689$.

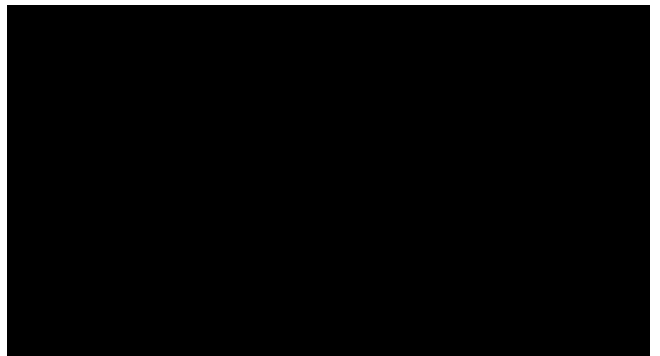


FIGURE 2. Respiratory deterioration: ribavirin versus control. Between trials test for heterogeneity (B-D chi-square test) is 1.95, $P=0.689$.

FIGURE 3. Clinical improvement with ribavirin for the treatment of RSV LRI: effect size and 95% CI, fixed effects model. Between trials test for heterogeneity (Q-statistic) is: 7.95; *P*-value=0.1.

administration remain significant problems.

It is worth noting that conclusions derived from this analysis cannot be generalized to immunocompromised children, since this subgroup of patients were not included in the original studies that were analyzed here.

Although the question of ribavirin efficacy was not answered by this meta-analysis, the results provide the justification for a new RCT, and are important in this regard. The results also provide support to those clinicians who withhold the use of the agent in patients meeting the criteria described by the AAP. This meta-analysis has summarized the evidence on ribavirin efficacy.

The major limitation to this overview is the small number of patients included in the published trials. Furthermore, the primary outcomes of such studies do not have clear clinical implication. Thus, even after combining the results in all published trials, the meta-analysis is hampered by limited power.

Meta-analysis provides important information in deciding whether to embark on a further trial. This analysis found that ribavirin was effective in reducing the number of days of ventilation and days on oxygen in ventilated patients. A precise estimate of this effect will impact on decisions about ribavirin use. The concern about the quality of one of the included trials would support the need for further trials even in ventilated subjects. 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 should be targeted towards high-risk or ventilated patients who stay in hospital longer than previously healthy children.³⁵ Results of the meta-analysis form the most accurate data on which to base sample size calculations.

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