Bronchodilators for bronchiolitis (Review)

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TABLE OF CONTENTS

[Intervention Review]

Bronchodilators for bronchiolitis

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ABSTRACT

Background

Bronchiolitis is an acute, viral lower respiratory tract infection affecting infants and often treated with bronchodilators.

Objectives

To assess the effects of bronchodilators on clinical outcomes in infants with acute bronchiolitis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 1) which contains the Acute Respiratory Infections Group's Specialized Register, MEDLINE (1966 to March week 2 2010) and EMBASE (2003 to March 2010).

Selection criteria

Randomized controlled trials (RCTs) comparing bronchodilators (other than epinephrine) with placebo for bronchiolitis.

Data collection and analysis

Two authors assessed trial quality and extracted data. Unpublished data were obtained from trial authors.

Main results

We included 28 trials (1912 infants) with bronchiolitis. In 10 inpatient and 10 outpatient studies, oxygen saturation did not improve with bronchodilators (mean difference (MD) -0.45, 95% confidence interval (CI) -0.96 to 0.05, n = 1182). Outpatient bronchodilator treatment did not reduce the rate of hospitalization (12% in bronchodilator group versus 16% in placebo, odds ratio (OR) 0.78, 95% CI 0.47 to 1.29, n = 650). Inpatient bronchodilator treatment did not reduce the duration of hospitalization (MD 0.06, 95% CI -0.27 to 0.39, n = 349). In seven inpatient and eight outpatient studies, average clinical score decreased slightly with bronchodilators (standardized mean difference (SMD) -0.37, 95% CI -0.62 to -0.13, n = 1006).

Oximetry and clinical score outcomes showed significant heterogeneity. Including only studies at low risk of bias significantly reduced heterogeneity measures for oximetry (I^2 statistic = 17%) and average clinical score (I^2 statistic = 26%), while having little impact on the overall effect size of oximetry (MD -0.38, 95% CI -0.75 to 0.00, P = 0.05) and average clinical score (SMD -0.26, 95% CI -0.44 to -0.08, P = 0.005).

Effect estimates for outpatients were slightly larger than for inpatients for oximetry (outpatients MD -0.57, 95% CI -1.13 to 0.00 versus inpatients MD -0.29, 95% CI -1.10 to 0.51) and average clinical score (outpatients SMD -0.49, 95% CI -0.86 to -0.11 versus inpatients SMD -0.20, 95% CI -0.43 to 0.03). Adverse effects included tachycardia and tremors.

Authors' conclusions

Bronchodilators do not improve oxygen saturation, do not reduce hospital admission after outpatient treatment, do not shorten the duration of hospitalization and do not reduce the time to resolution of illness at home. The small improvements in clinical scores for outpatients must be weighed against the costs and adverse effects of bronchodilators.

PLAIN LANGUAGE SUMMARY

Bronchodilators for bronchiolitis for infants and young children

Bronchiolitis is an acute, highly contagious, viral infection of the lungs that is common in infants. It causes the small airways in the lungs to become inflamed, blocking the free passage of air so that the infant becomes breathless, wheezy and short of oxygen. Bronchodilators are drugs often used as aerosols to widen the air passages by relaxing the bronchial muscle. They are effective in helping infants and adults with asthma. Howver, unlike asthmatics, infants with bronchiolitis are usually wheezing for the first time and wheezing for a different reason, that is to say, because their airways are clogged with debris. Therefore, infants with bronchiolitis may be less likely to respond to bronchodilators.

This review of trials found no effect of bronchodilators on oxygen saturation. Some infants treated as outpatients showed a short-term improvement in respiratory scores, but infants hospitalized for bronchiolitis showed no significant benefit of bronchodilator treatment. This review also found that bronchodilators do not reduce the need for hospitalization, do not shorten the length of stay in hospital or shorten illness duration at home. Side effects of bronchodilators include rapid heart beat and shakiness. Given these side effects and little evidence that they are effective, bronchodilators are not helpful in the management of bronchiolitis.

This review is limited by the small number of studies that use the same outcomes. The small number of infants included in each of these studies limits the ability to show statistically important differences between bronchodilator and placebo treatment. This review is also limited by the use of clinical scores that may vary from one observer to the next. Also older studies included children who had wheezed before and may have asthma.

BACKGROUND

Description of the condition

Bronchiolitis is an acute, highly communicable lower respiratory tract infection characterized by "cough, coryza (runny nose), fever, expiratory wheezing, grunting, tachypnea (fast breathing), retractions and air trapping" (Welliver 1992). It has significant morbidity, accounting for 17% of all infant hospitalizations (nine admissions per 1000 child-years) in New York State (McConnochie 1995). Infants with bronchiolitis are wheezing for the first time, unlike asthmatics in whom bronchospasm causes recurrent wheezing. It should be emphasized that definitions of bronchiolitis vary between countries. Bronchiolitis refers to an illness starting as an upper respiratory infection followed by signs of acute respiratory distress and diffuse bilateral crepitations, in addition to signs of bronchiolar obstruction such as air trapping, wheezing and high-pitched rhonchi (Disney 1960).

Description of the intervention

Bronchodilators have been commonly used in the management of bronchiolitis. A Canadian study (Law 1993) found that 78% of those hospitalized with bronchiolitis received bronchodilators. A survey of pediatric allergists and pulmonologists in the United States (Newcomb 1989) found that 86% recommended a trial of bronchodilators for this condition. Similarly, in a survey of pediatric infectious disease specialists in Europe, the majority used bronchodilators for treatment of bronchiolitis (Kimpen 1997). However, bronchodilator efficacy for this illness is not universally accepted and bronchodilators are seldom used to treat bronchi-

olitis in the United Kingdom (Goodman 1993). Significant practice variation in the treatment of infants admitted for bronchiolitis or respiratory syncytial virus (RSV) pneumonia has been documented in the US (Wilson 2001), Europe (Barben 2003; de Bilderling 2003) and New Zealand (Vogel 2003).

How the intervention might work

Bronchodilators work by reversing bronchoconstriction of the airways due to bronchospasm induced by asthma triggers, viruses, exposure to toxic inhalants, etc. Because infants with bronchiolitis present with wheezing, a hallmark of asthma, bronchodilators have been used to manage wheezing.

Why it is important to do this review

Randomized controlled trials (RCTs) of bronchodilators in bronchiolitis, whether for ambulatory or hospitalized children, have yielded variable results. Three prior meta-analyses (Flores 1997; Hartling 2003; Kellner 1996) and a systematic review (King 2004) have shown that bronchodilators may improve clinical symptom scores but they do not affect disease resolution, need for hospitalization or length of stay.

OBJECTIVES

Because of the widespread use of bronchodilators despite conflicting evidence regarding their efficacy, we undertook a systematic review of all randomized placebo-controlled trials of bronchodilators for bronchiolitis. We review the quality of studies and provide a quantitative summary of the effects of bronchodilators. The question addressed by the meta-analysis was: are bronchodilators better than placebo in the management of bronchiolitis, as measured by improvement in oxygen saturation, clinical scores, admission to hospital, duration of hospitalization, or time to resolution of illness.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized placebo-controlled trials of bronchodilators for bronchiolitis. Methods and results were examined if the title or abstract indicated that patients with bronchiolitis were studied in a prospective randomized clinical trial. Both published and unpublished studies could be included as long as inclusion criteria were fulfilled.

Types of participants

Infants and young children up to 24 months with bronchiolitis. All trials used the term "bronchiolitis" to refer to an acute lower respiratory tract infection with wheezing.

Types of interventions

Bronchodilator therapy, including albuterol, salbutamol, terbutaline, ipratropium bromide and adrenergic agents. Studies of inhaled steroids were not included. Routes of administration were: nebulized, oral and subcutaneous. Although included in the original review, studies of epinephrine in bronchiolitis were excluded from the updates since these studies are included in the Cochrane Review Epinephrine for bronchiolitis (Hartling 2004).

Types of outcome measures

Outcome measures of interest were those that assessed signs or symptoms and were, therefore, considered to have the most clinical relevance: oxygen saturation as measured by pulse oximetry, clinical score, admission to hospital, duration of hospital stay and time to resolution of illness. Studies which assessed pulmonary function alone were excluded from the original review. Although it was decided to include pulmonary function tests as an additional outcome for the 2006 and 2010 updates, only two published trials met the inclusion criteria.

Primary outcomes

The primary outcome is oxygen saturation, as this outcome often drives the clinical decision to hospitalize an infant with bronchiolitis. This outcome is objectively measured using pulse oximetry.

Secondary outcomes

The secondary outcomes are improvement in clinical scores, admission to hospital, duration of hospitalization and time to resolution of illness. These outcomes are more subjective and subject to interrater variability. Pulmonary function tests are also included as these are objective measures of the effect of bronchodilators on airway resistance and compliance.

Search methods for identification of studies

Electronic searches

In 1998, three computerized bibliographic databases were searched for all publications in all languages examining bronchodilator therapy of bronchiolitis: the National Library of Medicine MEDLINE database (1966 to September 1994); the Excerpta Medica database (1974 to November 1994); and Reference Update® (Research Information Systems, Carlsbad, California) (November 8, 1993, June 29, 1994 and April 26, 1995). The MEDLINE search was repeated June 2, 1998. The search terms "explode bronchiolitis" and "albuterol" or "ipratropium" or "adrenergic agents" or "bronchodilator agents" were used. In addition, the bibliographies of all articles selected were searched for relevant studies.

For the 2010 updated review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library* 2010, Issue 1) which contains the Acute Respiratory Infections Group's Specialized Register, MEDLINE (1966 to Week 2, March 2010), EMBASE (1998 to March 2010) and reference lists of articles. In addition, we reviewed the files of one author (AG) and conducted a handsearch of reference lists of new studies. We searched presentations given at the Pediatric Academic Societies meetings in 2009 and 2010 for pending studies and found no clinical trials.

We searched MEDLINE and CENTRAL using the following keywords and MeSH terms. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format (Lefebvre 2009) These search terms were adapted to search EMBASE.com (Appendix 1).

MEDLINE (OVID)

1 exp BRONCHIOLITIS/
2 bronchiolit$
3 or/1-2 (2208)
4 exp Bronchodilator Agents/
5 bronchodilator$
6 exp ALBUTEROL/
7 albuterol
8 salbutamol
9 exp IPRATROPIUM/
10 ipratropium
11 exp Adrenergic Agents/
12 adrenergic agent$
13 or/4-12
14 3 and 13

Searching other resources

We scanned reference lists of identified articles and contacted authors of the identified trials and other experts in the field. There were no language or publication restrictions.

Data collection and analysis

Selection of studies

In the original review, two review authors (AG, AB) independently reviewed the articles. In the 2010 update, two review authors (AG, MB) reviewed the search results and independently reviewed new studies. There was complete agreement between the two review authors regarding the articles selected for inclusion in the review.

Data extraction and management

Both review authors (AG, MB) independently extracted data and achieved consensus on what data to include. Unpublished data were requested from trial authors when necessary.

Assessment of risk of bias in included studies

The quality of each study was evaluated by assessing whether the following five sources of bias were adequately reported: 1) sequence allocation was carried out satisfactorily; 2) allocation to treatment groups was concealed; 3) the trial was double-blinded (Schulz 1995); 4) incomplete data was addressed; and 5) selective reporting was not present. Both review authors of the 2010 update completed this review.

Measures of treatment effect

Oxygen saturation as measured by pulse oximetry, clinical score based on a multi-item clinical scale and admission to hospital were selected to measure the effect of bronchodilators on outpatients. Because a number of inpatient studies were subsequently published, duration of hospitalization was added as an outcome measure. These outcomes were thought to be the most clinically relevant and to have the largest amount of experimental data reported. Because two longer term outpatient studies were published, time to resolution of illness was also added as an outcome measure. Respiratory rate was not selected as an isolated measure because of many uncontrollable factors which influence respiratory rate (Gadomski 1994b -neb).

A number of different scoring systems were used in the included studies (*see* Characteristics of included studies table). A summary of the components of the most widely used clinical scoring systems can be found in Hartling 2003. Thirteen of 28 included studies utilized the partially validated clinical scoring system, that is to say, the Respiratory Distress Assessment Instrument (RDAI) or the Respiratory Assessment Change Score (RACS). Clinical scores were reported in two ways. In several trials, the results were reported as the proportion of infants and children with an improved score based on an a priori determination of significant clinical improvement (improvement in clinical score, a dichotomous variable). Analysis 1.2 defines events as the proportion of participants

who did not meet pre-determined criteria for clinical score improvement. In seven inpatient and eight outpatient trials, the results were reported as the average score or change in score in each treatment group (average clinical score, a continuous variable).

Time to resolution of illness (ROI), measured from the period of study enrolment to the time the infant returned to baseline health status, is scored by the primary caretaker at home. ROI comprises parental assessment of degree of improvement of respiratory symptoms scored on a 4-point ordinal scale (worse = 1, same = 2, improved = 3, symptoms resolved = 4) (Cruz 1995).

Duration of hospitalization was measured by length of stay, derived from the time of admission and discharge, as opposed to specific measures of improvement. The exception to this is Dobson 1998, which defined duration as time to reach predetermined discharge criteria.

The original review excluded trials that used pulmonary function tests (PFT) as the sole outcome as this was considered insufficient for assessment of benefit. During updates of this review, inclusion of PFT data was included because PFT data are objective, while recognizing that changes in PFT measures may achieve statistical significance but have little clinical significance. In this update, we found one additional PFT study (Levin 2008), bringing the total number of PFT studies to nine. However, seven of these studies did not fulfil inclusion criteria and only two studies (Levin 2008; Totapally 2002) could be included. However, due to different PFT measures used, the outcomes of these studies could not be combined. Therefore, PFT data are not included as outcome measures.

Unit of analysis issues

For the three continuous variables (oxygen saturation, average clinical score and duration of hospitalization), the effect of treatment compared with placebo was determined by the unbiased estimate of effect size (ES), with its 95% confidence intervals (CI) (Bracken 1989). The average clinical scores were converted to the standardized mean difference (SMD) because a variety of clinical scoring systems with different ranges were utilized by the included studies. In all scoring systems, higher scores indicate greater severity of illness.

For average clinical score, an ES of less than zero (that is to say, reduction of severity scores) indicates a benefit, and an ES of more than zero (that is to say, increased severity scores) indicates that treatment is detrimental. Similarly, for oximetry an ES of less than zero (that is to say, lower mean oxygen saturation with placebo) indicates a beneficial effect of treatment and an ES of more than zero (that is to say, higher mean oxygen saturation with placebo) indicates a detrimental effect.

For the two dichotomous variables (improvement in clinical score and hospital admission), the effect of treatment compared with placebo was determined using the odds ratio (OR). An overall OR of less than one indicates that treatment is beneficial, while an OR of more than one indicates that treatment is detrimental. For improvement in clinical score, an OR of less than one indicates that the odds of not improving were lower in the treatment group compared with the placebo group. For hospital admission, an OR of less than one indicates that the odds of being hospitalized were lower in the treatment group than the placebo group.

Results for oxygen saturation and average score (continuous) were stratified according to whether the study was conducted in an inpatient or outpatient setting. The rationale for this was that inpatients are more severely ill and, therefore, have a different response profile compared to outpatients. Also the time of outcome assessment varied according to whether the study was an inpatient or outpatient study. Inpatients were usually assessed within 24 hours of admission whereas outpatients were more consistently assessed 30 minutes to six hours after treatment was initiated. In this update, oral bronchodilator given at home (ascertained during a 14 day period following study enrolment) was added to Analysis 1.4 “Hospital admission after treatment”. In addition, time to resolution of illness was added as Analysis 1.6, but includes only two studies.

Some trials had more than one bronchodilator treatment arm, either varying the mode of delivery (nebulized, oral or metered dose inhaler (MDI)) or comparing different bronchodilators (for example, salbutamol and ipratropium). In the figures depicting these analyses, the descriptive labels for these trials are annotated to indicate the arm of the trial used in the comparison. For example ’Gadomski 1994a -neb’ and ’Gadomski 1994a -oral’ are the nebulized and oral treatment arms from the same study (Gadomski 1994a -neb). In a trial that had only one placebo arm but two active treatment groups (Karadag 2005 - IPR), placebo numbers were divided between comparisons to avoid double-counting of placebo participants.

Dealing with missing data

Given the nature of the clinical trials included in this review (short-term outpatient or longer term inpatient studies), the reported participant drop out rates were low (see Incomplete outcome data). We contacted the trial authors of two studies for missing statistics, such as standard deviations.

Assessment of heterogeneity

Statistical heterogeneity was assessed visually and with I^2 statistic and the Chi^2 test. For meta-analyses including a small number of studies, the I^2 statistic was used.

Assessment of reporting biases

In 2006, an unpublished study (Karadag 2005 - IPR) was included because it was an RCT of salbutamol, ipratropium and saline that included first-time wheezing infants admitted to hospital. This study was later published (Karadag 2008). A second unpublished inpatient study was an RCT comparing salbutamol, placebo and

epinephrine (Gurkan 2004). We obtained data for these studies from the trialists. There was only one placebo-controlled study excluded because it was only available in abstract form (Ferrer 1990). Pending clinical trials were sought in the Pediatric Academic Societies abstracts for 2009 and 2010 (none were found). Therefore, the likelihood of publication bias is low.

Data synthesis

A fixed-effect model was chosen initially for the meta-analysis (Thompson 1991). This model assumes that the true effect of treatment is similar in all trials and that any differences in treatment effect between trials are due to chance. It was expected that there would be some heterogeneity in the data due to the different treatment settings and measurement protocols (Thompson 1994). Where there was evidence of significant heterogeneity (I^2 statistic greater than 30%), we analyzed the results using both fixed-effect and random-effects models. If there was a difference in the results, we used the more conservative random-effects model.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses include analysis by outpatient or inpatient setting as the severity of illness differs between these two groups. We also analyzed nebulized versus oral bronchodilator studies separately, as well as outpatient versus home settings for oral bronchodilators. Methods for investigating heterogeneity of effects include comparison of the I^2 statistic and the Chi^2 test.

Sensitivity analysis

Sensitivity analysis included comparison of the estimates of the effect of bronchodilators in studies with a low risk of bias, studies that specifically included only first time wheezers and studies that only included infants less than or equal to 12 months of age. Studies with a low risk of bias were defined as having a "Yes" for all five items in the risk of bias table (see Included studies).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Of the 19 studies identified in the search for this update, five met criteria for inclusion. Most of the excluded studies were excluded because they did not include a placebo group.

Included studies

From a total of 28 trials included in the updated review, 17 trials were in infants wheezing for the first time (Can 1998; Chevallier 1995; Chowdhury 1995; Dobson 1998; Gadomski 1994a -neb; Gadomski 1994b -neb; Goh 1997; Gurkan 2004; Ho 1991; Karadag 2008; Klassen 1991; Lines 1990; Lines 1992; Patel 2002; Schuh 1990; Totapally 2002; Wang 1992). Five additional trials, in which results from participants with first-time wheezing could not be separated from those with recurrent wheezing were also included (Alario 1992; Henry 1983; Mallol 1987; Schweich 1992; Tal 1983). For the 2010 update, five new trials were included and all of these included first-time wheezing infants (Anil 2010 SAL 0.9%; Anil 2010 SAL 3%; Gupta 2008; Levin 2008; Ralston 2005; Tinsa 2009).

During the 2010 update, the study by Gupta 2008 was found to have the same methodology as Patel 2003; i.e., 14-day outpatient home study of oral albuterol versus placebo. This enabled Patel 2003, that was originally excluded, to be included in the 2010 update. Therefore, both of these studies were included in the 2010 update as they employed the same study methodology and outcome measure.

For the original review, seven trial authors provided upon request additional data not stated in their publications (Alario 1992; Gadomski 1994b -neb; Ho 1991; Klassen 1991; Lines 1992; Schuh 1990; Schweich 1992). In the 2006 update, additional data were requested and received for inclusion from three authors for: duration of hospitalization (Karadag 2005 - IPR), clinical score and oximetry outcomes at 24 hours (Patel 2002) and clinical score and oximetry (Gurkan 2004). In the 2010 update, additional unpublished data were requested and received from trial authors of two new studies (Ralston 2005; Tinsa 2009).

Laboratory methods to identify RSV included direct immunofluorescence microscopy, enzyme immunoassay and serum RSV titers. The range of participants who were RSV-positive was 3% to 100%, with more than 40% RSV-positive in 10 trials.

Excluded studies

Articles were excluded from the original review for the following reasons: 66 were not clinical trials; three RCTs did not have a placebo group (albuterol was compared with: racemic epinephrine (Sanchez 1993), ipratropium bromide (Schuh 1992) and corticosteroids (Springer 1990)); one was a cohort study of theophylline (Brooks 1981); one study was published as an abstract only (Ferrer 1990); one Russian study had an inadequate description of patients and methods (Tatochenko 1988); and two studies used evaluations of pulmonary function studies as the only outcome (Sly 1991; Stokes 1983). A log of rejected articles is available from the review authors upon request.

The original review included two studies of epinephrine compared to placebo (Kristjánsson 1993; Lowell 1987). As studies of epinephrine and bronchiolitis are considered separately in the

Cochrane Review Epinephrine for bronchiolitis (Hartling 2004), the 2006 update did not include any epinephrine trials. As part of the 2006 update, three trials were excluded that were included in the original review. Two trials were excluded as they were comparisons of epinephrine and placebo only (Kristjánsson 1993; Lowell 1987); a third study was excluded as it was not clearly placebo-controlled (Cengizlier 1997). Two placebo-controlled trials of nebulized epinephrine and bronchiolitis (Hariprakash 2003; Wainwright 2003) were excluded from the 2006 update.

During the 2006 update of this review, an additional nine RCTs were excluded because they did not include a placebo group: epinephrine compared to albuterol (Mull 2004); nebulized terbutaline with normal saline compared to terbutaline with hypertonic saline (Sarrell 2002); nebulized epinephrine with normal saline compared to epinephrine with hypertonic saline (Mandelberg 2003); nebulized salbutamol compared to nebulized ipratropium bromide (Ozyurek 2002); epinephrine versus albuterol (Bentur 2003); albuterol plus prednisone compared to albuterol (Goebel 2000); and three trials of epinephrine compared to salbutamol (Abu-Shukair 2001; Bertrand 2001; Ray 2002). A placebo-controlled trial of the extended use of oral albuterol (Patel 2003) included the following outcomes: time to resolution of illness, time to normal feeding, sleeping, quiet breathing, resolved cough and coryza assessed by daily telephone interview for 14 days. This study was originally excluded from the meta-analysis, but the addition of Gupta 2008 made it possible to include the study in this update.

Two trials were excluded from the original review (Sly 1991; Stokes 1983) which assessed pulmonary function tests (PFTs) as the sole outcome and another study of pulmonary function was excluded because it was not randomized (Sanchez 1993). The search carried out for the 2006 update found five more studies reporting pulmonary function as an outcome measure. As described below (Effects of interventions), it was decided to include such studies in the update provided they fulfilled all other inclusion criteria. However, when examined, seven of the eight studies assessing PFTs were excluded (Modl 2005; Numa 2001; Sanchez 1993; Sly 1991; Stokes 1983; Torres 1997; Wankum 2000) because they were not RCTs. Because Totapally 2002 reported other outcomes in addition to PFTs, it was included in the 2006 update. In the 2010 update, Levin 2008 studied PFT as an outcome and met inclusion criteria. However, because Totapally 2002 and Levin 2008 used different PFT techniques and measures that produced outcomes that could not be combined, PFT could not be included in an outcome in the 2010 update.

In the 2010 update, 12 trials were excluded. Of the 12 exclusions, nine trials were excluded as they were not placebo controlled (Beck 2007; Fernandez 2009; Gomez-y-Lopez 2007; John 2010; Kadir 2009; Langley 2005; Luo 2010; Simsek 2005; Walsh 2008), two trials were excluded as they were not randomized controlled trials (Hammer 1995; Soto 1985), and one trial was excluded because participants were given phenylephrine nasally (Ralston 2008).

Risk of bias in included studies

The design and methodological quality features of each study are shown in the Characteristics of included studies table. Generally the studies were of small size. The main problem with several included studies was an inability to identify participants who were first time wheezers versus recurrent wheezers. Other limitations to study quality included lack of standardized methods for outcome evaluation (timing of assessments, clinical scoring systems used) and lack of standardized intervention (various bronchodilators, drug dosages, routes of administration and nebulization delivery systems) used across the studies. A graphical representation of risk of bias among included studies is shown in Figure 1. A summary of methodological quality among included studies is given in Figure 2

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

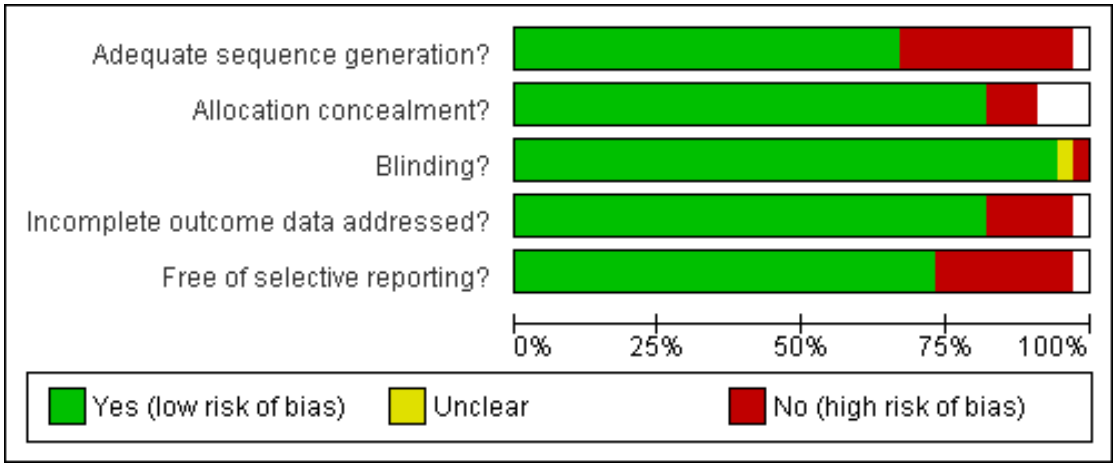
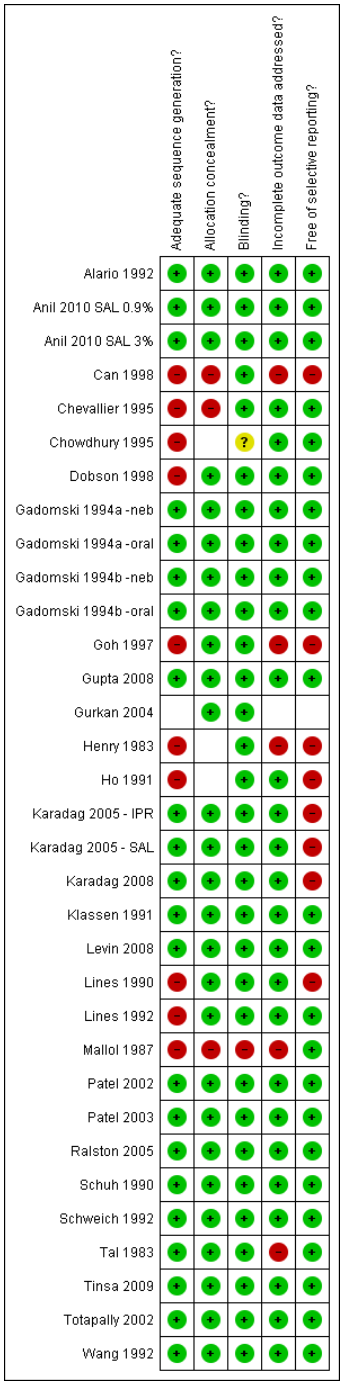


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Methods for sequence generation and allocation concealment were not described in older studies (Can 1998; Chevallier 1995; Chowdhury 1995; Henry 1983; Ho 1991; Lines 1990; Lines 1992; Mallol 1987) and abstract only studies (Gurkan 2004). More recent studies described methods for sequence generation, allocation concealment and use of placebo agents that were indistinguishable from bronchodilator agents.

Blinding

Most medical and research staff administering treatment and/or assessing subjects during the trial are described as being either blinded or masked during the conduct of the studies included in this review, thus reducing the potential for performance, detection or attrition bias. Only one study was described as single-blind (Mallol 1987). Another study was described in the abstract as being double-blind, but not detailed in the methods (Can 1998).

Incomplete outcome data

In the outpatient studies, there tended to be more missing data for follow-up measurements beyond 60 minutes because many patients were discharged from these settings before 90 or 120 minute assessments could be done. Because bronchodilators have short-term effects, some outpatient trialists did not include measurement of outcomes longer than 60 minutes post-treatment. Therefore, the outpatient results are biased towards those data measured at a shorter interval from treatment administration, so longer-term outcomes may have been missed.

Details regarding study attrition were often not well described in the included studies. Drop out rates range from 0 to 11% (Gupta 2008; Patel 2003). Few studies included study flow diagrams that could be used to assess differential drop out from the study groups (Anil 2010 SAL 0.9%; Gupta 2008; Patel 2003; Ralston 2005). Few studies employed intention-to-treat (ITT) analysis (Patel 2002; Patel 2003) when study participant attrition occurred.

Possible attrition bias might be a factor in three studies that excluded participants from analysis because they were 'therapeutic failures' (Tal 1983) or that withdrew participants for other reasons (Dobson 1998; Goh 1997).

Selective reporting

Evidence of selective reporting of outcomes was rare as most studies presented the outcome results that were described in the methods, with one exception, that is, that few studies provided data on heart rate following treatment. Because bronchodilators can increase heart rate, it is an important outcome to include, although for most studies, this information is included in the description of adverse effects and is not systemically addressed in all studies.

Other potential sources of bias

Adverse effects following treatment were often not systematically addressed in the study design and are not completely described in most studies included in this review.

Effects of interventions

Twenty-eight clinical trials studying 1912 infants with bronchiolitis were included in these analyses.

Oxygen saturation

In a random-effects analysis, bronchodilator recipients did not show a significant improvement in oxygen saturation as measured by pulse oximetry compared to placebo, as reflected by the mean difference (MD) -0.45, 95% CI -0.96 to 0.05 (Analysis 1.1).

Clinical score improvement

In seven trials (five inpatient and two outpatient), the clinical score of 64% of those infants treated with bronchodilators improved compared to 27% with placebo (OR for no improvement = 0.18, 95% CI 0.06 to 0.50, n = 365), using a random-effects model (Analysis 1.2). Inversely, there was a statistically significant difference in the proportion of bronchodilator-treated infants (36%) not demonstrating improvement in their clinical score compared with control infants (73%, OR 0.18, CI 0.06 to 0.50, n = 365). Included in this analysis are three studies that showed a great benefit (Alario 1992; Lines 1990; Mallol 1987) but were methodologically weaker than other studies and they included older participants who were recurrent wheezers.

The improvement in overall average clinical score was statistically significant (standardized mean difference (SMD) -0.37, 95% CI -0.62 to -0.13) (Analysis 1.3), but the small magnitude of this change limits its clinical significance. Inpatients demonstrated less overall improvement than outpatients, underscoring the short-term effect of bronchodilator treatment as most of the outpatient assessments occurred usually within one hour after treatment compared with longer time points in inpatients (see Subgroup analysis and investigation of heterogeneity). The small magnitude of difference in mean clinical score between bronchodilator and placebo groups is of questionable clinical importance, especially given the differences in scoring systems that were used.

Time to resolution of illness (ROI)

There is no difference between bronchodilator and placebo groups with respect to time to resolution of illness as measured by ROI in the two longer-term home based studies by Patel 2003 and Gupta 2008 (MD 0.29, 95% CI -0.43 to 1.00, n = 269). (Analysis 1.6). Thus, oral bronchodilators do not shorten the time to resolution of illness among infants treated at home; however only two studies examined this outcome.

Pulmonary function tests (PFT)

Two placebo-controlled studies utilizing PFT as an outcome (Levin 2008; Totapally 2002) met the inclusion criteria. However, these two studies utilized different PFT techniques that produced outcomes that cannot be combined. Totapally 2002 used tidal breathing flow-volume loops measured through close-fitting face masks to compare changes pre- and post-albuterol or saline inhalation for 20 infants with mild RSV-positive bronchiolitis. No significant differences in exhaled tidal volume were measured between albuterol treatments compared to saline. However, tidal expiratory flows near the end of inhalation (TEF10) decreased with albuterol. Levin 2008 measured peak inspiratory pressure and inspiratory system resistance pre- and post-bronchodilator or saline nebulization in 22 infants intubated and ventilated in an ICU setting for severe RSV-positive bronchiolitis. Small, but statistically significant, decreases in peak inspiratory pressure as well as significant increases in heart rate were observed after bronchodilator administration compared to no changes after saline. Interestingly, inspiratory resistance fell after all treatments, including saline. The differences in severity of illness, PFT methodology and outcomes (volume versus pressure) preclude merging the results of these two PFT studies.

Subgroup analyses

Although there was no overall difference in oximetry scores, the subgroup analysis was marginally statistically significant for outpatients (MD -0.57, 95% CI -1.13 to 0.00) but not for inpatients (WMD -0.29, 95% CI -1.10 to 0.51). Even so, the difference between placebo and treatment groups was less than one point (Analysis 1.1).

Subgroup analyses showed a slightly greater effect size with bronchodilators in outpatient studies, where there were shorter follow-up durations than for inpatient studies. This was shown in the analysis of average clinical score where there was a modest effect for outpatient studies (SMD -0.49, 95% CI -0.86 to -0.11) but a smaller effect in inpatient studies (SMD -0.20, 95% CI -0.43 to 0.03) (Analysis 1.3).

However, the magnitude of these differences between inpatient and outpatient studies is of questionable clinical importance and the results of these subgroup analyses should be interpreted with caution. These differences may be due to shorter follow-up time, inclusion of participants with recurrent wheezing and lesser severity of illness among outpatients.

Hospital admission after treatment

The rate of hospitalization was not significantly reduced in bronchodilator recipients compared with placebo recipients (12% versus 16%; OR 0.78, 95% CI 0.47 to 1.29) (Analysis 1.4). Rate of hospitalization was not significantly different between oral bronchodilator or placebo groups followed in longer term studies (4.5% versus 5.2%; OR 0.86, 95% CI 0.28 to 2.64).

Duration of hospitalization

The addition of one study (Tinsa 2009) in the 2010 update did not change the results for the duration of hospitalization outcome. There was no difference between bronchodilator and placebo groups in the length of stay (MD 0.06 days, 95% CI -0.27 to 0.39) (Analysis 1.5).

Heterogeneity

There was evidence of considerable heterogeneity for clinical score measures (dichotomized and average score) and oximetry, but not for hospital admission or duration of hospitalization. Where there was a difference between the effect estimate produced by the random- and fixed-effect models, we chose the more conservative random-effects model. Therefore, we used a random-effects model for oximetry and clinical score, and a fixed-effect model for hospital admission, duration of hospitalization and time to resolution of illness outcomes.

For oximetry, use of the fixed-effect model would have resulted in a slightly larger effect estimate that was statistically significant (-0.67, 95% CI -0.83 to -0.50) than the result found with the random-effects model -0.45 (95% CI -0.96 to 0.05). There was evidence of considerable heterogeneity with this outcome (P value less than 0.00001, I^2 = 82%) that may be attributed to measurement differences (Analysis 1.1). The studies measured pulse oximetry at multiple time points. The points selected for pooling were based on times that were most frequently used and were either short-term, at 60 minutes in outpatient studies, or longer term, at one or three days in inpatient studies. These variable time points for assessment reflect the nature of the studies, in that shorter times were used in outpatient studies while longer times were feasible for inpatients. Because of these factors, the random-effects model was considered more appropriate.

Sensitivity analysis

Fifteen studies were assessed as being at low risk of bias (Alario 1992; Anil 2010 SAL 0.9%; Anil 2010 SAL 3%; Gadomski 1994a -neb; Gadomski 1994a -oral; Gadomski 1994b -neb; Gadomski 1994b -oral; Gupta 2008; Klassen 1991; Levin 2008; Patel 2002;

Patel 2003; Ralston 2008; Schuh 1990; Schweich 1992; Tinsa 2009; Totapally 2002; Wang 1992). Including only low risk of bias studies in the analysis significantly reduced the heterogeneity measures for oximetry (I^2 statistic = 17%; Analysis 1.7) and average clinical score (I^2 statistic = 26%; Analysis 1.8), while having little impact on the overall effect size of oximetry (MD -0.38, 95% CI -0.75 to 0.00, P = 0.05; Analysis 1.7) and average clinical score (SMD -0.26, 95% CI -0.44 to -0.08, P = 0.005; Analysis 1.8). In other words, reducing the heterogeneity by removing studies with higher risk of bias did not uncover a treatment effect or change the magnitude of the effect size.

Low risk of bias sensitivity analysis did not significantly change the heterogeneity or effect estimates for hospital admission, duration of hospitalization, or time to resolution of illness.

Thirteen studies included infants of age less than or equal to 12 months (Chevallier 1995; Chowdhury 1995; Gupta 2008; Henry 1983; Ho 1991; Karadag 2008; Levin 2008; Mallol 1987; Patel 2002; Patel 2003; Tal 1983; Tinsa 2009; Totapally 2002). In this sensitivity analysis, the exclusion of several studies did not improve measures of heterogeneity, but led to unstable effect size estimates.

Seventeen studies explicitly described inclusion of first time wheezing infants (Anil 2010 SAL 0.9%; Chevallier 1995; Chowdhury 1995; Dobson 1998; Gadomski 1994a -neb; Gadomski 1994a -oral; Gadomski 1994b -neb; Gadomski 1994b -oral; Goh 1997; Gupta 2008; Ho 1991; Karadag 2008; Levin 2008; Patel 2002; Patel 2003; Ralston 2005; Schuh 1990; Tinsa 2009; Totapally 2002). This analysis led to reduced heterogeneity measures, reduced mean differences, and borderline significance for overall average clinical score (I^2 statistic = 12%, SMD -0.17, 95% CI -0.34 to -0.00, P = 0.05). However, no impact was observed for the other outcomes.

Adverse effects

Where adverse effects were reported, these were noted to be significantly or exclusively found in the study groups receiving bronchodilators and included: tachycardia (P value less than 0.05) (Klassen 1991; Lines 1990), decreased oxygen saturation (P value less than 0.05) (Ho 1991; Schweich 1992), flushing (one and four participants, respectively) (Alario 1992; Gadomski 1994b -neb), hyperactivity (three participants) (Gadomski 1994b -neb), tachycardia and prolonged cough (two participants) (Henry 1983) and tremor (one participant each) (Tal 1983; Wang 1992).

Amongst studies added in the 2006 update, tachycardia, mild hypertension and slight tremor were reported by Patel (Patel 2002). One infant receiving albuterol was transferred to the intensive care unit for 48 hours but did not require mechanical ventilation. No side effects were noted by Karadag (Karadag 2005 - IPR) except that one patient in the ipratropium group was subsequently excluded because of deteriorating clinical status. No adverse effects were described by Can 1998 or Totapally 2002.

In the 2010 update, no adverse effects were reported in three studies (Anil 2010 SAL 0.9%; Anil 2010 SAL 3%; Tinsa 2009). Adverse effects including trembling, vomiting and irritability were systematically addressed in the two home studies of oral bronchodilators (Gupta 2008; Patel 2003). While no difference was found in these symptoms between placebo and bronchodilator groups in one study (Patel 2003), more infants in the salbutamol group (six) were reported to have tremors versus the placebo group (none) in the other home study (Gupta 2008). Sigificant tachycardia (sustained heart rate over 200 beats per minute for more than 30 minutes) was reported in two infants receiving albuterol nebulization (Ralston 2005). Significant increases in heart rate were observed for all nebulized bronchodilators administered to intubated and ventilated infants compared to infants who received normal saline (Levin 2008).

DISCUSSION

Summary of main results

This 2010 update of the meta-analysis of trials of bronchodilators to treat infants with bronchiolitis shows no effect on oxygen saturation for outpatients or inpatients. Bronchodilators do not reduce the rate of hospital admission after outpatient treatment, do not shorten the duration of hospitalization, or shorten time to resolution of illness in home studies. They do produce small short-term improvements in clinical scores for infants treated as outpatients. However, this short-term benefit must be weighed against the costs and adverse effects of these agents. Newer studies add to the growing evidence that bronchodilators cause tachycardia and tremors. These factors tip the risk benefit balance toward greater risk than benefit of using bronchodilators for bronchiolitis.

There was significant heterogeneity in the analysis of trials that included oximetry and clinical score outcomes. Including only studies at low risk of bias in the meta-analysis significantly reduced the heterogeneity measures for average clinical score and oximetry, while having little impact on the overall effect size of oximetry and average clinical score outcomes.

Subgroup analyses showed a slightly greater effect size in outpatient studies, where there were shorter follow-up times, and more recurrent wheezers and less severely ill infants included, than in inpatient studies for both oximetry and average clinical score. But again, the effect sizes are small for both settings and are of minimal clinical significance (for oximetry: outpatients MD -0.57 versus inpatients -0.29 and for average clinical score: outpatients SMD -0.49 versus inpatients -0.20). Because few new studies were added, the 2010 update continues to show that bronchodilators produce a short-term statistically significant, but small improvement in average clinical score among outpatients that may not be clinically important. This finding, limited to outpatients and to clinical scores as an outcome, may be biased for showing a difference favoring

treatment because older studies included in this analysis included older participants with recurrent wheezing and/or asthma. The inclusion of asthmatic children, who are known to respond to bronchodilators, will falsely increase the apparent level of efficacy in patients with bronchiolitis.

Overall completeness and applicability of evidence

Increased detection of hypoxia by using pulse oximetry has been cited as one of the reasons that, in the US, hospitalization rates for bronchiolitis nearly doubled from 1988 to 1996, with no significant change in mortality during that time period (Shay 2001). Despite other reasons for increased hospitalization rates that include increased daycare attendance at younger ages and increased survival of premature infants (Shay 1999), variable pulse oximetry cut-off points for hypoxia necessitating oxygen administration probably contribute to increasing hospitalization rates as well as considerable practice variation. Clinically meaningful standardization of pulse oximetry end-points for hospitalization and definition of what the minimal clinically important difference is for this outcome needs to be defined.

The lack of benefit from bronchodilators in preventing hospitalization may be difficult to interpret. In several outpatient studies, the decision to admit was made after the study was completed. This decision was made by non-study physicians and further treatment may have been given, regardless of the intervention received during the study. Thus, this outcome may reflect other treatments as well as the initial intervention provided in the study.

Similarly, the duration of hospitalization was not altered by receipt of bronchodilators. However, hospital stay is affected by multiple factors other than the clinical status of the patient. Although randomization should balance these factors, length of hospital stay may be an insensitive measure. Among Canadian hospitals, duration of hospitalization did not vary significantly despite significant variation in the types of medications used to treat infants with bronchiolitis (Wang 1996).

The statistically significant but clinically small improvement in clinical score and the lack of improvement in oximetry with bronchodilators challenge the utility of these agents. The validity of the clinical score as an indicator of pulmonary status or relevant clinical change has not been proven (Hall 2007). Gadomski and coworkers have suggested that improvement in clinical scores may be due to changes in physiological state (for example, change from asleep to awake) rather than improved respiratory function with bronchodilator therapy (Gadomski 1994a -neb). Another issue is that the clinical scoring systems used in the studies included in this review varied considerably. Few have been tested for reliability or compared to a physiologic standard.

The cost of bronchodilator therapy for bronchiolitis is significant. In the USA, a conservative estimate of the total cost to provide bronchodilator therapy to children with primary RSV-positive bronchiolitis was USD 37,500,000 (Law 1993; McConnochie 1995; Newcomb 1989). More recent data suggest that the total cost of hospitalization in the USA has increased by 24% from USD 1.2 billion in 2000 to USD 1.5 billion in 2006 while the length of stay decreased slightly from 2.4 to 2.3 days (Wilson 2010).

The widespread use of bronchodilators in bronchiolitis is likely to be due to the similarity of symptoms and signs of bronchiolitis and asthma. Bronchodilators are effective in the treatment of asthma in older children and adults, where airway obstruction is caused by inflammation, bronchospasm and bronchial hyperreactivity (Levison 1991). However, a Cochrane Review of short acting beta-2 agonists for recurrent wheezing in children under two years of age showed no clear benefit of using bronchodilators in this age group (Chavasse 2002). Because the pathophysiology of bronchiolitis consists of terminal bronchiolar and alveolar inflammation with airway swelling and luminal debris, the primary mechanism underlying wheezing is airway obstruction and plugging rather than bronchospasm (La Via 1992). These reasons may explain why bronchodilators are not effective for infants with bronchiolitis.

Quality of the evidence

During the 2010 update, we found few new randomized placebo-controlled clinical trials. The number of studies using similar outcome measures remains small, which limits the reliability of the effect-size estimation. Most of the outcome effect estimates are small or show no difference from placebo. The estimates are imprecise as reflected by wide confidence intervals. Therefore, this meta-analysis continues to be limited by the small sample sizes, lack of standardized study design and outcome assessment across the studies. Thus, RCTs with large sample size, standardized methodology across clinical sites and consistent assessment methods are needed to completely answer the question of efficacy.

Interrater variability of current scoring methods can be high. Recent studies have shown that the RDAI has low intraclass correlation, poor construct and discriminative validity (Destino 2010; Walsh 2008). A more objective alternative to these outcomes is pulmonary function testing as performed by Levin 2008, although limited to infants with severe disease. Although the number of bronchiolitis studies utilizing PFTs has increased to nine, the methods and outcomes for measuring PFTs vary, thereby precluding comparability. In addition, only two studies employed a placebo-controlled RCT design. Future PFT studies should employ a placebo-controlled RCT design as well as standardized methods so that outcome data can be merged.

Another potentially objective measure is the use of computerized lung sounds analysis as demonstrated by Beck 2007. This study, that was excluded due to lack of a placebo group, used comparison of computerized quantification of wheezing and crackles to assess the effect of a single dose of nebulized epinephrine compared to albuterol. No difference was found between the two treatment

groups, but the study establishes the feasibility of this approach, which may be less subjective than clinical scoring.

Potential biases in the review process

One of the authors is a trialist.

Agreements and disagreements with other studies or reviews

The results of this meta-analysis support the American Academy of Pediatrics clinical practice guidelines for the management of bronchiolitis issued in 2006 (AAP 2006) because the effect estimates for clinical scoring have not changed. The AAP recommendations include a carefully monitored trial of an inhaled bronchodilator and continuation of the bronchodilator only if there is a documented positive clinical response using objective criteria to evaluate the response. However, this 2010 update provides increasing evidence of adverse effects, particularly tachycardia, that may outweigh the benefit of the small, transient improvement in clinical score among infants treated as outpatients for bronchiolitis. Therefore, if bronchodilators are trialed in this way, then careful monitoring for side effects is also needed.

The results of this meta-analysis also concur with recent reviews of the diagnosis and management of bronchiolitis (Wainwright 2010; Zorc 2010), that underscore the limited effectiveness of bronchodilators (as well as corticosteroids) in the outpatient management of bronchiolitis.

A meta-analysis conducted by Flores 1997 on the efficacy of beta-2 agonists included a subgroup of the studies presented in this systematic review. This review concluded that evidence for efficacy was inadequate given the short-term nature of outcomes (emergency department studies) and the inability to compare outcomes in studies of hospitalized patients (Flores 1997). A meta-analysis conducted by Hartling 2003 on the efficacy of epinephrine, an alpha and beta adrenergic bronchodilator, concluded that epinephrine may have short-term benefits for outpatients but that there is no evidence to support its use among inpatients. In addition, epinephrine did not reduce hospitalization rates. This review is consistent with these prior reviews, which describe a transient benefit of bronchodilator treatment, but no other significant treatment effect.

AUTHORS' CONCLUSIONS

Implications for practice

Bronchodilators produce small short-term improvements in clinical scores among infants with bronchiolitis treated as outpatients. However, given their high cost, adverse effects and lack of effect on oxygen saturation and other outcomes included in this meta-analysis, bronchodilators cannot be recommended for routine management of first-time wheezers who present with the clinical findings of bronchiolitis, in either inpatient or outpatient settings.

Implications for research

Prior to conducting further treatment trials, an objective outcome measure that correlates with pulmonary function tests and is independent of the level of alertness of the infant needs to be developed and validated. Measures such as need for hospital admission and duration of hospital stay, while important from a health service utilization perspective, may not be adequately sensitive to measure the improvement that may occur from treatment (Hall 2004; Hall 2007). Pulmonary function testing outcomes should be standardized so that outcome data can be merged across studies. Interrater variability as well as validity studies of the current scoring methods are needed to choose the most reliable and valid scoring system, if clinical scoring is used.

Treatment trials need to be conducted using placebo controls. RCTs with large sample size and standardized methodology across clinical sites are needed to completely answer the question of efficacy. Exclusion criteria must be consistently applied to exclude infants with recurrent wheezing, asthma or other pulmonary disease.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alario 1992

Methods	Randomized, double-blind, placebo-controlled crossover study
Participants	Outpatients less than 36 months old with acute wheezing and or respiratory distress less than 48 hours. N = 73. Mean age 16.1 months, 68% male, no underlying cardiac or lung disease. Country: USA
Interventions	Group 1: metaproterenol sulfate 10 mg (0.2 ml of a 5% solution). Group 2: 0.2 ml normal saline. Both diluted in 2 ml normal saline administered by nebulizer without oxygen via face mask. 20 to 25 minutes after initial treatment, participants crossed over
Outcomes	Respiratory rate, RDI score (color, wheezing, accessory muscle use, flaring, grunting, distress), oxygen saturation, side effects (tremors, vomiting, extreme irritability)
Notes	Included asthmatic participants or recurrent wheezers

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Anil 2010 SAL 0.9%

Methods	Randomized, double blind, placebo-controlled trial
Participants	Enrolled 186 children ages 1.5 to 24 months, treated as outpatients in a pediatric ED. Mean age 9.5 months, 65.1% male. Inclusion criterion was mild bronchiolitis (clinical score between 1 and 9). Exlusions were prior history of wheezing, previous treatment with bronchodilators and/or steroids, and lung or cardiac disease. Country: Turkey

Anil 2010 SAL 0.9% (*Continued*)

Interventions	All groups were pre-treated with 8 ml of nebulized normal saline. Treatment was 2.5 mg of salbutamol in 4 ml of 0.9% saline at 0 and 30 minutes. The placebo group received a 4 ml 0.9% saline solution nebulization. Two other study groups received epinephrine
Outcomes	Clinical score (RDAI), pulse oximetry, and heart rate at 0, 30, 60, and 120 minutes and hospital admission
Notes	All participants were reassessed for recurrent wheezing attacks in the following 6 months (by phone)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Anil 2010 SAL 3%

Methods	Randomized, double blind, placebo-controlled trial
Participants	Enrolled 186 children ages 1.5 to 24 months, treated as outpatients in a pediatric ED. Mean age 9.5 months, 65.1% male. Inclusion criterion was mild bronchiolitis (clinical score between 1 and 9). Exlusions were prior history of wheezing, previous treatment with bronchodilators and/or steroids, and lung or cardiac disease. Country: Turkey
Interventions	All groups were pre-treated with 8 ml of normal saline. Treatment was 2.5 mg of salbutamol in 4 ml of 3% saline at 0 and 30 minutes. The placebo group received a 4 ml 0.9% saline solution nebulization. Two other study groups received epinephrine
Outcomes	Clinical score (RDAI), pulse oximetry and heart rate at 0, 30, 60, and 120 minutes and hospital admission
Notes	All participants were reassessed for recurrent wheezing attacks in the following six months (by phone)

Risk of bias

Anil 2010 SAL 3% (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Can 1998

Methods	Double-blind randomized placebo-controlled trial
Participants	Outpatient (emergency department) study of 156 infants with acute bronchiolitis. Mean age 7.1 months. Excluded infants who were pre-term, had chronic disease, prior bronchodilator treatment, history of previous attack, symptoms for more than 1 week, HR more than 200 beats per minute, lethargy or RDS score more than 5 Country: Turkey
Interventions	Group 1: salbutamol nebulized 0.15 mg/kg in 2 ml saline Group 2: saline nebulized Group 3: mist tent Intervention was repeated at 30 minutes if RDS score more than 5
Outcomes	Outcomes: heart rate, oximetry, RDS score at 0, 30 and 60 minutes and percentage of participants with RDS score more than 5 at 30 and 60 minutes. Chest X-ray and laboratory studies (hemoglobin, hematocrit, leucocyte, neutrophils, eosinophils and IgE) were also compared
Notes	Subgroup analysis of infants less than 6 months versus those more than 6 months showed similar changes in RDS at 30 and 60 minutes. No differences in laboratory values noted among the three study groups. Chest X-ray findings consistent with bronchiolitis higher in Group 1 (88%) compared with 69% in Group 2 and 73% in Group 3

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	
Allocation concealment?	No	

Can 1998 (*Continued*)

Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	No	

Chevallier 1995

Methods	Double-blind, randomized controlled trial
Participants	Inpatients aged 1 to 6 months hospitalized with first episode of bronchiolitis. N = 104. Mean age 3.1 months, 67% male, no underlying lung/cardiac disease, preceding bronchodilator/steroids in the past 48 hours also excluded. 78% RSV positive Country: France
Interventions	Nebulized salbutamol (0.15 mg/kg/dose) or saline placebo administered using oxygen propellant 3 times at intervals of 1 hour
Outcomes	Respiratory rate, clinical scoring system (4 point score for each of retractions and wheezing), oximetry (used value taken at 30 minutes)
Notes	All participants less than 12 months of age

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	
Allocation concealment?	No	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Chowdhury 1995

Methods	Randomized controlled trial
Participants	Inpatients aged 23 days to 11 months, admitted with moderate bronchiolitis. Mean age 3.85 months, 73% male. No previous history of wheeze or bronchodilator use, no underlying lung/cardiac disease. 58% RSV positive Country: Saudi Arabia
Interventions	Group 1: salbutamol respiratory solution (ventolin 5 mg/ml) 0.15 mg/kg; Group 2: ipratropium bromide (0.025% solution) 12.5 micrograms/kg; Group 3: combination of above two at doses stated; Group 4: normal saline 0.3 ml/kg. All mixed with 2 ml normal saline and delivered with 100% oxygen at 6 to 7 L/min using nebulizer. 6 hourly for 36 hours
Outcomes	Modified RDAI Clinical Score (5 point score for each of wheezing: expiratory, inspiratory, location; retraction: supraclavicular, intercostal, subcostal; respiratory rate)
Notes	All participants less than 12 months of age

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	
Blinding? All outcomes	Unclear	Investigators blinded up to 36 hours, single blind
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Dobson 1998

Methods	Double-blind, randomized placebo-controlled trial
Participants	Inpatients aged less than 24 months admitted to inpatient unit with first episode of wheezing with moderately severe bronchiolitis defined as pulse oximetry < 94% and clinical score > 1. Mean age 5.6 months, 48% male, no underlying lung/cardiac disease. 81% RSV positive Country: USA
Interventions	Albuterol: 1.25 mg for patients less than 10 kg and 2.5 mg for patients more than 10 kg in normal saline for total volume of 3 ml or normal saline: 3 ml. Both administered with nebulized aerosol every 2 hours for first 24 hours, then every 4 hours for next 48 hours

Dobson 1998 (*Continued*)

Outcomes	Oygen saturation, clinical score (5 point score for general appearance, 4 point score for each of accessory muscle use and wheezing), duration of hospitalization (defined as time to each predetermined discharge criteria)
Notes	86% of the study population is less than 12 months of age. Adverse effects were compared between study groups. 3 participants were withdrawn from the albuterol group due to worsening hypoxaemia. Subgroup analysis of results for infants less than 12 months was done but results not published

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Gadomski 1994a -neb

Methods	Randomized, double-blind, placebo-controlled trial
Participants	Outpatients and emergency department subjects less than 18 months old with first-time wheezing. Mean age 5.9 months. No underlying lung/cardiac disease Country: Egypt
Interventions	Group 1: nebulized salbutamol (0.15 mg/kg/dose), Group 2: nebulized saline solution, Group 3: orally administered salbutamol (0.15 mg/kg/dose), Group 4: orally administered placebo. Nebulized groups received 2 treatments 30 minutes apart and oral-treated groups received one treatment. Nebulization performed within 10 to 12 minutes with flow rate 4 to 6 L/min using a foot-pump nebulizer, with room air, up-mist nebulizer and pediatric face mask
Outcomes	Respiratory rate, oxygen saturation, change in state of infant, study-specific clinical score (34 point scale for each of degree of grunting, nasal flaring, supraclavicular retractions, intercostal retraction, chest indrawing, air entry, air hunger, wheezing, general appearance)
Notes	Nebulized treatment group: in order to represent the results from the two bronchodilator treatment arms (nebulized and oral), this study is listed twice. Each treatment group had its own placebo group

Gadomski 1994a -neb (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Gadomski 1994a -oral

Methods	See Gadomski 1994a - neb
Participants	
Interventions	
Outcomes	
Notes	Oral treatment group: in order to represent the results from the two bronchodilator treatment arms (nebulized and oral), this study is listed twice. Each treatment group had its own placebo group

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Gadomski 1994b -neb

Methods	Randomized, double-blind, placebo-controlled clinical trial
Participants	Outpatients less than 15 months old, with first episode of wheezing. Median age 5.5 months, 56% male, no underlying lung/cardiac disease. 48% RSV positive Country: USA
Interventions	Group 1: nebulized salbutamol in 3 ml saline, Group 2: nebulized saline placebo in 3 ml saline, Group 3: oral salbutamol, Group 4: oral saline placebo. Dose of salbutamol 0.15 mg/kg/dose. Nebulized group received 2 nebulizations 30 minutes apart and oral groups received one dose. Nebulization with compressed air at 6 L/min via Up-mist nebulizer with pediatric face mask. Infants 7 kg or less received one unit dose of 1 mg salbutamol solution for inhalation (5 mg/ml) or one oral dose of 2.5 ml
Outcomes	Respiratory rate, heart rate, clinical score (4 point score for each of grunting, nasal flaring, supraclavicular and intercostal retractions, air entry, air hunger, duration of wheeze in respiratory cycle, location of wheeze, general appearance), oxygen saturation, infant's state. Side effects: flushing of face, hyperactivity, increased coughing, tremors
Notes	Nebulized treatment group: in order to represent the results from the two bronchodilator treatment arms (nebulized and oral), this study is listed twice. Each treatment group had its own placebo group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Gadomski 1994b -oral

Methods	Oral arm - see Gadomski 1994b - neb
Participants	
Interventions	
Outcomes	

Gadomski 1994b -oral (*Continued*)

Notes	Oral treatment group: in order to represent the results from the two bronchodilator treatment arms (nebulized and oral), this study is listed twice. Each treatment group had its own placebo group

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Goh 1997

Methods	Randomized, blinded trial
Participants	Inpatients less than 24 months old admitted for signs and symptoms consistent with clinical diagnosis of bronchiolitis. Mean age 5.2 to 7.4 months, 72% male. No history of previous wheezing, no underlying lung/cardiac disease. 42% RSV positive Country: Singapore
Interventions	Group 1: salbutamol 2.5 mg/ml; Group 2: ipratropium bromide 250 micrograms/ml; Group 3: normal saline; Group 4: humidified oxygen without nebulization. Administered over 10 to 15 minutes by face masks driven by oxygen flow rate of 6 to 8 L/min. Nebulized at 4 to 6 hourly intervals. Less than 6 months: 0.3 ml solution, more than 6 months: 0. 6 ml solution in 2 ml saline for nebulizations
Outcomes	Duration of hospitalizations, clinical score (5 point score for each of respiratory rate, subcostal retractions, presence of wheeze and 2 point score for each of presence of crepitations, oxygen requirement, nebulization, intravenous infusion). Used day 3 clinical scores
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	

Goh 1997 (*Continued*)

Allocation concealment?	Yes	Fourth study group receiving humidified oxygen was studied 1 year later without blinding or allocation concealment
Blinding? All outcomes	Yes	For three treatment groups (salbutamol, ipatropium and normal saline)
Incomplete outcome data addressed? All outcomes	No	10 participants excluded without information about which group they were assigned to
Free of selective reporting?	No	Length of hospitalization not provided for the randomized groups, oximetry data not provided

Gupta 2008

Methods	Randomized double blind placebo-controlled trial
Participants	Outpatients less than one year of age, with clinical diagnosis of acute bronchiolitis defined as first episode of wheezing with evidence of an acute viral respiratory tract infection. Included only if mild disease (RR <= 70 breaths/min, SpO_2 >= 95% in room air, no or mild accessory muscle use, and RDAI score <= 10). Exclusions: dehydration, lethargy, chronic cardiopulmonary disease, or prior bronchodilator use. Country: (North) India
Interventions	Group 1: oral salbutamol (0.1 mg/kg/dose) three times daily for a maximum of 7 days or until symptoms resolved. Group 2: oral placebo given 3 times daily for a maximum of 7 days or until symptoms resolved
Outcomes	Time to resolution of illness (ROI), defined as time from study enrolment to the time the infant returned to baseline health status, as determined by the principal caregiver on a 4-point scale. Time to resolution of individual symptoms that comprised the ROI also included. Outcomes were determined at 3, 7, and 14 days. Hospitalization was also reported
Notes	RDAI was used only at baseline. A total of 10 subjects were lost to follow-up, 7 (10%) in the salbutamol group and three (4.3%) in the placebo group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	

Gupta 2008 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Gurkan 2004

Methods	Randomized, placebo-controlled study
Participants	Inpatients aged between 2 and 24 months, with moderate acute viral bronchiolitis. Mean age 7.2 months, 68% male. 1. Diagnostic criteria were: an acute infection of the lower respiratory tract preceded by or accompanied by fever and/or rhinitis, and characterized by tachypnea, expiratory wheezing, and increased respiratory effort, as per Dobson 1998. Exclusions: infants with history of more than one hospitalization from wheezing; history of personal or familial atopy or presence of atopic dermatitis; chronic cardiac or pulmonary diseases; diagnosed immune deficiency disorder; recent use of corticosteroid or bronchodilator agent; concomitant severe diseases (pneumonia, meningitis, sepsis, etc) Country: Turkey
Interventions	Group 1: salbutamol 0.15 mg/kg dose. Group 2: adrenaline 0.5 mg (1 ml). Group 3: nebulized saline placebo - 4 ml. All groups received routine supportive management
Outcomes	Clinical score (adapted from Schuh 1990), heart rate, respiratory rate and oxygen saturation, temperature. (Clinical score included 4 point scale for each of general appearance, accessory muscle use, wheezing). Evaluations were conducted at admission, and 30 minutes, 1, 3, 12, 24 and 48 hours. 24 hour data were used to be as consistent as possible with other data
Notes	Unpublished data and study details provided by e-mail from author

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	

Henry 1983

Methods	Randomized, double-blind trial
Participants	Inpatients less than 1 year old with acute bronchiolitis. Mean age 4.3 months, 61% male, 68% RSV positive Country: UK
Interventions	6 hourly nebulized solutions of 250 micrograms of ipratropium bromide in 2 ml saline (n = 34) or normal saline alone (n = 32)

Henry 1983 (*Continued*)

Outcomes	Day to improvement in study specific clinical score. 4-point score for each of heart rate, respiratory rate, cough, rhinitis, nasal flaring, cyanosis, hyperinflation, tracheal tug, intercostal recession, subcostal recession, respiratory distress, crepitations, and rhonchi. Side effects: increased heart rate, persistent coughing
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	No	

Ho 1991

Methods	Randomized, double-blind, crossover trial
Participants	Setting: inpatients Hospitalized participants less than 6 months old with first episode of cough and wheeze due to acute bronchiolitis. Mean age 3 months, 52% male, no underlying heart/lung disease. All RSV positive Country: Australia
Interventions	Nebulized salbutamol (2 to 5 mg/2ml) or normal saline placebo (2 ml). Administered with nebulizer run from compressed gas supply with flow of 6 L/min. 30 to 40 minutes after initial treatment, participants crossed over
Outcomes	Oxygen saturation up to 30 minutes after each treatment
Notes	Short follow-up after intervention

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	
Blinding? All outcomes	Yes	

Ho 1991 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	No	

Karadag 2005 - IPR

Methods	Randomized, double-blind placebo-controlled trial
Participants	Setting: inpatients Infants less than one year of age, hospitalized for moderate to severe bronchiolitis, first episode of wheezing. Chest X-ray compatible with bronchiolitis. Mean age 5.1 ± 2.7 months. No prematurity; chronic neurological or cardiopulmonary disease, including asthma; proven or suspected acute bacterial infection; previous treatment with bronchodilators or corticosteroids; infants younger than 4 weeks old and who needed ventilation at neonatal period; symptoms present for more than 7 days; fever higher than 38. 5 C; or infants with mild bronchiolitis. Country: Turkey
Interventions	Group 1: nebulized salbutamol solution (ventolin, Glaxo) plus saline solution (0.9%) 2.5 ml every 6 hours. Group 2: ipratropium bromide (atrovent, Boehringer Ingelheim) 250 micrograms/2 ml plus 3 ml saline solution every 6 hours Group 3: normal saline received 5 ml every 6 hours
Outcomes	Changes in the oxygen saturation rates, clinical scores and duration of hospital stay. Adverse effects were recorded i.e. tachycardia and tremor after nebulization of each medication. The clinical score system was based on respiratory rate, degree of wheezing, degree of accessory muscle use, and general condition, described by Wang et al 1992. Improvement was defined as a decrease by two points in the total clinical score
Notes	Ipratropium (IPR) treatment group: in order to represent the results from the 2 bronchodilator treatment arms (ipratropium and salbutamol), this study is listed twice. The placebo group was divided between comparisons to avoid double-counting of placebo participants

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	

Karadag 2005 - IPR (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	No	

Karadag 2005 - SAL

Methods	See Karadag 2005 - IPR
Participants	
Interventions	
Outcomes	
Notes	Salbutamol (SAL) treatment group: in order to represent the results from the 2 bronchodilator treatment arms (ipratropium and salbutamol), this study is listed twice. The placebo group was divided between comparisons to avoid double-counting of placebo participants

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	No	

Karadag 2008

Methods	Same as Karadag 2005
Participants	
Interventions	
Outcomes	

Karadag 2008 (*Continued*)

Notes	This published manuscript describes the same study as Karadag 2005 that was published as an abstract

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	No	

Klassen 1991

Methods	Randomized, double-blind, placebo-controlled clinical trial
Participants	Outpatients treated in emergency department, aged less than 24 months old, with first episode of wheezing. Mean age 7.2 months, 57% male, no underlying lung/cardiac disease or previous bronchodilator use Country: Canada
Interventions	Two treatments at 30-minute intervals of either nebulized salbutamol (0.10 mg/kg in 2 ml normal saline) or similar volume (0.02 ml/kg) normal saline placebo. Administered for 5 to 8 minutes through updraft nebulizer with continuous flow of oxygen for 5 to 6 L/min
Outcomes	Respiratory rate, heart rate, oxygen saturation, RDAI score (5-point score for each of wheezing: expiration, inspiration, location; retractions: supraclavicular, intercostal, subcostal)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	

Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Levin 2008

Methods	Randomized, placebo-controlled, blinded prospective study
Participants	22 infants with respiratory syncytial virus bronchiolitis who were in respiratory failure and intubated and ventilated in a pediatric ICU. Only first time wheezers were included. Mean age 8.1 weeks, 64% male, with no underlying lung or cardiac disease. Country: United States
Interventions	Randomized to 4 groups: albuterol (3 ml of 0.083%, 2.5 mg/3ml), levalbuterol (3 ml of 1.25 mg/3ml), norepinephrine (0.5 ml of 2.25% solution) and normal saline. Nebulized every 6 hours by the endotracheal tube. Each participants acted as their own control
Outcomes	Peak inspiratory pressure, inspiratory respiratory system resistance, and heart rate measured before and 20 minutes after treatment
Notes	Participants recruited from December 2001 to March 2007. Study documented a significant increase in heart rate for all 3 bronchodilator treatment groups but not for the placebo group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Lines 1990

Methods	Double-blind, controlled study
Participants	Inpatients less than 18 months old admitted to hospital with bronchiolitis. Mean age 6. 2 months, 73% male, no underlying lung/cardiac disease Country: Australia
Interventions	2 doses given at 2 hour intervals. Either 0.2 ml salbutamol (5 mg/ml) or 0.2 ml saline in 4 ml of physiological saline given over 10 minutes with oxygen at 8 L/min through a Hudson mask
Outcomes	RDAI, oximetry, RACS (wheezing, retraction, respiratory rate), pulse rate
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	No	

Lines 1992

Methods	Randomized, double-blind, controlled, prospective clinical study
Participants	Inpatients less than 18 months old admitted with acute bronchiolitis. No underlying lung/cardiac disease Country: Australia
Interventions	Two doses (in 2 hour interval) of nebulized ipratropium bromide 1 ml (250 micrograms) in 4 ml saline or 5 ml saline placebo
Outcomes	Oxygen saturation, RACS, respiratory rate, heart rate
Notes	

Risk of bias

Item	Authors' judgement	Description

Lines 1992 (*Continued*)

Adequate sequence generation?	No	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Mallol 1987

Methods	Randomized trial
Participants	Inpatients less than 1 year old admitted with acute wheezing. Mean age 5.9 months, 67% male, no underlying lung/cardiac disease Country: Chile
Interventions	Group 1: nebulized fenoterol plus ipratropium bromide. Group 2: fenoterol. Group 3: fenoterol plus steroids. Group 4: aminophylline, IV, plus steroids and oral fenoterol (FNT). Group 5: nebulized normal saline (control). Pediatric nebulizers used with the bronchodilator and saline amounting to 4 ml. A flow of 6 L/min of compressed air, or occasionally, oxygen was used. Warm saline used. Dosage of drugs: nebulized FNT - 0. 04 ml/kg/dose every 6 hr (0.5% solution), nebulized IB - 250 micrograms/dose every 6 hr (0.025% solution), oral or IV aminophylline - less than 6 months (age in weeks *0. 3 + 8 = mg/kg/day, 4 equal doses every 6hr) or more than 6 months (15 mg/kg/day, 4 equal doses every 6 hr), steroids: dexamethasone (IV or IM, 0.3 mg/kg/dose initially, 0. 3 mg/kg/day, 3 equal doses every 8hr) or prednisone (oral 2 mg/kg/day, 3 equal doses every 8 hr)
Outcomes	Clinical score same as with Tal 1983. No adverse side effects
Notes	No distinction made between asthma and bronchiolitis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	
Allocation concealment?	No	
Blinding? All outcomes	No	Single blinding only

Mallol 1987 (*Continued*)

Incomplete outcome data addressed? All outcomes	No	Participants whose scores did not decrease at 24 hours were excluded from the study as "failures"
Free of selective reporting?	Yes	

Patel 2002

Methods	Randomized, double-blind, parallel group controlled trial
Participants	Inpatients less than 12 months old with clinical diagnosis of bronchiolitis. Mean age 4 months. No previous wheeze or bronchodilator use, prematurity, underlying chronic disease, immunocompromise, RSV immunoprophylaxis, or parents not fluent in English or French Country: Canada
Interventions	Group 1: epinephrine (0.03 ml/kg/dose of a 2.25% solution) Group 2: nebulized albuterol (0.03 ml/kg of a 5 mg/ml solution) Group 3: saline (0.03 ml/kg/dose of 0.9% solution of 0.9% sodium chloride)
Outcomes	Duration of hospitalization (LOS) was defined as time between study entry and time that infant left the inpatient ward, time from admission to normal hydration, oxygenation and minimal respiratory distress RDAI (Lowell 17 point categorical score)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Patel 2003

Methods	Randomized double blind placebo-controlled trial
Participants	129 infants, mean age 5.3 months, 60% male, seen in an emergency department setting for mild to moderate bronchiolitis, defined as first episode of wheezing in an infant with evidence of URI. Upon discharge, randomized to receive either oral albuterol or placebo. Exclusions were age older than 12 months, prior wheezing, prior bronchodilator use, underlying lung or cardiac disease, or admission to hospital. Country: Canada
Interventions	First dosage of medication was given in the ED before discharge. Oral albuterol was dosed at 0.1mg/kg per dose given three times per day for seven days. Placebo was also given 3 times per day for 7 days
Outcomes	Time to resolution of illness (ROI), measured on a daily basis by telephone interview until the score of 4 was documented. Secondary outcomes included time to normal feeding, normal sleeping, quiet breathing, resolved cough and resolved coryza. Hospitalization was also recorded
Notes	RDAI was used only at baseline. More infants in the albuterol group who did not complete 7 days of therapy as compared to placebo (8 in albuterol and 2 in placebo). There were two withdrawals from each study group. Total drop out for this study was 10.8%

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Ralston 2005

Methods	Randomized, double blind placebo-controlled trial
Participants	65 participants ages 6 weeks to 24 months, outpatients with acute bronchiolitis seen in an Urgent Care setting. Mean age 7.6 months, 55% male. Country: United States, high altitude (5000 feet). Inclusion criteria were RDAI score between 4 and 14. Exclusion criteria were prior wheezing or asthma, lung or cardiac disease, systemic steroid use, or physiologic instability at presentation

Ralston 2005 (*Continued*)

Interventions	Treatment was 5 mg of racemic albuterol in 3 ml of normal saline administered at 0 and 30 minutes, compared to 3 ml placebo nebulization of 0.9% saline. (A third group received 5 mg racemic epinephrine)	
Outcomes	Need for hospitalization or home oxygen. RDAI and oxygen saturation at 60 minutes were included as unpublished data	
Notes	Participants recruited from January 2000 to March 2004	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analysis was used
Free of selective reporting?	Yes	Clinical scores and oximetry data that were not published were obtained from the author for the 2010 update

Schuh 1990

Methods	Double-blind, placebo-controlled trial
Participants	Outpatients in emergency department, 6 weeks to 24 months old. Mean age 5.7 months. No prior history of wheeze or bronchodilators, no underlying lung/cardiac disease Country: Canada
Interventions	Group 1: 3 doses of 0.5% nebulized salbutamol, 0.15 mg/kg/dose at 1 hour intervals, Group 2: 2 doses of nebulized saline solution, followed by one dose of 0.5% nebulized salbutamol, 0.15 mg/kg/dose, 1 hour apart. All doses suspended in 3 ml normal saline solution, and delivered for 15 minutes by face mask and nebulizer, driven by oxygen at flow rate of 6 to 7 L/min
Outcomes	Respiratory rate, heart rate, accessory muscle score, wheezing score, transcutaneous oxygen saturation
Notes	
Risk of bias	

Schuh 1990 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Schweich 1992

Methods	Double-blind, placebo-controlled trial
Participants	Outpatients admitted to emergency department, aged less than 24 months old with wheezing. Mean age 7.35 months old, 48% male, no underlying cardiac/lung disease. Three infants in each study group had prior wheezing Country: USA
Interventions	2 doses of nebulized salbutamol (0.15 mg/kg in 3 ml normal saline) or placebo (0.03 ml/kg normal saline in 3 ml normal saline). Both administered with continuous-flow oxygen at 6 litres/min at interval of about 30 minutes
Outcomes	Respiratory rate, heart rate, wheeze score (5-point score for each of expiration, inspiration, location), retraction score (5 point score for each of supraclavicular, intercostal, subcostal) , oxygen saturation)
Notes	Included recurrent wheezers

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	

Schweich 1992 (*Continued*)

Free of selective reporting?	Yes	

Tal 1983

Methods	Randomized, double-blind trial	
Participants	Inpatients aged 1 to 12 months, hospitalized with bronchiolitis, asthma or WARI. Mean age 5.4 months, 62.5% male Country: USA	
Interventions	Intramuscular dexamethasone or placebo (double-blind) and salbutamol (oral and inhaled) or none (open) in all 4 possible combinations. Dexamethasone (4 mg/ml) or placebo (normal saline) administered intramuscularly, 0.075 ml/kg on admission and 0.025 ml/kg every 8 hours for next 3 days. Also, half of these patients were given salbutamol (via 2 routes simultaneously) or no additional treatment. Salbutamol: inhalation (0.5 ml salbutamol respiratory solution with 2 ml water) given on admission and subsequently every 6 hours, oral (salbutamol syrup, 0.15 mg/kg) every 8 hours	
Outcomes	Study specific clinical scoring system (4 point scale for each of respiratory rate, wheezing, cyanosis, use of accessory muscles). Measurements of arterial blood gases, blood pressure. Side effects: tremors	
Notes	Included asthmatic patients and recurrent wheezers	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	No	10 relative therapeutic failures and 2 complete therapeutic failures were excluded from analysis
Free of selective reporting?	Yes	

Tinsa 2009

Methods	Prospective, randomized, placebo-controlled double blind clinical trial
Participants	36 first-time wheezing infants ages 3 to 12 months admitted to hospital for moderate severity bronchiolitis. Inclusion criterion was RDAI score between 4 and 15. Excluded were children with underlying lung or cardiac disease, concurrent bronchodilator or corticosteroid treatment, and recurrent wheezing. Country: Tunisia
Interventions	Treatment was nebulized terbutaline at 0.15 mg/kg in 4 ml of normal saline every 4 hours. Placebo group received 4 ml of normal saline nebulized
Outcomes	RDAI score, respiratory rate, pulse oximetry and heart rate at 0, 30, 60, and 120 minutes after the first treatment and duration of hospitalization
Notes	1 participant withdrawn from placebo group due to worsening clinical status, necessitating transfer to the ICU

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Totapally 2002

Methods	Randomized, double-blind, placebo-controlled crossover study
Participants	Inpatients less than 12 months old with a first episode of wheezing due to RSV bronchiolitis. Mean age 5.8 months. Excluded preterm infants, underlying chronic disease or infants with grunting. Country: USA
Interventions	Group 1: albuterol nebulized (0.15 mg/kg in 3 ml saline). Group 2: saline (3 ml). All infants treated first with chloral hydrate. Participants crossed over at 6-hour intervals in random order
Outcomes	Tidal breathing flow loops, wheeze score, heart rate, respiratory rate, and pulse oximetry

Totapally 2002 (*Continued*)

Notes	Wheeze score was 0 for none, 1 for end exp 2 for audible with stethoscope 3 for audible without stethoscope

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Wang 1992

Methods	Randomized, double-blind factorial trial
Participants	Setting: inpatients Infants 2 to 24 months of age hospitalized for this first time with mild bronchiolitis. 55% male, no underlying cardiac/lung disease Country: Canada
Interventions	Group 1: salbutamol at 0.15 mg/kg/dose in 2 ml saline followed one hour later by 0.5 ml or 1 ml saline placebo. Group 2: 0.03 ml/kg saline in 2 ml saline followed by either 125 micrograms ipratropium bromide if less than 6 months old or 250 micrograms ipratropium bromide if older than 6 months. Group 3: both salbutamol and ipratropium bromide in doses indicated. Group 4: saline placebos in same volumes indicated
Outcomes	Oxygen saturation, study-specific clinical assessment (4-point score for each of respiratory rate, wheezing, retractions, general condition)
Notes	Infants with prior use of bronchodilators were included (1 in salbutamol, 2 in ipatropium, 4 in saline). 4 participants withdrawn from trial due to worsening: 1 in Group 1, 2 in Group 3, and 1 in Group 4

Risk of bias

Item	Authors' judgement	Description

Wang 1992 (*Continued*)

Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

RDI = Respiratory Distress Index
RDAI = Respiratory Distress Assessment Instrument
RACS = Respiratory Assessment Change Score
IV = intravenous
L/min = litres per minute
IM = intramuscular
WARI = Wheeze associated acute respiratory infection
MDI = metered dose inhaler
hr = hour
ED = emergency department

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abu-Shukair 2001	No placebo group
Beck 2007	No placebo group
Bentur 2003	No placebo group
Bertrand 2001	No placebo group
Brooks 1981	Not a randomized controlled trial
Cengizlier 1997	Control group was not given placebo
Chao 2003	Groups were stratified by age but no equivalent aged placebo group for the bronchodilator (terbutaline) group, therefore, no comparison could be made
Choong 1998	Poster abstract only

(*Continued*)

Cortes 1996	Not clearly randomized, insufficient information provided in brief report
Fernandez 2009	Study compared heliox versus oxygen to drive albuterol or epinephrine. No placebo group
Ferrer 1990	Only available in abstract form
Goebel 2000	No placebo group
Gomez-y-Lopez 2007	No placebo group
Hammer 1995	Not an RCT, no placebo group
Hariprakash 2003	Epinephrine versus placebo only
John 2010	No placebo group
Kadir 2009	No placebo group and not blinded
Kristjánsson 1993	Epinephrine versus placebo only
Langley 2005	No placebo group
Lowell 1987	Epinephrine versus placebo only
Luo 2003	No placebo group, quasi-experimental, not fully randomized
Luo 2010	No placebo group
Mandelberg 2003	No placebo group
Menon 1995	No placebo group
Milner 1995	Data not provided
Modl 2005	Not randomized or placebo controlled
Mull 2004	No placebo group
Ndrepepa 1998	Poster abstract only, available only in Turkish
Numa 2001	Not an RCT, no placebo group, epinephrine only
Ozyurek 2002	No placebo group
Ralston 2008	Nasal phenylephrine, not used as a bronchodilator

(*Continued*)

Ray 2002	No placebo group
Reijonen 1995	No placebo group
Sanchez 1993	Not RCT, no placebo group
Sarrell 2002	No placebo group
Schuh 1992	No placebo group
Shu 2001	Not randomized
Simsek 2005	No placebo group, abstract only
Sly 1991	Patients did not clearly have bronchiolitis
Soto 1985	Not an RCT, salbutamol only - no placebo group
Springer 1990	Results and analysis focused on pulmonary function tests
Stokes 1983	Excluded from original review as results and analysis focused on pulmonary function tests. Excluded from update as not clearly randomized, and water not a valid placebo
Tatochenko 1988	Criteria for diagnosis unclear
Torres 1997	No placebo group
Wainwright 2003	Epinephrine versus placebo only
Walsh 2008	Compared three doses of albuterol to one dose of epinephrine plus two saline nebulizers and therefore was not placebo controlled
Wankum 2000	Results and analysis focused on pulmonary function tests. Only 3 infants studied. Author contacted but no response
Zhen 2003	Poster abstract only
Zhou 2001	No placebo group

DATA AND ANALYSES

Comparison 1. Bronchodilators compared to placebo for treatment of acute bronchiolitis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oxygen saturation measured by pulse oximetry: inpatient and outpatient settings	24	1182	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.96, 0.05]
1.1 Inpatient studies	10	426	Mean Difference (IV, Random, 95% CI)	-0.29 [-1.10, 0.51]
1.2 Outpatient studies	14	756	Mean Difference (IV, Random, 95% CI)	Not estimable
2 No Improvement in clinical score (dichotomous)	7	365	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.06, 0.50]
2.1 Inpatient	5	208	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.05, 0.79]
2.2 Outpatient	2	157	Odds Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.46]
3 Average clinical score after treatment: by treatment setting (continuous)	19	1006	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.62, -0.13]
3.1 Inpatient studies	8	396	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.43, 0.03]
3.2 Outpatient studies	11	610	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-0.86, -0.11]
4 Hospital admission after treatment (outpatients)	10	650	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.47, 1.29]
4.1 Nebulized	7	344	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.45, 1.46]
4.2 Oral in ED setting	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.21]
4.3 Oral at home	2	269	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.28, 2.64]
5 Duration of hospitalization (inpatients)	6	349	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.27, 0.39]
6 Time to resolution of illness (outpatients)	2	269	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.43, 1.00]
7 Sensitivity analysis - oxygen saturation	15	793	Mean Difference (IV, Random, 95% CI)	Not estimable
8 Sensitivity analysis - average clinical score	14	714	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.44, -0.08]

WHAT'S NEW

Last assessed as up-to-date: 18 March 2010.

Date	Event	Description
27 May 2010	New citation required and conclusions have changed	New review author joined the lead author to complete this update, additional outcome measures included, conclusions changed

(*Continued*)

19 March 2010	New search has been performed	Searches conducted. Added to this update: five new included studies, one previously excluded study was included, and 12 new studies were excluded

HISTORY

Review first published: Issue 4, 1998

Date	Event	Description
22 August 2008	Amended	Converted to new review format.
19 October 2005	New search has been performed	This review was first published in 1998. The update process began in 2004 and was completed in 2006. Searches of the literature were conducted during 2005. Authors of published abstracts were contacted. In the update it was decided to include pulmonary function tests as an additional measure but there were insufficient studies with this measure that met all inclusion criteria. Five new trials were added to the update, a relatively small number given the time since the last update. For two outcomes, average clinical score and oximetry, the analyses were stratified according to treatment setting (inpatient or outpatient) rather than by drug delivery mechanism (oral or nebulized) as in the original review
1 June 1998	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

For the 2006 update, Anne Gadomski (AG) reviewed all the searches, selected studies and contacted authors to request unpublished data. AG identified outcomes of trials relevant for inclusion, reviewed the results and wrote the discussion and conclusions. Alice Bhasale (AB) assisted with some of the searches and selection of studies, data entry and analyses.

For the 2010 update, AG and Melissa Brower (MB) reviewed all the searches, selected studies, reviewed the included studies for risk of bias as well as outcomes, and reviewed meta-analysis results. MB performed the meta-analysis and sensitivity analysis. AG contacted authors to request unpublished data and updated the text of the review.

DECLARATIONS OF INTEREST

AM Gadomski is a trialist in included studies.

SOURCES OF SUPPORT

Internal sources

- National Prescribing Service Pty Ltd, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Oxygen saturation was designated as the primary outcome in the 2010 update. Risk of bias was assessed by two review authors and the risk of bias table was completed for all studies in the 2010 update. Sensitivity analysis for low risk of bias studies, studies including only first time wheezers and studies including only infants less or equal to 12 months of age was completed in the 2010 update.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Ambulatory Care [statistics & numerical data]; Bronchiolitis [*drug therapy]; Bronchodilator Agents [*therapeutic use]; Hospitalization [statistics & numerical data]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant