Efficacy of interventions for bronchiolitis in critically ill infants: a systematic review and meta-analysis

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CRD summary
This review assessed treatments for critically ill infants with bronchiolitis. The authors concluded that, currently, no treatment has been shown to be clearly effective, although surfactant appears promising and corticosteroids or ribavarin may be of benefit. There were some limitations to the review but, overall, the authors' cautious conclusions reflect the evidence.

Authors' objectives
To assess the efficacy of medical treatments for critically ill infants with bronchiolitis.

Searching
PubMed was searched from inception to October 2003 for studies reported in any language; the search terms were reported. The reference lists of retrieved reports were checked. The reviewers' personal files and conference proceedings were searched, while experts in the field were contacted for additional studies.

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

Specific interventions included in the review
Studies of any treatment for bronchiolitis were eligible for inclusion. The included studies used surfactant, ribavirin, immune globulin, systemic corticosteroids, vitamin A, interferon, erythropoietin and heliox. The control treatments included air placebo, normal saline or sterile water placebo, albumin placebo and no treatment.

Participants included in the review
Studies of paediatric patients in intensive care units (ICUs) were eligible for inclusion. Most of the included studies were in respiratory syncytial virus (RSV)-positive infants; some studies also included RSV-negative infants.

Outcomes assessed in the review
Studies that assessed mortality, ventilator days, or length of stay in the ICU or hospital were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently conducted the searches.

Assessment of study quality
The studies were assessed for the adequacy of allocation concealment. This was graded as adequate, unclear or inadequate. The review also assessed blinding. Two reviewers independently assessed validity and resolved any disagreements by consensus.

Data extraction
Two reviewers independently extracted the data, with any disagreements resolved by a third reviewer. The authors of studies with missing or unclear information were contacted for further data. Where possible, for each study, the mean ventilator, ICU and hospital days and the number of deaths were extracted for each treatment group.
Methods of synthesis

How were the studies combined?
The studies were grouped by intervention. Pooled weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated: in duration of mechanical ventilation and duration of ICU stay for surfactant versus control, and in duration of mechanical ventilation and length of hospital stay for systemic corticosteroids versus control. A random-effects model was used. Studies using other interventions were combined in a narrative.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic, taking a P-value of less than 0.05 to indicate significant heterogeneity. Potential reasons for significant heterogeneity were discussed.

Results of the review

Sixteen RCTs (n=523) were included.

Thirteen RCTs reported adequate allocation concealment. Twelve RCTs were double-blinded.

Surfactant (3 RCTs, n=79): the studies showed that, compared with the control, surfactant had no significant effect on days of ventilation (WMD -2.58 days, 95% CI: -5.34, 0.18, P=0.07) but significantly decreased ICU days (WMD -3.3 days, 95% CI: -6.38, -0.23, P=0.04). Statistically significant heterogeneity was found for both meta-analyses (P<0.00001). One RCT found decreases in days ventilated and ICU days that were much more than in the other two RCTs.

Systemic corticosteroids: the studies used different doses and durations of treatment. There was no statistically significant difference between systemic corticosteroids and control for days of ventilation (3 RCTs, n=137; WMD 0.62 days, 95% CI: -2.78, 1.53, P=0.57). Similarly, there was no significant difference for duration of hospital stay (2 RCTs, n=96; WMD -2.44 days, 95% CI: -9.30, 4.42, P=0.5). Significant between-study heterogeneity was found in the second analysis.

Ribavirin (one meta-analysis of 3 RCTs, n=104): the meta-analysis found that, compared with the control, ribavirin significantly reduced days of ventilation (WMD 1.2 days, 95% CI: -3.4, -0.2, P=0.03) and non-statistically significantly reduced hospital stay (WMD -1.9 days, 95% CI: -4.6, 0.9, P=0.20). There was no significant difference between treatments in mortality (relative risk 0.36, 95% CI: 0.07, 1.77, P=0.21). No significant heterogeneity was found for any of these meta-analyses.

Immune globulin (3 RCTs, n=35; 33 and 25 ventilated): the studies used different interventions. None of the studies found any statistically significant difference between immune globulin and the control for days ventilated or hospital stay.

Helium (1 RCT, n=13): the RCT provided no data on the effects of heliox on ICU stay.

There was no statistically significant difference in ICU days or ventilator days between control and vitamin A (1 RCT, n=9 in ICU), erythropoietin (1 RCT, n=44) or interferon (1 RCT, n=6 ventilated).

Authors' conclusions
Currently, no treatment has been shown to be clearly effective for critically ill children with bronchiolitis. The use of a surfactant appeared promising and corticosteroids or ribavirin may be of benefit.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. However, the results from three included RCTs were only reported as the results of a published meta-analysis. Several sources were searched, but the searching of only one electronic database might have resulted in the omission of other relevant studies. Including reports in any language minimised the possibility of language bias, while attempts to locate unpublished studies reduced publication bias; the authors stated that there were too few studies to assess publication bias. Two reviewers independently selected studies, assessed validity and extracted the data, thus reducing the potential for bias.
and errors. The validity assessment was inadequate as it was limited to allocation concealment and blinding.

The review included one meta-analysis, the results of which were apparently quoted by the authors without an assessment of the quality of this review. The finding of statistically significant heterogeneity suggests that a meta-analysis was not appropriate for combining studies of surfactants. However, having found heterogeneity, the reviewers did discuss potential reasons for differences among the studies. It was unclear why mortality rates were not mentioned in text relating to surfactant or corticosteroids. Overall, the evidence presented appears to support the authors’ cautious conclusion about treatments for bronchiolitis.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that adequately powered studies are required to identify the best treatments for critically ill children. They suggested that multicentre studies that assess continuous outcomes, such as duration of mechanical ventilation and ICU or hospital length of stay, may provide adequate power to detect clinical benefit. They also stated that there is a need to assess longer term outcomes such as the need for readmission and pulmonary medication.

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