Efficacy of beta2-agonists in bronchiolitis: a reappraisal and meta-analysis
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Authors' objectives
To evaluate the efficacy of beta2-agonists as bronchodilator therapy in bronchiolitis.

Searching
MEDLINE was searched up to January 1995 using 'bronchiolitis' and 'drug therapy' both as MeSH terms and as textwords. Additional studies were identified by review of the references of studies found on MEDLINE. Handsearches of the 1987 to 1994 editions of four major paediatric journals (American Journal of the Diseases of Children, Archives of the Diseases of Children, Journal of Pediatrics and Pediatrics) were conducted and the authors of studies were contacted when additional data was required. To identify unpublished RCTs, the Acute Respiratory Infection Review Group of the Cochrane Collaboration was contacted. The search was not restricted by language.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of inhaled beta2-agonists were included in the review. Studies which used outcomes evaluable only in a pulmonary laboratory were excluded.

Specific interventions included in the review
Bronchodilator therapy for bronchiolitis, specifically inhaled beta2-agonists (fenoterol and albuterol of varying dosages and number of doses). No specific comparator was required in the inclusion criteria. The original intention was also to evaluate oral beta2-agonist therapy, however only two studies were identified. These were subsequently excluded.

Participants included in the review
Children or infants with bronchiolitis who were not receiving concomitant therapy (such as other bronchodilators or corticosteroids) in addition to beta2-agonists. The following criteria for diagnosis of bronchiolitis were used: an acute communicable disease presenting predominantly in infancy that is characterised by wheezing (with or without cough, tachypnea and increased respiratory effort), accompanied by evidence of a viral illness such as coryza and fever.

Outcomes assessed in the review
The in-patient trials used a variety of outcome measures including a clinical scoring system which was not described in detail (1 trial), duration of hospital stay (2 trials), oxygen saturation (2 trials). The out-patient studies evaluated outcomes using four different clinical scoring systems, hospitalisation rate and physiological status (including respiratory rate, oxygen saturation and heart rate). The clinical scoring systems included a 3-point accessory muscle score based on severity of retractions and nasal flaring and a 3-point wheezing score based on the audibility of wheezes and their timing in the respiratory cycle (1 trial), the Respiratory Distress Assessment Instrument (2 trials) and the Severity of Illness Score (2 trials).

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
The validity of the primary studies was assessed using the criteria of Sacks et al. (see Other Publications of Related Interest). Additional aspects of research design considered to be particularly important in the evaluation of therapeutic interventions for bronchiolitis were also considered. These included checking for the presence of problems in selection and specification of patients such as those already taking bronchodilators, explicit criteria for diagnosis of bronchiolitis and documentation of pre-study duration of illness and baseline attributes. Any variation in treatment, such as dose of beta2-agonist, number of doses and type of nebuliser used, and the variability in study outcomes, were also assessed.
The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

**Methods of synthesis**
How were the studies combined?
The studies were split into in-patient and out-patient trials. A meta-analysis was performed for each outcome judged to be similar amongst trials. For dichotomous outcomes, such as the hospital admission rate, the overall event rate difference Mantel-Haenszel estimator and its 95% confidence interval (CI) were calculated using a pooled point estimate. This estimator is similar to other Mantel-Haenszel estimators of effect and is weighted similarly. For continuous variables, such as respiratory rate, the overall weighted mean difference and its 95% CI were calculated.

How were differences between studies investigated?
Statistical heterogeneity in effects amongst trials was determined for the main outcome (respiratory rate), using Cochran's Q. For those outcomes considered too diverse for meta-analysis, differences between the studies were discussed narratively.

**Results of the review**
Twenty RCTs were identified from the MEDLINE search, of which 8 focused on infants with bronchiolitis and used routine clinical rather than pulmonary laboratory outcomes. Three of these were in-patient studies (number of patients not stated) and 5 were out-patient studies (251 patients). No unpublished studies were identified.

The outcomes assessed in the in-patient trials were considered too diverse for a meta-analysis and a narrative review was undertaken. Of the 3 in-patient RCTs of beta2-agonists, of which all 3 were appropriately randomised and 2 were double-blinded, only one concluded that it is an effective therapy for bronchiolitis, in terms of statistically-significant improvements in clinical scores and shorter mean hospital stays. Another study found no such differences and the last found a significant reduction in oxygen saturation. There was significant variation in the patients, treatments and outcomes in these studies. Interventions used in the control groups in these studies were not specified.

The 5 out-patient trials were all appropriately randomised, double-blinded and placebo-controlled. Four different clinical scoring systems were used in the 5 trials; however, no review of the results was undertaken. A meta-analysis of 4 of the out-patient trials found that beta2-agonist therapy had no significant effect on the hospitalisation rate of patients compared to placebo (event rate difference 2.0, 95% CI: -9.3, 13.3). Beta2-agonists were also found to have little or no impact on physiological status (five status; 5 trials combined). The overall mean differences in respiratory rate was -0.5 (95% CI: -1.3, 0.3). There appeared to be significant variation in the results between individual trials. However, there was no evidence of statistical heterogeneity (chi-squared 6, d.f.=4, P<0.5). The results for oxygen saturation and heart rate were statistically significant, but the results were not considered to be clinically significant. The overall mean difference was 1.2 (95% CI: 0.8, 1.6) in oxygen saturation and 1.4 (95% CI: 0.8, 2.0) in heart rate.

**Authors' conclusions**
Conclusive evidence for the efficacy of beta2-agonist therapy for bronchiolitis remains unavailable. In the case of in-patient studies this can be attributed to the lack of well-designed trials. Lack of evidence for out-patient beta2-agonist therapy may be attributable to limitations in the therapeutic regimens and the outcome studied to date. Only very short-term responses to two or three treatments have been studied, whereas the regimens commonly used in practice (initial nebulisation followed by several days of home oral therapy) and more relevant outcomes (rate of return visits or overall rate of hospitalisation for the length of the illness) have never been studied. Conclusive evidence for the efficacy of beta2-agonist therapy for bronchiolitis requires a well-designed, multicentre RCT examining clinically-relevant outcomes and the regimens commonly used by paediatricians.
CRD commentary
This is a relatively well-conducted systematic review, however more detail regarding the methods used and studies included could have been provided. The literature search was specified, extensive handsearching was conducted and unpublished studies were also sought. The inclusion criteria used were explicitly stated. The validity of the studies was assessed using well-established criteria in addition to other criteria considered to be of importance in this area. The narrative review of the in-patient trials was well-conducted and the method of quantitative synthesis for the out-patient trials seems appropriate. On the whole, sufficient study details were provided regarding the selection and specification of patients, and variations in treatment of the interventions groups and outcomes measured were discussed.

The computerised search was limited to MEDLINE only which may have resulted in retrieval bias, and no specified control group appears to have been required in the inclusion criteria. The means of decision-making regarding the relevance and validity of the studies was not provided. Very limited primary data was provided for the in-patient studies: the number of patients in the studies and any interventions used in the control groups were not stated. In addition, no details of the actual results of the trials were provided and only the direction of effects found was discussed. It is unclear why no narrative review of the results of the clinical scoring system in the out-patient trials was provided. Given the limitations of the trials included, and the small number of patients available, the authors' conclusions appear appropriate.

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