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Bronchodilators for bronchiolitis (Review)

Gadomski AM, Scribani MB

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TABLE OF CONTENTS

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[Intervention Review]

Bronchodilators for bronchiolitis

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ABSTRACT

Background

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

Objectives

To assess the effects of bronchodilators on clinical outcomes in infants (0 to 12 months) with acute bronchiolitis.

Search methods

We searched CENTRAL 2013, Issue 12, MEDLINE (1966 to January Week 2, 2014) and EMBASE (1998 to January 2014).

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. We obtained unpublished data from trial authors.

Main results

We included 30 trials (35 data sets) representing 1992 infants with bronchiolitis. In 11 inpatient and 10 outpatient studies, oxygen saturation did not improve with bronchodilators (mean difference (MD) -0.43, 95% confidence interval (CI) -0.92 to 0.06, n = 1242). Outpatient bronchodilator treatment did not reduce the rate of hospitalization (11.9% in bronchodilator group versus 15.9% in placebo group, odds ratio (OR) 0.75, 95% CI 0.46 to 1.21, n = 710). Inpatient bronchodilator treatment did not reduce the duration of hospitalization (MD 0.06, 95% CI -0.27 to 0.39, n = 349).

Effect estimates for inpatients (MD -0.62, 95% CI -1.40 to 0.16) were slightly larger than for outpatients (MD -0.25, 95% CI -0.61 to 0.11) for oximetry. Oximetry outcomes showed significant heterogeneity (I^2 statistic = 81%). Including only studies with low risk of bias had little impact on the overall effect size of oximetry (MD -0.38, 95% CI -0.75 to 0.00) but results were close to statistical significance.

In eight inpatient studies, there was no change in average clinical score (standardized MD (SMD) -0.14, 95% CI -0.41 to 0.12) with bronchodilators. In nine outpatient studies, the average clinical score decreased slightly with bronchodilators (SMD -0.42, 95% CI -0.79 to -0.06), a statistically significant finding of questionable clinical importance. The clinical score outcome showed significant heterogeneity (I^2 statistic = 73%). Including only studies with low risk of bias reduced the heterogeneity but had little impact on the overall effect size of average clinical score (SMD -0.22, 95% CI -0.41 to -0.03).

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Sub-analyses limited to nebulized albuterol or salbutamol among outpatients (nine studies) showed no effect on oxygen saturation (MD -0.19, 95% CI -0.59 to 0.21, n = 572), average clinical score (SMD -0.36, 95% CI -0.83 to 0.11, n = 532) or hospital admission after treatment (OR 0.77, 95% CI 0.44 to 1.33, n = 404).

Adverse effects included tachycardia, oxygen desaturation and tremors.

Authors' conclusions

Bronchodilators such as albuterol or salbutamol 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. Given the adverse side effects and the expense associated with these treatments, bronchodilators are not effective in the routine management of bronchiolitis. This meta-analysis continues to be limited by the small sample sizes and the lack of standardized study design and validated outcomes across the studies. Future trials with large sample sizes, standardized methodology across clinical sites and consistent assessment methods are needed to answer completely the question of efficacy.

PLAIN LANGUAGE SUMMARY

Bronchodilators for bronchiolitis for infants with first-time wheezing

What is bronchiolitis?

Bronchiolitis is an acute, highly contagious, viral infection of the lungs that is common in infants 0 to 12 months of age. It occurs every year in the winter months. It causes the small airways in the lungs to become inflamed and fill with debris. The airways are narrowed and this leads to blocking of the free passage of air. The infant has a harsh cough, runny nose and usually a fever. S/he can become breathless, wheezy and short of oxygen.

Why review bronchodilators?

Bronchodilators are drugs often used as aerosols to widen the air passages by relaxing the bronchial muscle. They are effective in helping older children and adults with asthma. However, unlike asthmatics, infants with bronchiolitis are usually wheezing for the first time. They are wheezing for a different reason, that is to say, because their airways are clogged with debris. Therefore, infants with bronchiolitis are less likely to respond to bronchodilators.

Study characteristics

We reviewed the evidence about the effect of bronchodilators in infants with bronchiolitis. We found 30 trials that included a total of 1922 infants, in several countries. The evidence is current up to January 2014. We analyzed studies done in outpatient and inpatient settings separately. All bronchodilators were included in the review except for epinephrine because it is reviewed in another Cochrane review. Albuterol (otherwise known as salbutamol) is commonly used in studies, so we also reviewed this bronchodilator as a subgroup.

Key results

We found no effect of bronchodilators on oxygen saturation. 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 and do not shorten the length of the illness at home. Reviewing the subgroup of studies using albuterol (salbutamol), we found no effect of this bronchodilator on oxygen saturation or clinical scores. Side effects of bronchodilators include rapid heart beat, decrease in oxygen and shakiness. Given these side effects, little evidence that they are effective and the expense associated with these treatments, bronchodilators are not helpful in the management of bronchiolitis.

Quality of the evidence

This review is limited by the small number of studies that use the same measures and methods. For example, only 22 studies included only infants wheezing for the first time. Older studies included children who had wheezed before and may have had asthma. Thus these older studies favor the use of bronchodilators. Newer studies that excluded infants with prior wheezing and had a better study design do not show a benefit of bronchodilators. This review is also limited by the small number of infants included in each study. Lastly, clinical scores used to measure the effect of the bronchodilators in some studies may vary from one observer to the next, making this measure unreliable. Studies that include more infants, use better measures and have a stronger study design are needed to define the effectiveness of these medications.

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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). 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 or rales, in addition to signs of bronchiolar obstruction such as air trapping, wheezing and high-pitched rhonchi (Disney 1960).

Largely caused by respiratory syncytial virus (RSV), bronchiolitis results in significant morbidity and mortality on a global scale (Nair 2010). While the average RSV hospitalization rate is 5.2 per 1000 children under 24 months old in the US, infants younger than two months of age have a much higher hospitalization rate of 17.9 per 1000 children (Hall 2009; Hall 2013). The estimated cost of hospitalization in the US increased by 24% from USD 1.2 billion in 2000 to USD 1.5 billion in 2006, despite the fact that length of stay decreased slightly from 2.4 to 2.3 days (Wilson 2010). Combined with other medical encounters (outpatient and emergency department visits), the total cost of bronchiolitis in the US likely exceeds the year 2000 estimate of USD 652 million (Paramore 2004), because hospitalization rates have increased both in the US and Canada (Langley 2003; Shay 1999; Shay 2001).

Description of the intervention

Bronchodilators have been commonly used in the management of bronchiolitis. However, bronchodilator efficacy for this illness is not universally accepted and bronchodilators are seldom used to treat bronchiolitis in the United Kingdom (Goodman 1993). Significant practice variation in the treatment of infants admitted for bronchiolitis or RSV pneumonia has been documented in the US (Christakis 2005; Florin 2013; Wilson 2001), Europe (Barben 2003; de Bilderling 2003), Canada (Plint 2004), Australia and New Zealand (Babl 2008; Vogel 2003). Significant practice variation in emergency department bronchodilator use and bronchodilator prescription at discharge has also been documented in the US and Canada (Johnson 2013; Plint 2004).

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. Infants with bronchiolitis present with wheezing, a hallmark of asthma, therefore bronchodilators have been used to manage wheezing.

Why it is important to do this review

Given the considerable cost of hospitalization and significant degree of practice variation documented in various parts of the world, an evidenced-based approach to bronchiolitis management is indicated. This review focuses on a broad class of bronchodilators, which includes the most commonly used agents, albuterol and salbutamol (β_2-adrenergic agonists). Epinephrine, a bronchodilator with both alpha-adrenergic and beta-adrenergic effects, is meta-analyzed in a separate Cochrane review (Hartling 2011a; Hartling 2011b). Randomized controlled trials (RCTs) of bronchodilators in bronchiolitis, whether for ambulatory or hospitalized children, have yielded variable results. Prior meta-analyses (Flores 1997; Kellner 1996) and systematic reviews (Hartling 2011b; King 2004; Wainwright 2010) suggest that bronchodilators may improve clinical symptom scores for outpatients but they do not affect disease resolution or length of hospital stay. Some evidence-based clinical reviews and practice guidelines conflict regarding their recommendations about the use of bronchodilators. Several recommend that bronchodilators should not be used routinely to treat bronchiolitis (DeNicola 2013; Guia Salud 2010; SIGN 2006; Wagner 2009; Wainwright 2010; Zorc 2010), while others suggest the option of a single trial of bronchodilator inhalation with careful assessment of response (AAP 2006; CCHMC 2010).

Cincinnati guidelines suggest that neither bronchodilators, steroids, antivirals nor antibacterial agents should be routinely used (CCHMC 2010). In particular, use of antibiotics and steroids should be strongly discouraged, whereas administration of bronchodilators or epinephrine are considered as an option, particularly when there is a family history for allergy, asthma or atopy.

OBJECTIVES

To assess the effects of bronchodilators on clinical outcomes in infants (0 to 12 months) with acute bronchiolitis.

There is widespread use of bronchodilators despite conflicting evidence regarding their efficacy, therefore we updated this systematic review of all randomized placebo-controlled trials of bronchodilators for bronchiolitis. We have reviewed the quality of studies and provided 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 in infants, as measured by improvement in oxygen saturation, clinical scores, admission to hospital, duration of hospitalization, pulmonary function tests 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. We examined the methods and results 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 the 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

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of inhaled steroids were not included. Routes of administration were: nebulized, oral and subcutaneous. Although included in the original review, we excluded studies of epinephrine in bronchiolitis from the updates since these studies are included in the Cochrane Review 'Epinephrine for bronchiolitis' (Hartling 2011a).

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. We added pulmonary function tests as an additional outcome in the 2006, 2010 and 2014 updates.

Primary outcomes

1. 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

1. Improvement in clinical scores.
2. Admission to hospital.
3. Duration of hospitalization.
4. Time to resolution of illness.
5. Pulmonary function tests.

These outcomes are more subjective and subject to interrater variability. Pulmonary function tests are objective measures of the effect of bronchodilators on airway resistance and compliance.

Search methods for identification of studies

Electronic searches

For this 2014 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 12 (accessed 20 January 2014), which contains the Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 2010 to January week 2, 2014) and EMBASE (March 2010 to January 2014). Details of previous searches are in Appendix 1.

We used the following search strategy to search CENTRAL and MEDLINE. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision- maximizing version (2008 revision); Ovid format (Lefebvre 2011). We adapted these search terms to search EMBASE (see Appendix 2). There were no language or publication restrictions.

MEDLINE (OVID)

1 exp Bronchiolitis/
2 bronchiolit*.tw.
3 1 or 2
4 exp Bronchodilator Agents/
5 bronchodilator*.tw,nm.
6 Albuterol/
7 albuterol.tw,nm.
8 salbutamol.tw,nm.
9 Terbutaline/
10 terbutaline.tw,nm.
11 Ipratropium/
12 ipratropium.tw,nm.
13 exp Adrenergic Agents/
14 adrenergic agent*.tw,nm.

Searching other resources

We scanned the reference lists of identified articles and contacted authors of the identified trials and other experts in the field.

Data collection and analysis

Selection of studies

In the original review, two review authors (AG, AB) independently reviewed the articles. In the 2010 and 2014 updates, two review authors (AG, MS) 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, MS) independently extracted data and achieved consensus on what data to include. We requested unpublished data from trial authors when necessary.

Assessment of risk of bias in included studies

Both review authors (AG, MS) rated the quality of each included trial by assessing whether the following five sources of bias were adequately reported (Higgins 2011): 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 were addressed; and 5) selective reporting was not present.

Measures of treatment effect

We selected oxygen saturation as measured by pulse oximetry, clinical scores based on a multi-item clinical scale and admission to hospital to measure the effect of bronchodilators on outpatients. We added duration of hospitalization as an outcome measure for inpatients. We thought these outcomes to be the most clinically relevant and to have the largest amount of experimental data reported. Two longer-term outpatient studies were published, therefore we also added time to resolution of illness 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. Fourteen of 30 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 1.3 defines events as the proportion of participants who did not meet pre-determined criteria for clinical score improvement. In eight inpatient and nine outpatient trials, the results were reported as the average score or

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change in score in each treatment group (average clinical score, a continuous variable (Analysis 1.4).

Time to resolution of illness (ROI), measured from the period of study enrollment to the time the infant returned to baseline health status, is scored by the primary caregiver at home. ROI comprises parental assessment of degree of improvement of respiratory symptoms scored on a four-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.

For the three continuous variables (oxygen saturation, average clinical score and duration of hospitalization) and the ordinal variable of ROI, we determined the effect of treatment compared with placebo using the unbiased estimate of effect size (ES), with its 95% confidence intervals (CI) (Bracken 1989). For oxygen saturation, duration of hospitalization and ROI, we measured effect using the mean difference (MD) between treatment and placebo. We converted the average clinical scores 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), we determined the effect of treatment compared with placebo 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.

Pulmonary function test (PFT) data are objective measures but changes in PFT measures may achieve statistical significance while having little clinical significance. In this update, we found one additional PFT study (Scarlett 2012), bringing the total number of PFT studies to 10. However, seven of these studies did not fulfill the inclusion criteria and only three studies could be included (Levin 2008; Scarlett 2012; Totapally 2002). However, due to the different PFT measurement techniques used, the outcomes of these studies could not be combined. Therefore, PFT data are not included as outcome measures.

Unit of analysis issues

We stratified results for oxygen saturation and average score (continuous) 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 addition, we added oral bronchodilator given at home (ascertained during a 14-day period following study enrollment) to Analysis 1.6 'Hospital admission after treatment'.

Cross-over studies

Three trials employed cross-over designs (Alario 1992; Ho 1991; Totapally 2002). Pulse oximetry data from Alario 1992, recorded 20 minutes after either nebulized metaproterenol or 0.9% saline first among 74 outpatients (37 in each group), were included in Analysis 1.1. Clinical score data for outpatients aged 12 months or younger (17 in metaproterenol group and 20 in 0.9% saline group) were available and thus included in Analysis 1.3 and Analysis 1.4. Pulse oximetry data from Ho 1991 included 30-minute readings for 13 inpatients receiving salbutamol first and eight inpatients receiving 0.9% saline first. Cross-over data were not included. The PFT results presented by Totapally 2002 were not combined with other PFT results because different PFT measurement techniques were used by the PFT studies.

Studies with multiple treatment groups

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), or different diluents (0.9% saline versus 3% saline). 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. For Ipek 2011, the 3% saline study groups were excluded from analysis.

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 11 studies for missing statistics, such as standard deviations.

Assessment of heterogeneity

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

Assessment of reporting biases

In 2006, an unpublished study was included because it was a RCT of salbutamol, ipratropium and saline that included first-time wheezing infants admitted to hospital (Karadag 2005 - IPR). This study was later published (Karadag 2008). A second unpublished inpatient study was a RCT comparing salbutamol, placebo and epinephrine (Gurkan 2004). We obtained data for these studies from the trialists. There were two placebo-controlled studies excluded

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because they were only available in abstract form (Ferrer 1990; Karaatmaca 2010). Pending clinical trials were sought in the Pediatric Academic Societies abstracts for 2012 and 2013 (none were found). 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, we requested additional data and received these 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 this 2014 update, we requested additional unpublished data and received these from Scarlett 2012. Therefore, the likelihood of publication bias is low.

Data synthesis

We chose a fixed-effect model initially for the meta-analysis (Thompson 1991). This model assumes that the true effect of treatment is the same in all trials and that any differences in treatment effect between trials are due to chance. We 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. They are commonly used, therefore albuterol or salbutamol subgroup analysis was added in this 2014 update. 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 younger than or equal to 12 months of age. We defined studies with a low risk of bias as having a ranking of 'low risk' for all five items in the 'Risk of bias' table (see Included studies). In this 2014 update, we included studies using the same clinical score (RDAI) in a sensitivity analysis.

RESULTS

Description of studies

Results of the search

Of the 21 studies identified in the search for this 2014 update, two met the criteria for inclusion. Most of the excluded studies were excluded because they did not include a placebo group (see Characteristics of excluded studies table).

Included studies

From a total of 30 trials (35 data sets) included in this review, 23 trials were in infants wheezing for the first time (Anil 2010 SAL 0.9%; Anil 2010 SAL 3%; Can 1998; Chevallier 1995; Chowdhury 1995; Dobson 1998; Gadomski 1994a - neb; Gadomski 1994b - neb; Goh 1997; Gupta 2008; Gurkan 2004; Ho 1991; Karadag 2008; Klassen 1991; Levin 2008; Lines 1990; Lines 1992; Patel 2002; Patel 2003; Ralston 2005; Schuh 1990; Tinsa 2009; Totapally 2002; Wang 1992). For this 2014 update, we included two new trials, both of which included first-time wheezing infants (Ipek 2011; Scarlett 2012). We also included five additional trials, in which results from participants with first-time wheezing could not be separated from those with recurrent wheezing (Alario 1992; Henry 1983; Mallol 1987; Schweich 1992; Tal 1983).

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

We excluded a total of 62 studies from this review (see Characteristics of excluded studies table). We made 46 of these exclusions because the trials were not placebo-controlled (Absar 2008; Abu-Shukair 2001; Alansari 2013; Barlas 1998; Beck 2007; Bentur 2003; Bertrand 2001; Cengizlier 1997; Chao 2003; Del Vecchio 2012; Fernandez 2009; Florin 2012; Frasson 2012; Goebel 2000; Gomez-y-Lopez 2007; Gonzalez 1994; Hammer 1995; John 2006; John 2010; Kadir 2009; Kim 2011; Langley 2005; Luo 2003; Luo 2010; Luo 2012; Mandelberg 2003; Menon 1995; Modaressi 2012; Modl 2005; Mull 2004; Numa 2001; Ozyurek 2002; Ray 2002; Reijonen 1995; Sanchez 1993; Sarrell 2002; Schuh 1992; Sharma 2013; Simsek 2005; Simsek-Kiper 2011; Soto 1985; Springer 1990; Stokes 1983; Torres 1997; Walsh 2008; Zhou 2001).

We excluded six trials because they contained limited data due to publication in abstract form only (Choong 1998; Ferrer 1990; Karaatmaca 2010; Milner 1995; Ndrepepa 1998; Zhen 2003). We excluded two additional studies as abstract-only (Ren 2011; Sezer 2010), but the data were later published as included studies in Scarlett 2012 and Ipek 2011, respectively.

We have excluded four trials because they were not RCTs (Brooks 1981; Cortes 1996; Shu 2001; Wankum 2000), one trial because it did not include nebulized delivery of bronchodilators (Ralston 2008), two studies because they did not have clear definitions of bronchiolitis (Sly 1991; Tatochenko 1988) and one study because it published a research protocol only (no outcomes data) (Belcastro 2010). We omitted four trials of epinephrine versus placebo, excluded in previous versions of this review (Hariprakash 2003; Kristjánsson 1993; Lowell 1987; Wainwright 2003), from this 2014 update as they have been addressed by another Cochrane Review (Hartling 2011a).

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 older 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

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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.

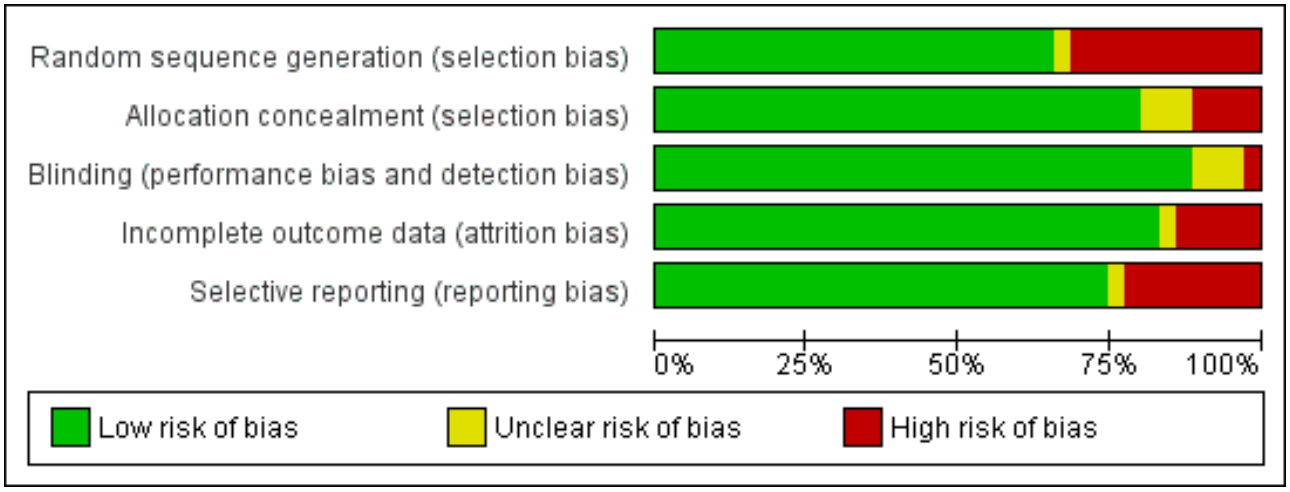

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Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

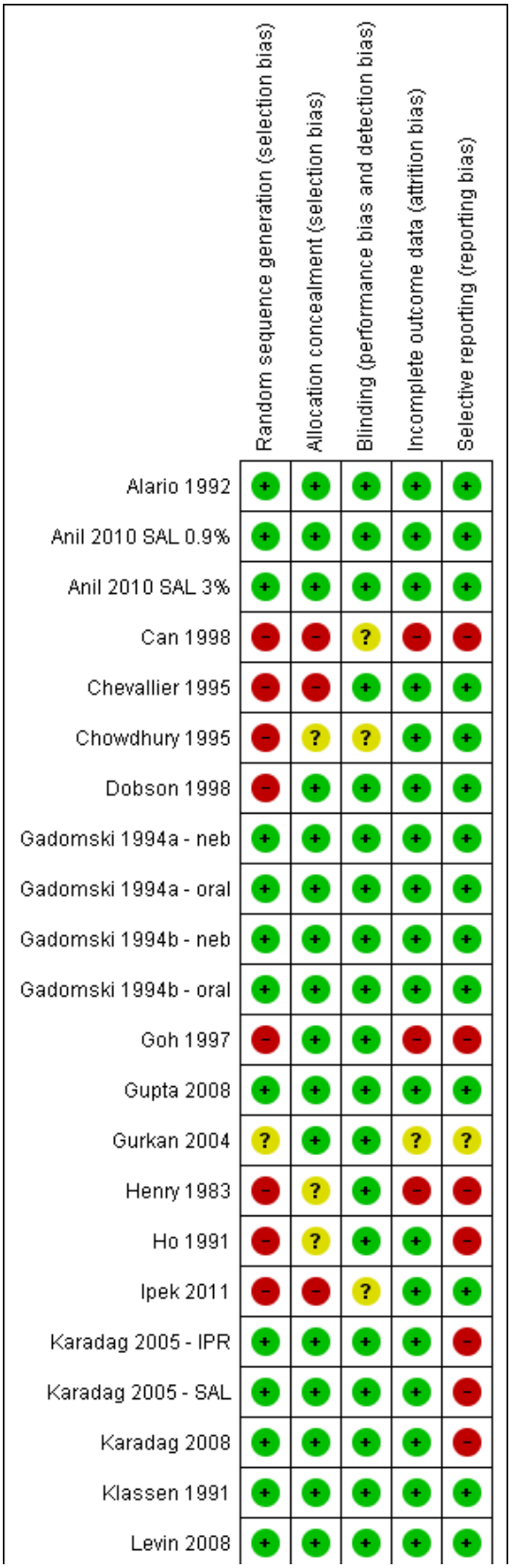

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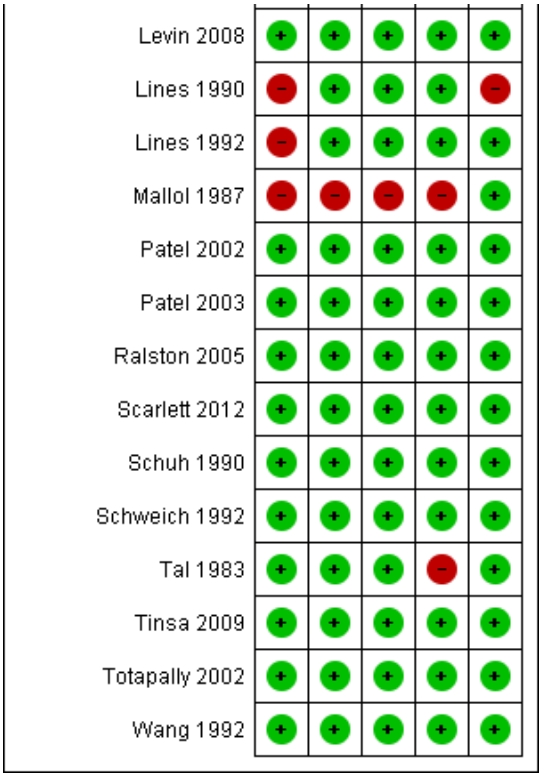
Figure 2. (Continued)



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), or in 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. Ipek 2011 allocated infants to the study groups by consecutive order to the short stay unit.

Blinding

Most medical and research staff administering treatment or assessing participants during the trial (or both) 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). Two studies were described in the abstract as being double-blind but this was not detailed in the methods (Can 1998; Ipek 2011).

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. Bronchodilators have short-term effects, therefore 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 sustained 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 13% (Gupta 2008; Patel 2003; Scarlett 2012). 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 when study participant attrition occurred (Patel 2002; Patel 2003).

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; Scarlett 2012).

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. Bronchodilators can increase heart rate, therefore 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.

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Effects of interventions

Primary outcome

1. 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) -0.43, 95% confidence interval (CI) -0.92 to 0.06 (Analysis 1.1).

Nine outpatient studies included treatment protocols that included albuterol or salbutamol nebulization only (Anil 2010 SAL 0.9%; Anil 2010 SAL 3%; Can 1998; Gadomski 1994a - neb; Gadomski 1994b - neb; Ipek 2011; Klassen 1991; Ralston 2005; Schuh 1990; Schweich 1992). When reduced to these nine studies, outpatient oximetry measures showed reduced heterogeneity and also reduced mean differences that were not statistically significant (I^2 statistic = 0%; MD -0.19, 95% CI -0.59 to 0.21; Analysis 1.2).

Secondary outcomes

1. Improvement in clinical scores

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 (odds ratio (OR) for no improvement = 0.18, 95% CI 0.06 to 0.50, n = 365), using a random-effects model (Analysis 1.3). Included in this analysis are three studies that were methodologically weaker than other studies and included older participants who were recurrent wheezers (Alario 1992; Lines 1990; Mallol 1987).

The improvement in overall average clinical score was statistically significant (standardized MD (SMD) -0.30, 95% CI -0.54 to -0.05) (Analysis 1.4), but the small magnitude of this change limits its clinical significance. Inpatients demonstrated no improvement compared to 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.

We performed a sub-analysis among nine outpatient studies with treatment protocols that included albuterol or salbutamol nebulization only (Anil 2010 SAL 0.9%; Anil 2010 SAL 3%; Can 1998; Gadomski 1994a - neb; Gadomski 1994b - neb; Ipek 2011; Klassen 1991; Ralston 2005; Schuh 1990; Schweich 1992). As shown in Analysis 1.5, similar levels of heterogeneity were found but the treatment effect was not significant (I^2 statistic = 85%; SMD -0.36, 95% CI -0.83 to 0.11, P value = 0.13).

2. Admission to hospital

The rate of hospitalization was not significantly reduced in bronchodilator recipients compared with placebo recipients in outpatient studies (11.9% versus 15.9%; OR 0.75, 95% CI 0.46 to 1.21) (Analysis 1.6). Rate of hospitalization was not significantly different between oral bronchodilator or placebo groups followed in longer-term home-based studies (4.5% versus 5.2%; OR 0.86, 95% CI 0.28 to 2.64).

3. Duration of hospitalization

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 1.7).

4. Time to resolution of illness

There is no difference between bronchodilator and placebo groups with respect to time to resolution of illness as measured 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 1.8). Thus, oral bronchodilators do not shorten the time to resolution of illness among infants treated at home. However, only two studies examined this outcome.

5. Pulmonary function tests

In this 2014 update, one placebo-controlled study utilizing PFT as an outcome met the inclusion criteria (Scarlett 2012). This study utilized tidal breathing analysis using respiratory inductive plethysmography to measure phase angle (thoracoabdominal synchrony). Changes in tidal breathing measures were compared pre- and post-albuterol or saline inhalation for 20 infants hospitalized for bronchiolitis. Totapally 2002 used tidal breathing analysis of 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. Although both studies measured peak expiratory flow to total expiratory time (Tpef/Te), the different PFT techniques used preclude merging these measurements for meta-analysis. These studies documented no significant changes in tidal breathing and Tpef/Te measures as well as clinical scores between albuterol nebulization and the 0.9% saline study groups after treatment. Scarlett 2012 also documented that the RDAI clinical score did not correlate with phase angle (results included in Analysis 1.4). Levin 2008 measured peak inspiratory pressure and inspiratory system resistance pre- and post-bronchodilator or 0.9% saline nebulization in 22 infants with severe RSV-positive bronchiolitis who were intubated and ventilated in an ICU setting. 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. Differences in severity of illness, PFT methodology and outcomes (volume versus pressure) preclude merging the results of these three placebo-controlled trials that used PFT measures.

Subgroup analyses

Subgroup analysis of oximetry showed no statistically significant effects for either outpatients (MD -0.25, 95% CI -0.61 to 0.11) or inpatients (MD -0.62, 95% CI -1.40 to 0.16) (Analysis 1.1).

Subgroup analyses of clinical score 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 -0.42, 95% CI -0.79 to -0.06) compared to the effect in inpatient studies (SMD -0.14, 95% CI -0.41 to 0.12) (Analysis 1.4).

However, the magnitude of these differences between inpatient and outpatient studies is of questionable clinical importance (e.g.

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a MD of -0.62 in pulse oximetry is not clinically relevant) 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.

Subgroup analysis limiting bronchodilators to albuterol or salbutamol among outpatients showed no effect on oxygen saturation (MD -0.19, 95% CI -0.59 to 0.21) (Analysis 1.2). Nebulized albuterol or salbutamol outpatient treatment had no effect on average clinical score (SMD -0.36, 95% CI -0.83 to 0.11, Analysis 1.5) or hospital admission after treatment (OR 0.32, 95% CI 0.03 to 3.21, Analysis 1.6). Oral albuterol or salbutamol given at home had no impact on hospital admission after treatment (OR 0.86, 95% CI 0.28 to 2.64, Analysis 1.6).

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 (-0.66, 95% CI -0.82 to -0.49) than the result found with the random-effects model (-0.43, 95% CI -0.92 to 0.06). There was evidence of considerable heterogeneity with this outcome (P value < 0.00001, I^2 statistic = 81%) 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. These factors mean that we considered the random-effects model more appropriate.

Sensitivity analysis

We assessed 16 studies 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; Scarlett 2012; 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 1.9) and average clinical score (I^2 statistic = 37%; Analysis 1.10), while having little impact on the overall effect size of oximetry (MD -0.38, 95% CI -0.75 to 0.00, P value = 0.05; Analysis 1.9) and average clinical score (SMD -0.22, 95% CI -0.41 to -0.03, P value = 0.02; Analysis 1.10). In other words, reducing the heterogeneity by removing studies with higher risk of bias did not uncover a clinically relevant treatment effect or materially 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 after treatment in an outpatient setting, duration of hospitalization or time to resolution of illness at home.

Fourteen studies included infants aged 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; Scarlett 2012; 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.

Nineteen 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; Ipek 2011; Karadag 2008; Levin 2008; Patel 2002; Patel 2003; Ralston 2005; Scarlett 2012; Schuh 1990; Tinsa 2009; Totapally 2002). Limiting the analysis of average clinical score to first-time wheezers led to a non-significant treatment effect and also reduced heterogeneity measures and reduced mean differences (I^2 statistic = 30%, SMD - 0.10, 95% CI -0.28 to 0.08, P value = 0.13). However, no impact was observed for the other outcomes.

Three studies of outpatients utilized identical clinical score measurement, that is, the complete RDAI (Anil 2010 SAL 0.9%; Anil 2010 SAL 3%; Klassen 1991; Ralston 2005) (Analysis 1.11). Limiting the analysis of average clinical score to these three studies showed substantially decreased heterogeneity (I^2 statistic = 47%) when compared to all outpatient studies (I^2 statistic = 81%). However, there was virtually no change in effect size (SMD -0.11, 95% CI -0.48 to 0.25, P value = 0.54).

Adverse effects

Where adverse effects were reported, we note that these were exclusively found in the study groups receiving bronchodilators and they 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 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 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 two 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

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have tremors versus the placebo group (none) in the other home study (Gupta 2008). Significant 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).

This 2014 update includes Scarlett 2012, who reported a paradoxical response to albuterol in an infant whose phase angle increased after receiving albuterol (the expected response was a decrease).

DISCUSSION

Summary of main results

This 2014 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 and do not shorten the time to resolution of illness in home studies.

The two new studies add to the evidence that β_2-adrenergic agonists, i.e. albuterol (US) or salbutamol (as it is known elsewhere), are not effective for treating bronchiolitis. While they may produce small short-term improvements in clinical scores for infants treated as outpatients, this short-term benefit is not justified given the costs and adverse effects of these agents. These bronchodilators cause tachycardia and tremors, therefore routine use of bronchodilators for infants with bronchiolitis is not indicated.

What we learned from new sensitivity analysis. This meta-analysis is limited by the 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. However, again the effect sizes are small for both settings and are of minimal clinical significance (for oximetry: outpatients mean difference (MD) -0.25 versus inpatients -0.62; for average clinical score: outpatients standardized MD (SMD) -0.42 versus inpatients -0.14). These findings may be biased toward 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 endpoints for hospitalization and definition of what the minimal clinically important difference is for this outcome are now defined in clinical practice guidelines.

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 and social considerations, 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 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 β_2-adrenergic agonists for recurrent wheezing in children under two years of age showed no clear benefit of using bronchodilators in this age group (Chavasse 2002). The pathophysiology of bronchiolitis consists of terminal bronchiolar and alveolar inflammation with airway swelling and luminal debris, therefore the primary mechanism underlying wheezing is airway obstruction and plugging of the small airway diameters rather than bronchospasm (La Via 1992). In addition, it may be difficult to administer the nebulization to young infants effectively. Lastly, the relative lack or immaturity of the β_2-receptor in the bronchial wall smooth muscle in infants further limits the potential effectiveness of β_2-adrenergic agonists. These factors may explain why bronchodilators are not effective for infants with bronchiolitis.

Quality of the evidence

The lack of improvement in oximetry with bronchodilators and the heterogeneity of clinical scoring 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 colleagues 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).

The clinical scoring systems used in the studies included in this review varied considerably. Few have been tested for validity, reliability or compared to a physiologic standard or proven

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to correlate with clinically significant improvement (Mull 2004; Scarlett 2012; Zorc 2010), or predict the need for oxygen (McCallum 2013) or hospital admission from the emergency department (Destino 2010). Interrater variability of current scoring methods can be high. The most commonly used score, the RDAI, has low intraclass correlation, poor construct and discriminative validity (Destino 2010; Destino 2012; Walsh 2008). Sensitivity analysis of studies that used the RDAI show substantially decreased heterogeneity but no treatment effect (Analysis 1.11).

During this 2014 update, we found few new randomized, placebo-controlled clinical trials. The adequacy of the outcome measures used to measure infant response to bronchodilators remains limited. 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 and the lack of standardized study design and reliable outcome assessment across the studies. Thus, randomized controlled trials (RCTs) with large sample sizes, standardized methodology across clinical sites and consistent assessment methods are needed to answer completely the question of efficacy.

A more objective alternative to these outcomes is pulmonary function testing (PFT) as performed by Levin 2008, although limited to infants with severe disease. Although the number of bronchiolitis studies utilizing PFTs has increased to 10, the methods and outcomes for measuring PFTs vary, thereby precluding comparability. In addition, only three studies employed a placebo-controlled RCT design comparing measures pre- and post-treatment with a bronchodilator. Future PFT studies should employ a placebo-controlled RCT design as well as standardized methods so that outcome data can be merged.

Potential biases in the review process

One of the authors is a trialist and a member of the American Academy of Pediatrics Subcommittee on the Diagnosis and Management of Bronchiolitis.

Agreements and disagreements with other studies or reviews

The results of this meta-analysis concur with recent reviews (Hartling 2011b; Wainwright 2010; Zorc 2010), which underscore the limited effectiveness of bronchodilators, particularly as they relate to β_2-adrenergic agonists in the outpatient management of bronchiolitis. This review is also consistent with these prior reviews in the conclusion that there is no significant treatment effect of bronchodilators for infants hospitalized with bronchiolitis (Hartling 2011b).

AUTHORS' CONCLUSIONS

Implications for practice

Given their high cost, adverse effects and lack of effect on oxygen saturation and other outcomes included in this meta-analysis, bronchodilators are not effective in the 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 answer completely 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, cross-over 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. Children received nebulized metaproterenol, either as an initial treatment or after a control treatment with normal saline solution. Only initial treatment results are included
Outcomes	Respiratory rate, RDI score (color, wheezing, accessory muscle use, flaring, grunting, distress), oxygen saturation, side effects (tremors, vomiting, extreme irritability). RDI results were available for 37 infants aged ≤ 12 months
Notes	Included asthmatic participants or recurrent wheezers. “Responders to metaproterenol therapy” included 40% of those aged 12 months or younger versus 52% of those aged 24 months or older

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	

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Alario 1992 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk
Incomplete outcome data (attrition bias) All outcomes	Low risk
Selective reporting (reporting bias)	Low risk

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). Exclusions 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 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. 2 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

Anil 2010 SAL 3%

Methods	Randomized, double blind, placebo-controlled trial

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Anil 2010 SAL 3% *(Continued)*

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). Exclusions 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. 2 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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 3 study

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Can 1998 *(Continued)*

	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No detail provided in the methods section of the manuscript; but abstract mentions "double blind" in the methods
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete
Selective reporting (reporting bias)	High risk	Non-significant findings on heart rate not presented

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	

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Chevallier 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk
Selective reporting (reporting bias)	Low risk

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	Unclear risk	Unclear; insufficient detail provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Investigators blinded up to 36 hours, single-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

Dobson 1998

Methods	Double-blind, randomized, placebo-controlled trial

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Dobson 1998 *(Continued)*

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
Outcomes	Oxygen 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 hypoxemia. Subgroup analysis of results for infants less than 12 months was done but results not published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

Gadomski 1994a - neb

Methods	Randomized, double-blind, placebo-controlled trial
Participants	Outpatients and emergency department participants 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 1 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)

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Gadomski 1994a - neb *(Continued)*

Notes	Nebulized treatment group: in order to represent the results from the 2 bronchodilator treatment arms (nebulized and oral), this study is listed twice. Each treatment group had its own placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

Gadomski 1994a - oral

Methods	See Gadomski 1994a - neb
Participants	
Interventions	
Outcomes	
Notes	Oral treatment group: in order to represent the results from the 2 bronchodilator treatment arms (nebulized and oral), this study is listed twice. Each treatment group had its own placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

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Gadomski 1994a - oral *(Continued)*

Selective reporting (reporting bias)	Low risk

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 1 dose. Nebulization with compressed air at 6 L/min via Up-mist nebulizer with pediatric face mask. Infants 7 kg or less received 1 unit dose of 1 mg salbutamol solution for inhalation (5 mg/ml) or 1 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 2 bronchodilator treatment arms (nebulized and oral), this study is listed twice. Each treatment group had its own placebo group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

Gadomski 1994b - oral

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

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Gadomski 1994b - oral *(Continued)*

Outcomes	
Notes	Oral treatment group: in order to represent the results from the 2 bronchodilator treatment arms (nebulized and oral), this study is listed twice. Each treatment group had its own placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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 µg/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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	Low risk	Fourth study group receiving humidified oxygen was studied 1 year later without blinding or allocation concealment

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Goh 1997 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	For 3 treatment groups (salbutamol, ipratropium and normal saline)
Incomplete outcome data (attrition bias) All outcomes	High risk	10 participants excluded without information about which group they were assigned to
Selective reporting (reporting bias)	High risk	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 1 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) 3 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 participants were lost to follow-up, 7 (10%) in the salbutamol group and 3 (4.3%) in the placebo group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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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 1 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear; not published
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	Unclear

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 µg of ipratropium bromide in 2 ml saline (n = 34) or normal saline alone (n = 32)
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 re-

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Henry 1983 *(Continued)*

	cession, respiratory distress, crepitations and rhonchi. Side effects: increased heart rate, persistent coughing
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete data
Selective reporting (reporting bias)	High risk	Yes

Ho 1991

Methods	Randomized, double-blind, cross-over 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	Unclear risk	Unclear; insufficient detail provided
Blinding (performance bias and detection bias)	Low risk	

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Ho 1991 *(Continued)*

All outcomes	
Incomplete outcome data (attrition bias) All outcomes	Low risk
Selective reporting (reporting bias)	High risk

Ipek 2011

Methods	Randomized, double-blind, placebo-controlled trial
Participants	Setting: short-stay unit of a pediatric emergency department Infants between 1 and 23 months of age, seen for moderate bronchiolitis, first episode of wheezing. Patients with history of preceding viral URI, followed by wheezing and crackles on auscultation and a clinical bronchiolitis severity score (CBSS) of 4 to 8. Mean age 7.96 ± 3.91 months. Exclusion criteria were: prematurity; birth weight < 2500 g; chronic neurological or cardiopulmonary disease, including asthma; infants younger than 1 month old and greater than 2 years; proven immune deficiency, consolidation or atelectasis on CXR; oxygen saturation < 85% on room air Country: Turkey
Interventions	Group 1: nebulized salbutamol 0.15 mg/kg plus normal saline (NS) every 20 minutes for 3 doses Group 2: nebulized salbutamol 0.15 mg/kg plus hypertonic saline (HS) every 20 minutes for 3 doses Group 3: hypertonic saline every 20 minutes for 3 doses Group 4: normal saline every 20 minutes for 3 doses
Outcomes	Changes in CBSS, respiratory rate, oxygen saturation, heart rate assessed at 0, 20, 40 and 60 minutes; corticosteroid need, hospitalization ratios
Notes	Sezer 2010 was a published abstract using the same trial data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Consecutive patients enrolled
Allocation concealment (selection bias)	High risk	Consecutive allocation to treatment groups; insufficient detail provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient detail provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data; no withdrawals
Selective reporting (reporting bias)	Low risk	

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Karadag 2005 - IPR

Methods	Randomized, double-blind, placebo-controlled trial
Participants	Setting: inpatients Infants less than 1 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 µg/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 1992. Improvement was defined as a decrease by 2 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Data on heart rate mentioned but not presented in results

Karadag 2005 - SAL

Methods	See Karadag 2005 - IPR
Participants	
Interventions	

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Karadag 2005 - SAL *(Continued)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	See Karadag 2005 - IPR

Karadag 2008

Methods	Same as Karadag 2005
Participants	
Interventions	
Outcomes	
Notes	This published manuscript describes the same study as Karadag 2005 that was published as an abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias)	Low risk	

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Karadag 2008 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	See Karadag 2005 - IPR

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	2 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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

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Levin 2008 *(Continued)*

Interventions	Randomized to 4 groups: albuterol (3 ml of 0.083%, 2.5 mg/3 ml), levalbuterol (3 ml of 1.25 mg/3 ml), 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	Low risk	

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Lines 1990 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk
Incomplete outcome data (attrition bias) All outcomes	Low risk
Selective reporting (reporting bias)	High risk

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	2 doses (with 2-hour interval) of nebulized ipratropium bromide 1 ml (250 µg) in 4 ml saline or 5 ml saline placebo
Outcomes	Oxygen saturation, RACS, respiratory rate, heart rate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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

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Mallol 1987 *(Continued)*

	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 hours (0.5% solution), nebulized IB - 250 µg/dose every 6 hours (0.025% solution), oral or IV aminophylline - less than 6 months (age in weeks *0.3 + 8 = mg/kg/day, 4 equal doses every 6 hours) or more than 6 months (15 mg/kg/day, 4 equal doses every 6 hours), steroids: dexamethasone (IV or IM, 0.3 mg/kg/dose initially, 0.3 mg/kg/day, 3 equal doses every 8 hours) or prednisone (oral 2 mg/kg/day, 3 equal doses every 8 hours)
Outcomes	Clinical score same as with Tal 1983. No adverse side effects
Notes	No distinction made between asthma and bronchiolitis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Single blinding only
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants whose scores did not decrease at 24 hours were excluded from the study as "failures"
Selective reporting (reporting bias)	Low risk	

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	—

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Patel 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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 0.1 mg/kg per dose given 3 times per day for 7 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 2 withdrawals from each study group. Total drop out for this study was 10.8%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias)	Low risk	

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Patel 2003 *(Continued)*

All outcomes	
Incomplete outcome data (attrition bias) All outcomes	Low risk
Selective reporting (reporting bias)	Low risk

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. 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 Country: United States, high altitude (5000 feet)
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	Clinical scores and oximetry data that were not published were obtained from the author for the 2010 update

Scarlett 2012

Methods	Randomized, double-blind, placebo-controlled trial

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Scarlett 2012 *(Continued)*

Participants	Inpatients younger than or equal to 12 months of age with a first episode of wheezing due to RSV bronchiolitis. Mean age in placebo group 8.8 weeks, albuterol 20.1 weeks (despite randomization, albuterol-treated infants were significantly older than placebo-treated infants, P value < 0.0001). Excluded preterm infants, underlying chronic lung disease, previous history of wheezing or treatment with bronchodilators before current illness, previous treatment with RSV prophylaxis therapy, history of respiratory infection 3 weeks before enrollment, hemodynamically significant congenital heart disease, immune-compromised state, albuterol therapy within 6 hours of administration of the study drug, gastro-esophageal reflux requiring medical therapy, neurodevelopmental delay, severe bronchiolitis requiring admission to pediatric intensive care Country: USA
Interventions	Group 1: albuterol nebulized (0.1 mg/kg in 3 ml saline). Group 2: saline (3 ml)
Outcomes	Respiratory inductive plethysmography (RIP) for a total of 30 breaths, ratio of time to peak expiratory flow to total expiratory time (Tpef/Te), RDAI, oxygen saturation, respiratory rate
Notes	Only infants with a 10% increase in heart rate were included in the final analysis. 3 participants excluded because they did not maintain quiet sleep. Ren 2011 was a published poster abstract using the same trial data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Performed by research pharmacy (unpublished information)
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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 1 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

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Schuh 1990 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

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. 3 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 liters/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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	

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Schweich 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk
Selective reporting (reporting bias)	Low risk

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	High risk	10 relative therapeutic failures and 2 complete therapeutic failures were excluded from analysis
Selective reporting (reporting bias)	Low risk	

Tinsa 2009

Methods	Prospective, randomized, placebo-controlled, double-blind clinical trial

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Tinsa 2009 *(Continued)*

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

Totapally 2002

Methods	Randomized, double-blind, placebo-controlled, cross-over 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, pulse oximetry, ratio of time to peak expiratory flow to total expiratory time (Tpef/Te)
Notes	Wheeze score was: 0 for none 1 for end exp 2 for audible with stethoscope 3 for audible without stethoscope

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Totapally 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

Wang 1992

Methods	Randomized, double-blind, factorial trial
Participants	Setting: inpatients Infants 2 to 24 months of age hospitalized for the 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 1 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 µg ipratropium bromide if less than 6 months old or 250 µg 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 ipratropium, 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	

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Wang 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk
Selective reporting (reporting bias)	Low risk

CBSS = clinical bronchiolitis severity score
CXR = chest X-ray
ED = emergency department
HR = heart rate
hr = hour
HS = hypertonic saline
ICU = intensive care unit
IM = intramuscular
IV = intravenous
L/min = liters per minute
MDI = metered dose inhaler
NS = normal saline
RACS = Respiratory Assessment Change Score
RDAI = Respiratory Distress Assessment Instrument
RDI = Respiratory Distress Index
RDS = Respiratory Distress Score
RR = respiratory rate
RSV = respiratory syncytial virus
SpO_2 = oxygen saturation
URI = upper respiratory infection
WARI = wheeze associated acute respiratory infection

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

Study	Reason for exclusion
Absar 2008	No placebo group
Abu-Shukair 2001	No placebo group
Alansari 2013	No placebo group
Barlas 1998	No placebo group
Beck 2007	No placebo group
Belcastro 2010	Research protocol only - no patient outcomes data
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

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Study	Reason for exclusion
Choong 1998	Poster abstract only
Cortes 1996	Not clearly randomized, insufficient information provided in brief report
Del Vecchio 2012	Not a randomized controlled trial, no placebo group
Fernandez 2009	Study compared heliox versus oxygen to drive albuterol or epinephrine. No placebo group
Ferrer 1990	Only available in abstract form
Florin 2012	No placebo group
Frasson 2012	Abstract only; testing method of nebulization; no placebo group
Goebel 2000	No placebo group
Gomez-y-Lopez 2007	No placebo group
Gonzalez 1994	No placebo group
Hammer 1995	Not a RCT; no placebo group
John 2006	No placebo group
John 2010	No placebo group
Kadir 2009	No placebo group and not blinded
Karaatmaca 2010	Abstract only
Kim 2011	No placebo group
Langley 2005	No placebo group
Luo 2003	No placebo group; quasi-experimental; not fully randomized
Luo 2010	No placebo group
Luo 2012	No placebo group
Mandelberg 2003	No placebo group
Menon 1995	No placebo group
Milner 1995	Data not provided
Modaressi 2012	No placebo group
Modl 2005	Not randomized or placebo-controlled
Mull 2004	No placebo group
Ndrepepa 1998	Poster abstract only, available only in Turkish
Numa 2001	Not a RCT; no placebo group; epinephrine only

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Study	Reason for exclusion
Ozyurek 2002	No placebo group
Ralston 2008	Nasal phenylephrine, not used as a bronchodilator
Ray 2002	No placebo group
Reijonen 1995	No placebo group
Ren 2011	Poster abstract only
Sanchez 1993	Not a RCT; no placebo group
Sarrell 2002	No placebo group
Schuh 1992	No placebo group
Sezer 2010	Abstract only
Sharma 2013	No placebo group
Shu 2001	Not randomized
Simsek 2005	No placebo group; abstract only
Simsek-Kiper 2011	Nebulized epinephrine versus salbutamol; no placebo group
Sly 1991	Patients did not clearly have bronchiolitis
Soto 1985	Not a 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
Walsh 2008	Compared 3 doses of albuterol to 1 dose of epinephrine plus 2 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

RCT: randomized controlled trial

DATA AND ANALYSES

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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	25	1242	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.92, 0.06]
1.1 Inpatient studies	12	495	Mean Difference (IV, Random, 95% CI)	-0.62 [-1.40, 0.16]
1.2 Outpatient studies	13	747	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.61, 0.11]
2 Sub-analysis - oxygen saturation (outpatients treated with albuterol/salbutamol)	10	572	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.59, 0.21]
3 Improvement in clinical score (dichotomous)	7	365	Odds Ratio (M-H, Random, 95% CI)	0.18 [0.06, 0.50]
3.1 Inpatient	5	208	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.05, 0.79]
3.2 Outpatient	2	157	Odds Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.46]
4 Average clinical score after treatment: by treatment setting (continuous)	21	1086	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.54, -0.05]
4.1 Inpatient studies	9	416	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.41, 0.12]
4.2 Outpatient studies	12	670	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.79, -0.06]
5 Sub-analysis - average clinical score (outpatients treated with albuterol/salbutamol)	9	532	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.83, 0.11]
6 Hospital admission after treatment (outpatients treated with albuterol or salbutamol)	11	710	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.46, 1.21]
6.1 Nebulized	8	404	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.44, 1.33]
6.2 Oral in ED setting	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.21]
6.3 Oral at home	2	269	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.28, 2.64]
7 Duration of hospitalization (inpatients)	6	349	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.27, 0.39]

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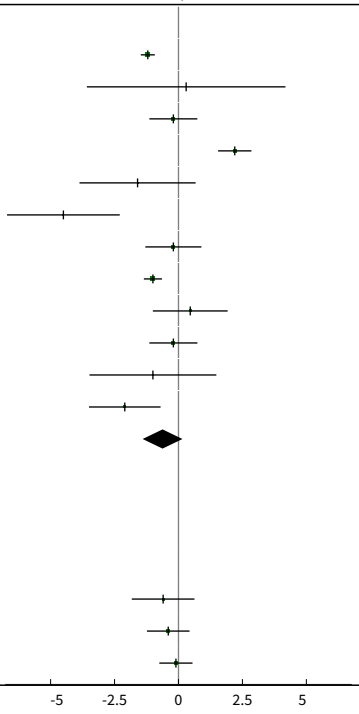
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Time to resolution of illness (outpatients)	2	269	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.43, 1.00]
9 Sensitivity analysis - oxygen saturation low risk of bias studies	15	793	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.75, 0.00]
9.1 Inpatient	4	210	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.77, 0.48]
9.2 Outpatient	11	583	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.66, 0.08]
10 Sensitivity analysis - average clinical score low risk of bias studies	15	734	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.41, -0.03]
10.1 Inpatient	5	228	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.35, 0.37]
10.2 Outpatient	10	506	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.54, -0.09]
11 Sensitivity analysis - average clinical score using RDAI (outpatients)	4	240	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.48, 0.25]

Analysis 1.1. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 1 Oxygen saturation measured by pulse oximetry: inpatient and outpatient settings.

Study or subgroup	Placebo N	Placebo Mean(SD)	Bronchodilator N	Bronchodilator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 Inpatient studies							
Chevallier 1995	17	93.2 (0.4)	16	94.4 (0.4)		6.47%	-1.2[-1.47,-0.93]
Dobson 1998	29	93.5 (6)	23	93.2 (7.8)		1.28%	0.3[-3.58,4.18]
Gurkan 2004	12	95.6 (1.2)	18	95.8 (1.4)		5.32%	-0.2[-1.14,0.74]
Ho 1991	8	97.6 (0.7)	13	95.4 (0.8)		5.91%	2.2[1.55,2.85]
Karadag 2005 - IPR	11	92.2 (2.6)	22	93.8 (4)		2.73%	-1.6[-3.87,0.67]
Karadag 2005 - SAL	12	92.2 (2.6)	24	96.7 (4.1)		2.83%	-4.5[-6.7,-2.3]
Lines 1990	23	95.6 (2)	26	95.8 (1.9)		4.96%	-0.2[-1.3,0.9]
Lines 1992	14	93 (0.4)	17	94 (0.6)		6.39%	-1[-1.35,-0.65]
Patel 2002	48	96.2 (3.3)	51	95.8 (4.1)		4.16%	0.46[-1,1.92]
Tinsa 2009	19	97 (1.3)	16	97.2 (1.5)		5.31%	-0.2[-1.14,0.74]
Totapally 2002	9	94 (2.4)	10	95 (3.1)		2.45%	-1[-3.48,1.48]
Wang 1992	17	95.1 (2.7)	40	97.2 (1.8)		4.29%	-2.1[-3.5,-0.7]
Subtotal * **	**219**		**276**			**52.11%**	**-0.62[-1.4,0.16]**
Heterogeneity: Tau^2=1.36; Chi^2=112.89, df=11(P<0.0001); I^2=90.26%							
Test for overall effect: Z=1.57(P=0.12)							
1.1.2 Outpatient studies							
Alario 1992	37	94.8 (3.1)	37	95.4 (2.2)		4.67%	-0.6[-1.82,0.62]
Anil 2010 SAL 0.9%	18	98.7 (1.2)	36	99.1 (1.9)		5.55%	-0.4[-1.23,0.43]
Anil 2010 SAL 3%	19	98.7 (1.2)	36	98.8 (1.1)		5.92%	-0.1[-0.75,0.55]



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Study or subgroup	Placebo N	Placebo Mean(SD)	Bronchodilator N	Bronchodilator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Can 1998	52	95 (1.9)	52	93.9 (16.3)		1.02%	1.1[-3.36,5.56]
Gadomski 1994a - neb	32	94 (4.4)	32	94 (4.1)		3.01%	0[-2.08,2.08]
Gadomski 1994a - oral	32	94 (3.4)	32	93 (5)		2.99%	1[-1.09,3.09]
Gadomski 1994b - neb	18	97 (2)	21	97 (2)		4.6%	0[-1.26,1.26]
Gadomski 1994b - oral	22	97 (2)	15	98 (2)		4.48%	-1[-2.31,0.31]
Ipek 2011	30	96.3 (3.4)	30	96.1 (3.1)		3.8%	0.23[-1.41,1.87]
Klassen 1991	41	95 (4)	42	95 (4)		3.64%	0[-1.72,1.72]
Ralston 2005	25	89.3 (6.8)	23	88.5 (5.1)		1.61%	0.8[-2.56,4.16]
Schuh 1990	19	95.9 (2.3)	21	96.1 (2.2)		4.29%	-0.2[-1.6,1.2]
Schweich 1992	12	91.8 (3.8)	13	95.1 (2.7)		2.3%	-3.3[-5.9,-0.7]
Subtotal * **	**357**		**390**			**47.89%**	**-0.25[-0.61,0.11]**
Heterogeneity: Tau²=0; Chi²=9.89, df=12(P=0.63); I²=0%							
Test for overall effect: Z=1.38(P=0.17)							
Total * **	**576**		**666**			**100%**	**-0.43[-0.92,0.06]**
Heterogeneity: Tau²=0.95; Chi²=128.83, df=24(P<0.0001); I²=81.37%							
Test for overall effect: Z=1.71(P=0.09)							
Test for subgroup differences: Chi²=0.71, df=1 (P=0.4), I²=0%							

Favours treatment -5 -2.5 0 2.5 5 Favours placebo

Analysis 1.2. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 2 Sub-analysis - oxygen saturation (outpatients treated with albuterol/salbutamol).

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Anil 2010 SAL 0.9%	18	98.7 (1.2)	36	99.1 (1.9)		23.31%	-0.4[-1.23,0.43]
Anil 2010 SAL 3%	19	98.7 (1.2)	36	98.8 (1.1)		38.42%	-0.1[-0.75,0.55]
Can 1998	52	95 (1.9)	52	93.9 (16.3)		0.81%	1.1[-3.36,5.56]
Gadomski 1994a - neb	32	94 (4.4)	32	94 (4.1)		3.72%	0[-2.08,2.08]
Gadomski 1994b - neb	18	97 (2)	21	97 (2)		10.18%	0[-1.26,1.26]
Ipek 2011	30	96.3 (3.4)	30	96.1 (3.1)		6.03%	0.23[-1.41,1.87]
Klassen 1991	41	95 (4)	42	95 (4)		5.45%	0[-1.72,1.72]
Ralston 2005	25	89.3 (6.8)	23	88.5 (5.1)		1.43%	0.8[-2.56,4.16]
Schuh 1990	19	95.9 (2.3)	21	96.1 (2.2)		8.26%	-0.2[-1.6,1.2]
Schweich 1992	12	91.8 (3.8)	13	95.1 (2.7)		2.38%	-3.3[-5.9,-0.7]
Total * **	**266**		**306**			**100%**	**-0.19[-0.59,0.21]**
Heterogeneity: Tau²=0; Chi²=6.88, df=9(P=0.65); I²=0%							
Test for overall effect: Z=0.94(P=0.35)							

Favours treatment -10 -5 0 5 10 Favours placebo

Analysis 1.3. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 3 Improvement in clinical score (dichotomous).

Study or subgroup	Bronchodilator n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 Inpatient					

Favours treatment 0.002 0.1 1 10 500 Favours placebo

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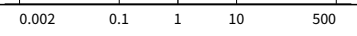
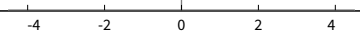
Study or subgroup	Bronchodilator n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Henry 1983	16/34	17/32		17.35%	0.78[0.3,2.06]
Lines 1990	4/26	19/23		14.23%	0.04[0.01,0.17]
Lines 1992	5/17	7/14		14.45%	0.42[0.09,1.83]
Mallol 1987	4/31	12/15		13.51%	0.04[0.01,0.19]
Tal 1983	3/8	4/8		11.66%	0.6[0.08,4.4]
Subtotal (95% CI)	**116**	**92**		**71.2%**	**0.2[0.05,0.79]**
Total events: 32 (Bronchodilator), 59 (Placebo)					
Heterogeneity: Tau^2=1.86; Chi^2=17.63, df=4(P=0); I^2=77.31%					
Test for overall effect: Z=2.29(P=0.02)					
1.3.2 Outpatient					
Alario 1992	18/38	35/36		11.19%	0.03[0,0.21]
Klassen 1991	20/42	30/41		17.61%	0.33[0.13,0.84]
Subtotal (95% CI)	**80**	**77**		**28.8%**	**0.11[0.01,1.46]**
Total events: 38 (Bronchodilator), 65 (Placebo)					
Heterogeneity: Tau^2=2.89; Chi^2=5.28, df=1(P=0.02); I^2=81.04%					
Test for overall effect: Z=1.67(P=0.09)					
Total (95% CI)	**196**	**169**		**100%**	**0.18[0.06,0.5]**
Total events: 70 (Bronchodilator), 124 (Placebo)					
Heterogeneity: Tau^2=1.37; Chi^2=22.87, df=6(P=0); I^2=73.76%					
Test for overall effect: Z=3.29(P=0)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%					



Favours treatment — Favours placebo

Analysis 1.4. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 4 Average clinical score after treatment: by treatment setting (continuous).

Study or subgroup	Bronchodilator N	Bronchodilator Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.4.1 Inpatient studies							
Goh 1997	60	3.2 (1.7)	29	3.1 (1.8)		5.57%	0.06[-0.39,0.5]
Gurkan 2004	18	4.2 (0.8)	12	4.7 (0.8)		4.16%	-0.61[-1.36,0.14]
Karadag 2005 - IPR	22	4.9 (1.8)	11	5.3 (1.4)		4.26%	-0.23[-0.96,0.49]
Karadag 2005 - SAL	24	4.1 (1.4)	12	5.3 (1.4)		4.28%	-0.84[-1.56,-0.12]
Patel 2002	51	5.3 (2.9)	48	6.2 (3)		5.78%	-0.28[-0.68,0.11]
Scarlett 2012	10	4.9 (2.9)	10	2.8 (2.2)		3.48%	0.78[-0.14,1.7]
Tinsa 2009	16	4.7 (2.4)	19	4.6 (1.3)		4.53%	0.05[-0.61,0.72]
Totapally 2002	10	1 (0.7)	9	0.6 (0.8)		3.49%	0.48[-0.44,1.39]
Wang 1992	38	2.8 (1.5)	17	3.2 (1.7)		4.96%	-0.25[-0.83,0.32]
Subtotal ***	**249**		**167**			**40.51%**	**-0.14[-0.41,0.12]**
Heterogeneity: Tau^2=0.06; Chi^2=12.49, df=8(P=0.13); I^2=35.96%							
Test for overall effect: Z=1.06(P=0.29)							
1.4.2 Outpatient studies							
Alario 1992	17	17.5 (4.2)	20	22.4 (5.1)		4.41%	-1.02[-1.71,-0.33]
Anil 2010 SAL 0.9%	36	1.5 (1.4)	18	1.8 (1.4)		4.99%	-0.21[-0.78,0.36]
Anil 2010 SAL 3%	36	2.3 (0.9)	19	1.8 (1.4)		5.01%	0.45[-0.11,1.01]
Can 1998	52	5.2 (1.8)	52	10.2 (3.5)		5.51%	-1.78[-2.24,-1.33]



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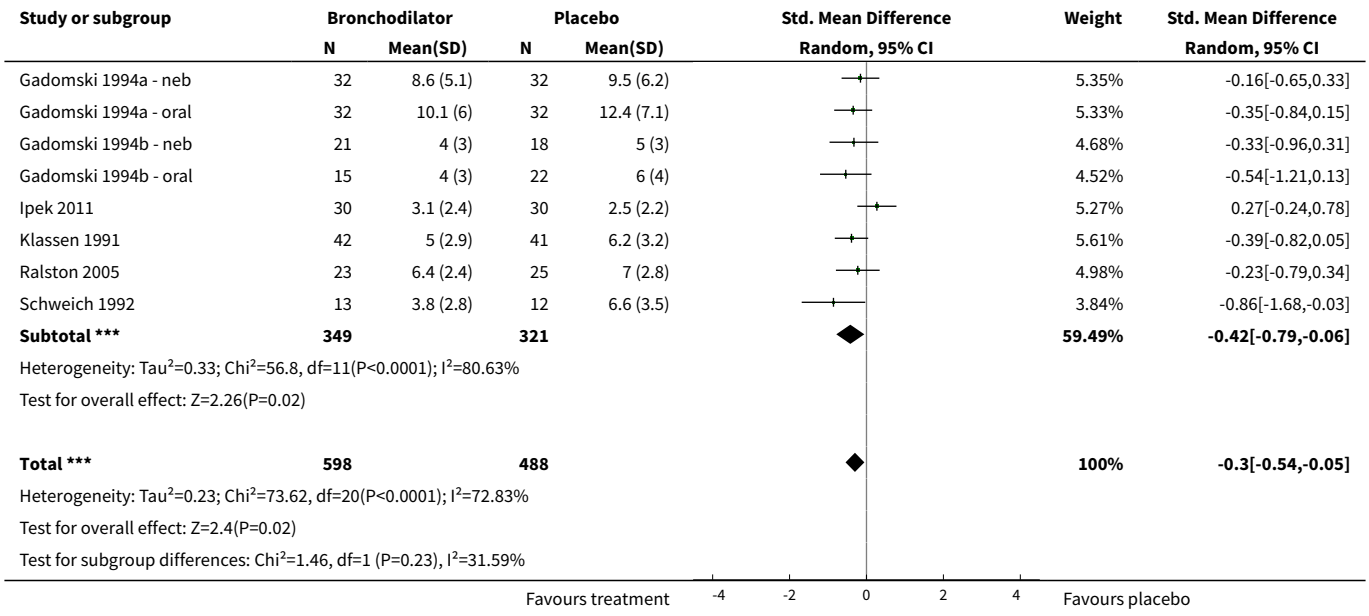
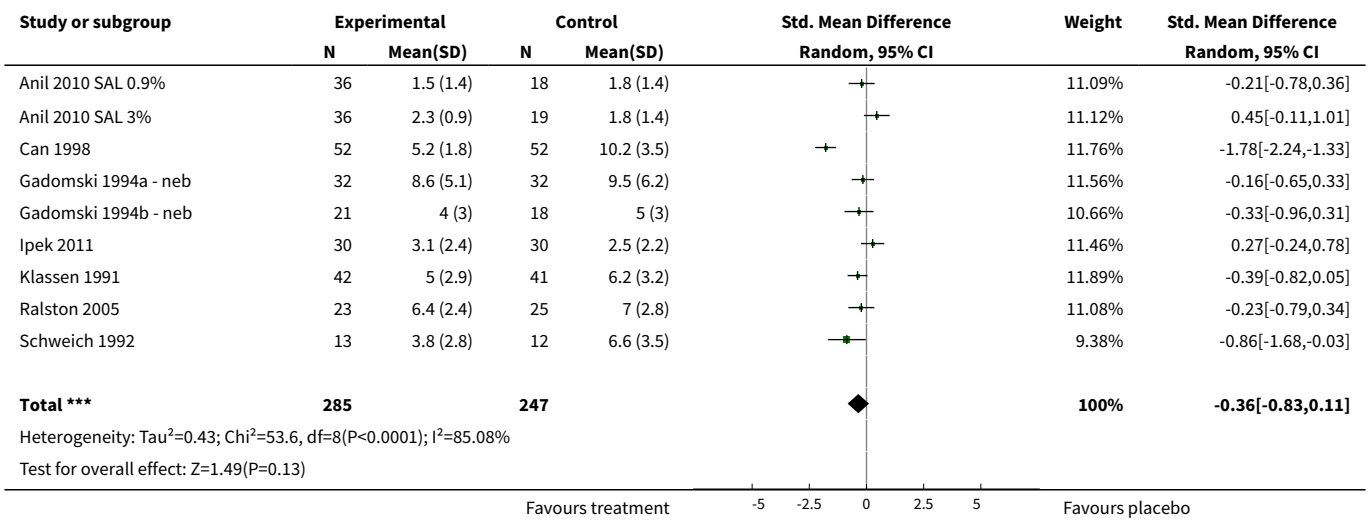


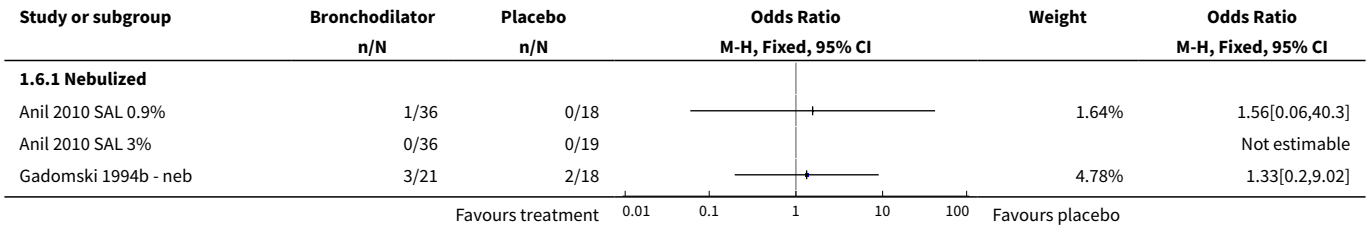
Study or subgroup	Bronchodilator N	Bronchodilator Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Gadomski 1994a - neb	32	8.6 (5.1)	32	9.5 (6.2)		5.35%	-0.16[-0.65,0.33]
Gadomski 1994a - oral	32	10.1 (6)	32	12.4 (7.1)		5.33%	-0.35[-0.84,0.15]
Gadomski 1994b - neb	21	4 (3)	18	5 (3)		4.68%	-0.33[-0.96,0.31]
Gadomski 1994b - oral	15	4 (3)	22	6 (4)		4.52%	-0.54[-1.21,0.13]
Ipek 2011	30	3.1 (2.4)	30	2.5 (2.2)		5.27%	0.27[-0.24,0.78]
Klassen 1991	42	5 (2.9)	41	6.2 (3.2)		5.61%	-0.39[-0.82,0.05]
Ralston 2005	23	6.4 (2.4)	25	7 (2.8)		4.98%	-0.23[-0.79,0.34]
Schweich 1992	13	3.8 (2.8)	12	6.6 (3.5)		3.84%	-0.86[-1.68,-0.03]
Subtotal * **	**349**		**321**			**59.49%**	**-0.42[-0.79,-0.06]**
Heterogeneity: Tau^2=0.33; Chi^2=56.8, df=11(P<0.0001); I^2=80.63%							
Test for overall effect: Z=2.26(P=0.02)							
Total * **	**598**		**488**			**100%**	**-0.3[-0.54,-0.05]**
Heterogeneity: Tau^2=0.23; Chi^2=73.62, df=20(P<0.0001); I^2=72.83%							
Test for overall effect: Z=2.4(P=0.02)							
Test for subgroup differences: Chi^2=1.46, df=1 (P=0.23), I^2=31.59%							

Analysis 1.5. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 5 Sub-analysis - average clinical score (outpatients treated with albuterol/salbutamol).



Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Anil 2010 SAL 0.9%	36	1.5 (1.4)	18	1.8 (1.4)		11.09%	-0.21[-0.78,0.36]
Anil 2010 SAL 3%	36	2.3 (0.9)	19	1.8 (1.4)		11.12%	0.45[-0.11,1.01]
Can 1998	52	5.2 (1.8)	52	10.2 (3.5)		11.76%	-1.78[-2.24,-1.33]
Gadomski 1994a - neb	32	8.6 (5.1)	32	9.5 (6.2)		11.56%	-0.16[-0.65,0.33]
Gadomski 1994b - neb	21	4 (3)	18	5 (3)		10.66%	-0.33[-0.96,0.31]
Ipek 2011	30	3.1 (2.4)	30	2.5 (2.2)		11.46%	0.27[-0.24,0.78]
Klassen 1991	42	5 (2.9)	41	6.2 (3.2)		11.89%	-0.39[-0.82,0.05]
Ralston 2005	23	6.4 (2.4)	25	7 (2.8)		11.08%	-0.23[-0.79,0.34]
Schweich 1992	13	3.8 (2.8)	12	6.6 (3.5)		9.38%	-0.86[-1.68,-0.03]
Total * **	**285**		**247**			**100%**	**-0.36[-0.83,0.11]**
Heterogeneity: Tau^2=0.43; Chi^2=53.6, df=8(P<0.0001); I^2=85.08%							
Test for overall effect: Z=1.49(P=0.13)							

Analysis 1.6. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 6 Hospital admission after treatment (outpatients treated with albuterol or salbutamol).



Study or subgroup	Bronchodilator n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Nebulized					
Anil 2010 SAL 0.9%	1/36	0/18		1.64%	1.56[0.06,40.3]
Anil 2010 SAL 3%	0/36	0/19			Not estimable
Gadomski 1994b - neb	3/21	2/18		4.78%	1.33[0.2,9.02]

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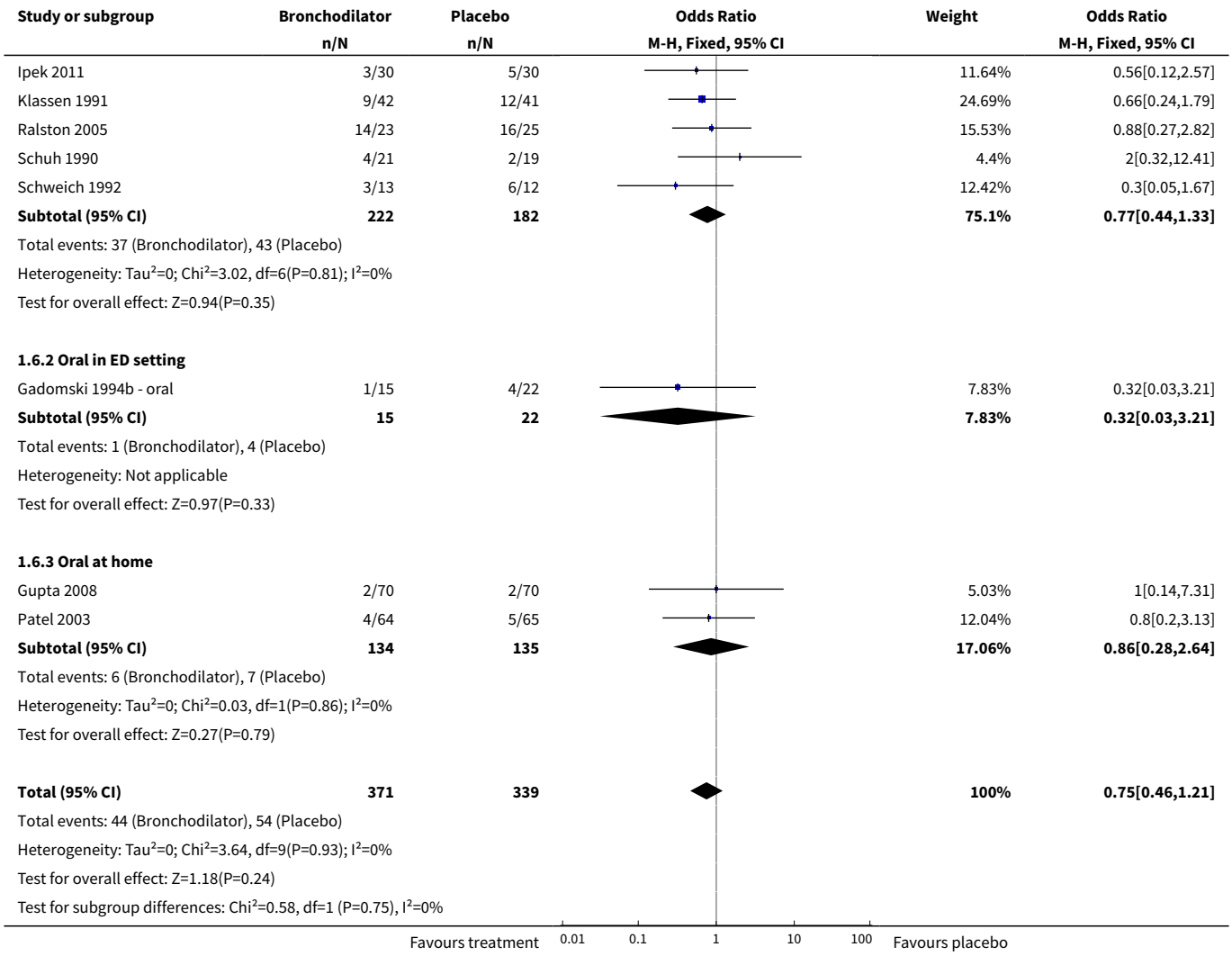
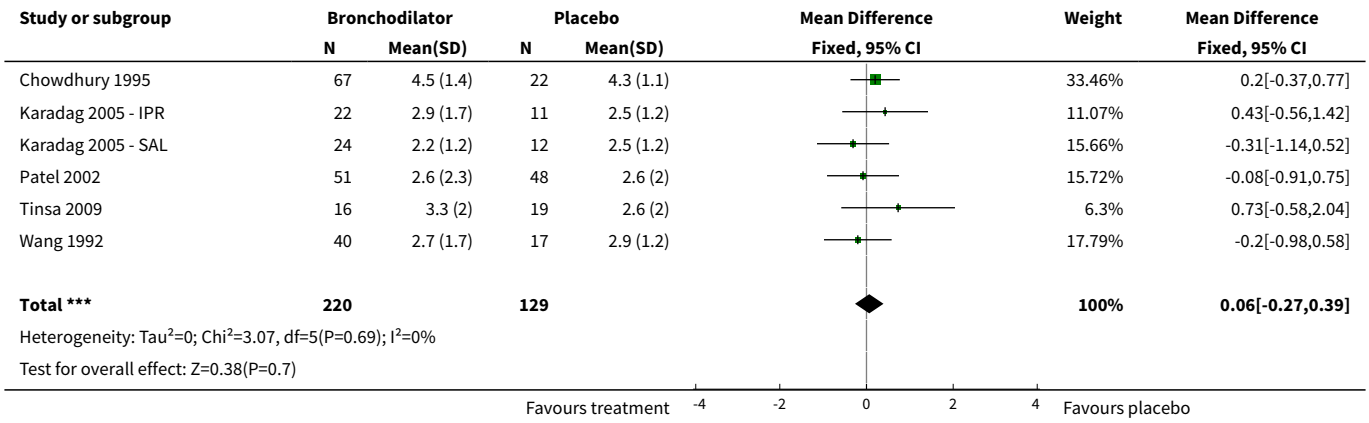


Analysis 1.7. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 7 Duration of hospitalization (inpatients).



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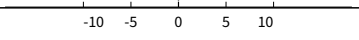
Analysis 1.8. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 8 Time to resolution of illness (outpatients).

Study or subgroup	Bronchodilator N	Bronchodilator Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gupta 2008	70	5.2 (2.6)	70	5 (2.5)		71.25%	0.2[-0.64,1.04]
Patel 2003	64	8.9 (4)	65	8.4 (3.7)		28.75%	0.5[-0.83,1.83]
Total ***	**134**		**135**			**100%**	**0.29[-0.43,1]**
Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.71); I²=0%							
Test for overall effect: Z=0.79(P=0.43)							



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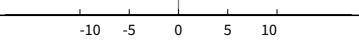
Analysis 1.9. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 9 Sensitivity analysis - oxygen saturation low risk of bias studies.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.9.1 Inpatient							
Patel 2002	48	96.2 (3.3)	51	95.8 (4.1)		5.74%	0.46[-1,1.92]
Tinsa 2009	19	97 (1.3)	16	97.2 (1.5)		11.64%	-0.2[-1.14,0.74]
Totapally 2002	9	94 (2.4)	10	95 (3.1)		2.19%	-1[-3.48,1.48]
Wang 1992	17	95.1 (2.7)	40	97.2 (1.8)		6.18%	-2.1[-3.5,-0.7]
Subtotal ***	**93**		**117**			**25.75%**	**-0.65[-1.77,0.48]**
Heterogeneity: Tau²=0.74; Chi²=7.21, df=3(P=0.07); I²=58.37%							
Test for overall effect: Z=1.13(P=0.26)							
1.9.2 Outpatient							
Alario 1992	37	94.8 (3.1)	37	95.4 (2.2)		7.72%	-0.6[-1.82,0.62]
Anil 2010 SAL 0.9%	18	98.7 (1.2)	36	99.1 (1.9)		13.78%	-0.4[-1.23,0.43]
Anil 2010 SAL 3%	19	98.7 (1.2)	36	98.8 (1.1)		18.72%	-0.1[-0.75,0.55]
Gadomski 1994a - neb	32	94 (4.4)	32	94 (4.1)		3.03%	0[-2.08,2.08]
Gadomski 1994a - oral	32	94 (3.4)	32	93 (5)		3%	1[-1.09,3.09]
Gadomski 1994b - neb	18	97 (2)	21	97 (2)		7.38%	0[-1.26,1.26]
Gadomski 1994b - oral	22	97 (2)	15	98 (2)		6.89%	-1[-2.31,0.31]
Klassen 1991	41	95 (4)	42	95 (4)		4.3%	0[-1.72,1.72]
Ralston 2005	25	89.3 (6.8)	23	88.5 (5.1)		1.22%	0.8[-2.56,4.16]
Schuh 1990	19	95.9 (2.3)	21	96.1 (2.2)		6.19%	-0.2[-1.6,1.2]
Schweich 1992	12	91.8 (3.8)	13	95.1 (2.7)		2%	-3.3[-5.9,-0.7]
Subtotal ***	**275**		**308**			**74.25%**	**-0.29[-0.66,0.08]**
Heterogeneity: Tau²=0; Chi²=9.17, df=10(P=0.52); I²=0%							
Test for overall effect: Z=1.52(P=0.13)							
Total ***	**368**		**425**			**100%**	**-0.38[-0.75,0]**
Heterogeneity: Tau²=0.09; Chi²=16.82, df=14(P=0.27); I²=16.78%							
Test for overall effect: Z=1.96(P=0.05)							
Test for subgroup differences: Chi²=0.35, df=1 (P=0.55), I²=0%							



Favours treatment — Favours placebo

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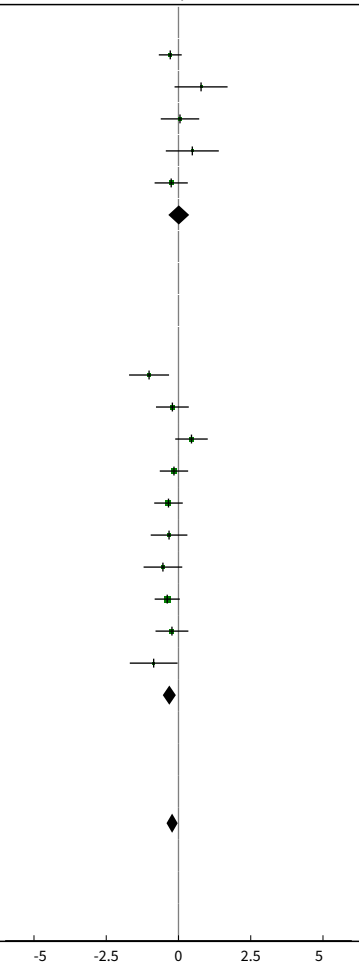
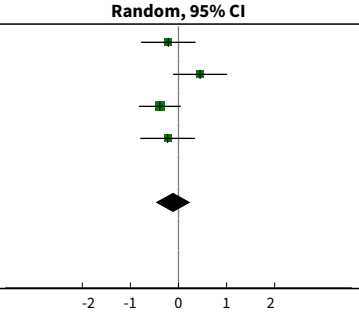
Analysis 1.10. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 10 Sensitivity analysis - average clinical score low risk of bias studies.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.10.1 Inpatient							
Patel 2002	51	5.3 (2.9)	48	6.2 (3)		10.44%	-0.28[-0.68,0.11]
Scarlett 2012	10	4.9 (2.9)	10	2.8 (2.2)		3.58%	0.78[-0.14,1.7]
Tinsa 2009	16	4.7 (2.4)	19	4.6 (1.3)		5.8%	0.05[-0.61,0.72]
Totapally 2002	10	1 (0.7)	9	0.6 (0.8)		3.58%	0.48[-0.44,1.39]
Wang 1992	38	2.8 (1.5)	17	3.2 (1.7)		7.04%	-0.25[-0.83,0.32]
Subtotal ***	**125**		**103**			**30.44%**	**0.01[-0.35,0.37]**
Heterogeneity: Tau²=0.06; Chi²=6.33, df=4(P=0.18); I²=36.79%							
Test for overall effect: Z=0.05(P=0.96)							
1.10.2 Outpatient							
Alario 1992	17	17.5 (4.2)	20	22.4 (5.1)		5.49%	-1.02[-1.71,-0.33]
Anil 2010 SAL 0.9%	36	1.5 (1.4)	18	1.8 (1.4)		7.14%	-0.21[-0.78,0.36]
Anil 2010 SAL 3%	36	2.3 (0.9)	19	1.8 (1.4)		7.21%	0.45[-0.11,1.01]
Gadomski 1994a - neb	32	8.6 (5.1)	32	9.5 (6.2)		8.45%	-0.16[-0.65,0.33]
Gadomski 1994a - oral	32	10.1 (6)	32	12.4 (7.1)		8.4%	-0.35[-0.84,0.15]
Gadomski 1994b - neb	21	4 (3)	18	5 (3)		6.19%	-0.33[-0.96,0.31]
Gadomski 1994b - oral	15	4 (3)	22	6 (4)		5.75%	-0.54[-1.21,0.13]
Klassen 1991	42	5 (2.9)	41	6.2 (3.2)		9.59%	-0.39[-0.82,0.05]
Ralston 2005	23	6.4 (2.4)	25	7 (2.8)		7.13%	-0.23[-0.79,0.34]
Schweich 1992	13	3.8 (2.8)	12	6.6 (3.5)		4.22%	-0.86[-1.68,-0.03]
Subtotal ***	**267**		**239**			**69.56%**	**-0.32[-0.54,-0.09]**
Heterogeneity: Tau²=0.05; Chi²=13.9, df=9(P=0.13); I²=35.23%							
Test for overall effect: Z=2.75(P=0.01)							
Total ***	**392**		**342**			**100%**	**-0.22[-0.41,-0.03]**
Heterogeneity: Tau²=0.05; Chi²=22.28, df=14(P=0.07); I²=37.15%							
Test for overall effect: Z=2.25(P=0.02)							
Test for subgroup differences: Chi²=2.26, df=1 (P=0.13), I²=55.77%							



Analysis 1.11. Comparison 1 Bronchodilators compared to placebo for treatment of acute bronchiolitis, Outcome 11 Sensitivity analysis - average clinical score using RDAI (outpatients).

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Anil 2010 SAL 0.9%	36	1.5 (1.4)	18	1.8 (1.4)		23.18%	-0.21[-0.78,0.36]
Anil 2010 SAL 3%	36	2.3 (0.9)	19	1.8 (1.4)		23.4%	0.45[-0.11,1.01]
Klassen 1991	42	5 (2.9)	41	6.2 (3.2)		30.28%	-0.39[-0.82,0.05]
Ralston 2005	23	6.4 (2.4)	25	7 (2.8)		23.14%	-0.23[-0.79,0.34]
Total ***	**137**		**103**			**100%**	**-0.11[-0.48,0.25]**
Heterogeneity: Tau²=0.06; Chi²=5.64, df=3(P=0.13); I²=46.79%							
Test for overall effect: Z=0.62(P=0.54)							



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APPENDICES

Appendix 1. Details of previous 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.

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

Embase.com

17. #13 AND #16
16. #14 OR #15
15. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((doubl* OR singl*) NEAR/2 (mask* OR blind*)):ab,ti
14. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
13. #3 AND #12
12. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
11. 'adrenergic agent':ab,ti OR 'adrenergic agents':ab,ti
10. 'adrenergic receptor stimulating agent'/exp
9. ipratropium:ab,ti
8. 'ipratropium bromide'/de
7. albuterol:ab,ti OR salbutamol:ab,ti
6. 'salbutamol'/exp
5. bronchodilat*:ab,ti
4. 'bronchodilating agent'/exp
3. #1 OR #2
2.

*:ab,ti
1. 'bronchiolitis'/exp

Appendix 2. Embase.com search strategy

#17 #3 AND #8 AND #16

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#16 #11 NOT #15
#15 #12 NOT #14
#14 #12 AND #13
#13 'human'/de
#12 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de
#11 #9 OR #10
#10 random*:ab,ti OR placebo*:ab,ti OR trial:ti OR allocat*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR (doubl* NEXT/1 blind*):ab,ti
#9 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#8 #4 OR #5 OR #6 OR #7
#7 albuterol:ab,ti OR salbutamol:ab,ti OR terbutaline:ab,ti OR ipratropium:ab,ti OR 'adrenergic agent':ab,ti OR 'adrenergic agents':ab,ti
#6 'salbutamol'/de OR 'terbutaline'/de OR 'ipratropium bromide'/de OR 'adrenergic receptor stimulating agent'/exp
#5 bronchodilator*:ab,ti
#4 'bronchodilating agent'/exp
#3 #1 OR #2
#2 bronchiolit*:ab,ti
#1 'bronchiolitis'/exp

FEEDBACK

Bronchodilators for bronchiolitis, 16 November 2014

Summary

It's not clear to me if bronchiolitis is affecting infants less than 12 months old, why the studies inclusion criteria was infants less than 24 months old? Older infants may have more bronchospasm than younger and they should be analyzed separately.

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Renato Cutrera MD, PhD
Chief Pediatric Respiratory Unit
Ospedale Pediatrico Bambino Gesù

WHAT'S NEW

Date	Event	Description
3 March 2015	Feedback has been incorporated	Feedback comment published

HISTORY

Review first published: Issue 4, 1998

Date	Event	Description
20 January 2014	New search has been performed	Searches updated. We included two new studies (Ipek 2011; Scarlett 2012) and excluded 17 new trials (Absar 2008; Alansari 2013; Barlas 1998; Belcastro 2010; Del Vecchio 2012; Florin 2012; Frasson 2012; Gonzalez 1994; John 2006; Karaatmaca 2010; Kim 2011; Luo 2012; Modaressi 2012; Ren 2011; Sezer 2010; Sharma 2013; Simsek-Kiper 2011).
20 January 2014	New citation required but conclusions have not changed	We expanded the sensitivity analyses to include studies using the Respiratory Distress Assessment Instrument. A subgroup analysis of albuterol and salbutamol did not change our conclusions. Four previously excluded studies of epinephrine versus placebo were omitted from this update (Hariprakash 2003; Kristjánsson

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Date	Event	Description
		1993; Lowell 1987; Wainwright 2003), due to the Cochrane Review 'Epinephrine for bronchiolitis' (Hartling 2011a).
27 May 2010	New citation required and conclusions have changed	A new review author joined the lead author to complete this update; additional outcome measures included; conclusions changed.
19 March 2010	New search has been performed	Searches conducted. Added to this update: five new studies were included, one previously excluded study was included and 12 new studies were excluded.
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 and 2014 updates, AG and Melissa (Brower) Scribani (MS) reviewed all the searches, selected studies, reviewed the included studies for risk of bias as well as outcomes and reviewed meta-analysis results. MS performed the meta-analysis and sensitivity analysis. AG contacted authors to request unpublished data and updated the text of the review.

DECLARATIONS OF INTEREST

Ann Gadomski is a trialist in included studies and is a member of the AAP Subcommittee on Diagnosis and Management of Bronchiolitis. Melissa Scribani: none known.

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. Two review authors assessed risk of bias and completed the 'Risk of bias' table for all studies in the 2010 update. We completed 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 in the 2010 update. We completed sensitivity

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analysis for studies using RDAI in the 2014 update. We added subgroup analyses limited to studies using either albuterol or salbutamol in 2014.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans; Infant; Infant, Newborn

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