Efficacy of bronchodilator therapy in bronchiolitis: a meta-analysis
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Authors' objectives
To determine if bronchodilators are efficacious in treating bronchiolitis in infants.

Searching
MEDLINE was searched from January 1966 to September 1994, Excerpta Medica from January 1974 to November 1995, and Reference Update on selected dates (November 8, 1993; June 29, 1994; and April 26, 1995), using the search terms (explode)'bronchiolitis' combined with 'albuterol', 'ipratropium', 'adrenergic agents' or 'bronchodilator agents'. Addition material was obtained by examining the authors' files and the bibliographies of all retrieved articles.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials were included.

Specific interventions included in the review
Albuterol; albuterol and ipratropium or bromide; ipratropium; metaproterenol sulfate; epinephrine; racemic epinephrine; fenoterol and ipratropium. The drugs were given either by nebuliser, orally, or subcutaneously.

Participants included in the review
All patients included in the primary analysis were wheezing for the first time. For the secondary analysis patients were included regardless of previous wheezing. All children were under 24 months of age and were both in- and out-patients. In all but two of the studies, children had mild or moderately-severe illness; in the other two studies, although disease status was not stated, it appears that children with severe illness were excluded.

Outcomes assessed in the review
Clinical scores, based on a multi-item scale, oxygen saturation (oximetry), and admission to hospital (admission). Clinical scores were extracted from the studies and reported in two ways: as the proportion of patients with an improved score based on a priori determination of significant clinical improvement; and as the average score or change in score in each treatment group.

How were decisions on the relevance of primary studies made?
The retrieved articles were assessed for relevance by two independent investigators. Only trials where wheezing was reported in the patients for the first time were selected for the primary analysis. For the secondary analysis, patients with previous wheezing, trials using beta-adrenergic agents only, and out-patient trials of patients with first-time wheezing were included.

Assessment of study quality
The quality of each study was evaluated by assessing whether double-blinding and concealment of allocation to treatment groups were adequately reported, based on the criteria of Schulz et al. (see Other Publications of Related Interest). The papers were assessed for validity by two independent investigators.

Data extraction
The data were extracted by two independent investigators.

Methods of synthesis
How were the studies combined?
A fixed-effect model was used in the meta-analysis; this assumes that the true effect is similar in all trials and that variability between trials is due to chance. For average score and oximetry, effect sizes were calculated with 95% confidence intervals (CIs). For average score, an effect size less than 0 (reduced severity) indicates a benefit, while for oximetry, an effect size less than 0 (reduced oxygen saturation) indicates a detrimental effect.

For score q improved and admission, the effect of treatment compared with placebo was determined by the Mantel-Haenszel relative risk (RR) with 95% CIs. An RR less than 1 indicates that the treatment is beneficial.

How were differences between studies investigated?
The small sample size of individual studies makes the detection of heterogeneity difficult in the meta-analysis; for this reason, the authors use a higher than usual P-value of 0.1 or less to indicate significant heterogeneity. A Breslow-Day test of homogeneity was used to determine the level of heterogeneity.

Results of the review
Primary analysis: 8 trials with a total of 485 children.

Secondary analysis: 15 trials with a total of 734 children.

Primary analysis results:
- average score effect size, -0.32 (95% CI: -0.54, -0.11, p<0.01; heterogeneity analysis result, H=0.96);
- score q improved RR, 0.76 (95% CI: 0.60, 0.95, p=0.02; H=0.53);
- hospitalisation RR, 0.85 (95% CI: 0.47, 1.53, p=0.58; H=0.56); and
- oximetry effect size, 0.14 (95% CI: -0.04, 0.33, p=0.13; H<0.01).

Secondary analysis: the results were similar to the primary analysis, but some results were more heterogeneous.

Cost information
The cost of treatment for those children requiring ambulatory care for bronchiolitis in the USA is estimated to be US$50 per child at a coverage rate of 80%. The estimated total annual cost to provide bronchodilator therapy to children with primary respiratory syncytial virus and bronchiolitis would be US$37.5 million.

Authors' conclusions
Bronchodilators produce modest short-term improvement in clinical features of mild or moderately-severe bronchiolitis. The results for oximetry are too varied and invalidate the meta-analysis, thus preventing conclusions from being drawn. The reported data show no benefit to prevent hospitalisation in this population without severe disease.

CRD commentary
A well-reported and thorough review. The authors are to be commended for recognising the inappropriateness of combining heterogeneous studies and exploring the reasons for this heterogeneity.

The sample sizes of the primary studies is small and the outcome measures reported were very different across the trials. The potential publication and related bias may result in an overestimation of the treatment effect.

Implications of the review for practice and research
Further studies are needed to determine if the improvement in clinical score is sufficiently large to routinely initiate bronchodilator therapy. Future studies should: distinguish between patients with first-time wheezing and those with recurrent wheezing; distinguish between severely-ill children; and evaluate the outcome of therapy throughout the
course of illness.

**Bibliographic details**

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**Other publications of related interest**

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