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Short acting beta2-agonists for recurrent wheeze in children under two years of age (Review)

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[Intervention Review]

Short acting beta2-agonists for recurrent wheeze in children under two years of age

Richard JPG Chavasse¹, Paul Seddon², Anna Bara³, Michael C McKean⁴

¹Queen Mary's Hospital for Children, Carshalton, UK. ²Royal Alexandra Children's Hospital, Brighton, UK. ³Medical Research Unit, Clinical Trials Unit, London, UK. ⁴Paediatrics, Newcastle upon Tyne NHS Trust, Newcastle upon Tyne, UK

Contact address: Richard JPG Chavasse, Queen Mary's Hospital for Children, Wrythe Lane, Carshalton, SM5 1AA, UK.
richard.chavasse@epsom-sthelier.nhs.uk.

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ABSTRACT

Background

Wheeze is a common symptom in infancy and is a common cause for both primary care consultations and hospital admission. Beta2-adrenoceptor agonists (b2-agonists) are the most frequently used as bronchodilator but their efficacy is questionable.

Objectives

To determine the effectiveness of b2-agonist for the treatment of infants with recurrent and persistent wheeze.

Search methods

We identified relevant trials using the Cochrane Airways Group Specialised register composed of records identified in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and PUBMED. We used the following terms to search the database: Wheeze or asthma and Infant or Child and Short acting beta-agonist or Salbutamol (variants), Albuterol, Terbutaline (variants), Orciprenaline, Fenoterol.

Selection criteria

Randomised controlled trials comparing the effect of b2-agonist against placebo in children under two years of age who had two or more previous episodes of wheeze, not related to another form of chronic lung disease.

Data collection and analysis

Eight studies met the criteria for inclusion in this meta-analysis. The studies investigated patients in three settings: at home (three studies), in hospital (two studies) and in the pulmonary function laboratory (three studies). The main outcome measure was change in respiratory rate except for community based studies where symptom scores were used.

Main results

The studies were markedly heterogeneous and between study comparisons were limited. Improvement in respiratory rate, symptom score and oxygen saturation were noted in one study in the emergency department following two salbutamol nebulisers but this had no impact on hospital admission. There was a reduction in bronchial reactivity following salbutamol. There was no significant benefit from taking regular inhaled salbutamol on symptom scores recorded at home.

Authors' conclusions

There is no clear benefit of using b2-agonists in the management of recurrent wheeze in the first two years of life although there is conflicting evidence. At present, further studies should only be performed if the patient group can be clearly defined and there is a suitable outcome parameter capable of measuring a response.

PLAIN LANGUAGE SUMMARY**Short acting beta2-agonists for recurrent wheeze in children under two years of age**

Beta-agonists such as salbutamol are the most frequently prescribed reliever medication for asthma. They work well in adults and children but their effectiveness in infants is less clear. Eight trials were reviewed involving 229 patients in four different settings. Although infants have the capability to respond to salbutamol, there is only limited relief of acute symptoms when given to acutely ill patients. This did not impact on requirement for hospital admission or length of hospital stay. Regular salbutamol has not been shown to offer protection against developing symptoms.

BACKGROUND

Wheeze in infancy is a common symptom and the prevalence has increased over the past 25 years (Strachan 1995). Between 30 and 40% of infants wheeze at some time during the first six years of life (Martinez 1995). Acute wheeze is a common cause for admission to hospital as well as being a major burden on the primary care health service (Strachan 1995), however the majority of infants (60%) wheeze transiently and are asymptomatic by six years of age (Martinez 1995).

The aetiology of wheeze in infancy is varied. In young children, recurrent wheeze is commonly associated with viral upper and lower respiratory tract infections and less frequently with atopy, which is usually associated with asthma in older age groups (Silverman 1995). Maternal smoking during pregnancy also predisposes infants to obstructive lung disease and congenital small airways (Tager 1993). Postnatal smoke exposure from either parent predisposes children to recurrent wheeze due to recurrent upper respiratory tract infections. Less frequently, other forms of chronic lung disease, such as cystic fibrosis and bronchopulmonary dysplasia, may also present with wheeze. The various aetiologies of infant wheeze are likely to be associated with different responses to interventions (Silverman 1995).

The available treatments for wheeze in infancy have generally been medications that have proved successful in treating asthma in adults and older children. The previous assumption that 'all that wheezes is asthma' has led to the frequent use of bronchodilators and preventers (i.e. inhaled corticosteroids) in patients under two years of age. Beta2-adrenoceptor agonists (b2-agonists), such as salbutamol, are the main group of bronchodilators used in the older population. The response to b2-agonists in a heterogeneous group of children under two years of age has not been well quantified, so clinicians do not have any firm research to base their treatment decisions. Nevertheless, they remain the most frequently prescribed medication for wheeze in this age-group (Chavasse 1999b) and are the recommended treatment in many international guidelines (BTS 1997, NIH 1997). Suggested reasons for perceived lack of efficacy include the difficulty in the effective administration of the drug, immaturity of the b2-receptors in the bronchial wall smooth muscle, airway obstruction caused more by virus-induced airway inflammation and oedema rather than smooth muscle constriction (Clough 1993), and congenitally small airway calibre in infants associated with antenatal passive smoking.

b2-agonists are used frequently as bronchodilators for children under the age of two years with recurrent wheezing. This review was designed to test whether there is evidence to support this treatment in patients under two years of age with recurrent wheeze (defined as greater than two episodes of wheeze)?

OBJECTIVES

To determine the effectiveness of inhaled beta-agonist for the treatment of infants with recurrent and persistent wheeze associated with or without upper respiratory tract viral infections.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing the effect of b2-agonist against that of placebo in children under two years of age who fulfil the criteria. Studies encompassing the management of recurrent wheeze at home, in the emergency department or on the ward were included. Response to beta-agonist using pulmonary function tests in this group of patients was also considered.

Types of participants

To be included, children had to be under two years of age. They had to have had two or more episodes of wheeze which was not related to another form of chronic lung disease (i.e. chronic lung disease of prematurity, bronchopulmonary dysplasia and cystic fibrosis). Studies of first episode of wheeze, frequently related to acute viral bronchiolitis were excluded. Children born before 34 weeks of gestation or with neonatal respiratory illness were excluded.

Types of interventions

The randomised administration of a single or multiple doses of nebulised, inhaled or oral beta-agonist versus placebo.

Types of outcome measures

The main primary outcome was the change in respiratory rate following treatment. This is a basic sign and is recorded in all physical examinations. As respiratory rate is unlikely to be recorded in community studies in which the primary observer is not medically qualified, this has been substituted by symptom score, usually recorded in a parent held diary.

HOME:

Primary - Symptom score
Secondary - Admission rate, Percentage of symptom free days, Additional doses of bronchodilator required.

EMERGENCY DEPARTMENT:

Primary - Change in respiratory rate.
Secondary - Oxygen saturation, heart rate, and admission rate.

HOSPITAL WARD:

Primary - Change in respiratory rate.
Secondary - Oxygen saturation, heart rate and length of hospital stay.

PULMONARY FUNCTION:

Primary - Change in respiratory rate.
Secondary - Change forced expiratory flow, airway resistance or conductance and lung volumes and bronchial hyperreactivity.

Search methods for identification of studies

We identified relevant trials using the Cochrane Airways Group trials register based on Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and PUBMED. The database search used the following terms:

Wheeze or asthma and Infant or Child and Short acting beta-agonist or Salbutamol (variants), Albuterol, Terbutaline (variants), Orciprenaline, Fenoterol

Data collection and analysis

We obtained full text copies of all the trials which clearly or potentially fulfil the inclusion criteria. Two reviewers (RCA, PS) independently assessed the trials for inclusion. There was no disagreement between the reviewers.

The methodology of the trials was assessed for adequacy of concealment using the Cochrane approach:

A = Adequate

B = Uncertain

C = Clearly inadequate

We also ascertained reported methodology independently using two reviewers with the Jadad's score ([Jadad 1996](#)). Any disagreement was dealt with by consensus or by the opinion of a third party. We contacted authors of all included trials to confirm methodology and data extraction and grouped the studies into parallel and crossover design. We included data from the crossover studies as the difference between active and placebo arms, except one trial in which the original analysis had included analysis of the first arm separately from the crossover study and only this parallel data was included in the review ([Kraemer 1991](#)).

RESULTS

Description of studies

Eight studies met the criteria for inclusion. The patients included in these studies were all under two years of age. They had a previous history of wheeze, with no apparent history of acute viral bronchiolitis. The studies investigated patients in three settings: at home (three studies), in hospital (two studies) and in the pulmonary function laboratory (three studies).

The studies varied in design, with five being parallel group and three being crossover. The drug delivery system also varied with four using metered dose inhaler with spacer and mask and three using nebulisers. One study used oral syrup. The outcomes varied in all studies with little comparable data.

The parallel group studies included a total of 213 participants. One hundred and four participants were studied at home, sixty-nine in hospital (twenty eight in the emergency room prior to admission, forty one following admission) and forty in the pulmonary function laboratory.

The crossover studies included a total of 68 participants. Forty-eight of these participants were included in one study in which all the participants were aged under one year at recruitment and were studied over an eight week period at home. The remaining participants were studied in the pulmonary function laboratory.

Three studies included a multiple dose strategy. Two of these used two activations of salbutamol (200 mcg) three times per day for four or six weeks via a Babyhaler and mask ([Chavasse 1999a](#); [Kraemer 1997](#) respectively). One used salbutamol syrup, 1 mg, three times per day for five days then as required for nine days ([Fox 1996](#)). The remaining five studies followed a single dose strategy, two used two

doses of nebulised salbutamol at a dose of 0.15 mg/kg ([Prahl 1986](#); [Bentur 1992](#)), one a single nebulised dose of 2.5 mg ([Prendiville 1987a](#)), one an inhaled dose of 800 mcg ([Clarke 1993](#)) and one 600 mcg by inhaler and spacer ([Kraemer 1991](#)).

We considered in total twenty-nine other studies for inclusion but excluded them. Nine studies were excluded as the participants recruited were heterogeneous with a proportion having acute viral bronchiolitis and others recurrent episodes of wheeze. Three were excluded on the basis that the age range of participants recruited extended beyond two years although the authors have been contacted to extract any relevant data. Sixteen studies were excluded due to lack of an adequate control group (six) or randomisation (10) or both (see table of excluded studies). One study only enrolled healthy subjects.

Risk of bias in included studies

[Bentur 1992](#): Grade B, Jadad score 4.

From publication, randomisation not described, blinding described.

[Chavasse 1999a](#): Grade A, Jadad score 5.

From author and publication, randomisation by computer generated code concealed in sealed envelopes. Blinding described.

[Clarke 1993](#): Grade B, Jadad score 3.

From publication, randomisation and blinding not described. Concealment not described.

[Fox 1996](#): Grade B, Jadad score 4.

From publication, randomisation not described. Blinding by double dummy. Concealment not described.

[Kraemer 1991](#): Grade B, Jadad score 3.

From publication, randomisation not described. Blinding described. Concealment not described.

[Kraemer 1997](#): Grade B, Jadad score 3.

From publication, randomisation, blinding and concealment not described.

[Prahl 1986](#): Grade B, Jadad score 2.

From publication, randomisation, blinding and concealment not described.

[Prendiville 1987a](#): Grade B, Jadad score 2.

From publication, randomisation, blinding and concealment not described.

Effects of interventions

We identified thirty-seven trials of B2-agonists in infants, from which eight were found to be randomised controlled trials. We extracted results from six of the eight papers. Data could not be extracted from the remaining two studies; [Clarke 1993](#) presented results as medians and [Prahl 1986](#) presented data as the absolute sum of all the scores for the whole group together without mean or standard deviation and thus no data was able to be entered using the Cochrane statistical software.

PARALLEL GROUP STUDIES

The results of the parallel group studies (Prahl 1986; Kraemer 1991; Bentur 1992; Fox 1996; Kraemer 1997) show a small overall response to salbutamol.

One study (Bentur 1992) was performed entirely in the emergency department during an acute exacerbation of wheeze. Twenty-eight participants were assessed following either 0.3 mg/kg salbutamol nebulised in two divided doses over one hour or placebo. The participants showed an improvement (fall) in respiratory rate of 7.7 breaths per minute following salbutamol compared to 2.6 breaths per minute following placebo, a difference of -5.1 breaths per minute, 95% CI -9.45 to -0.75). There was an improvement in symptom score (which assessed heart rate, respiratory rate, wheeze and accessory muscle on a zero to three scale) of 2.9 points following salbutamol versus 0.4 points following placebo (difference -2.5, 95% CI -3.88 to -1.12). There was an improvement in oxygen saturation of 1.3% after salbutamol compared to a deterioration of -0.3% following placebo (difference 1.6, 95% CI 0.33 to 2.87). Despite these beneficial effects, there was no significant effect on the requirement for hospital admission (Odds ratio (OR) 1.95, 95% CI 0.27 to 13.98).

Three other studies reported the effect of salbutamol on symptom scores (Prahl 1986; Fox 1996, Kraemer 1997). Fox used a score comprising cough, wheeze and breathlessness, with each variable scored from zero to three points twice daily by the parent. No difference was noted on any day of follow-up over a fourteen day period between participants receiving oral salbutamol 1 mg three times per day (tds) or placebo (Fox 1996). Kraemer used a score of cough, wheeze, sleep problems and expectorations also recorded in a diary by the parents. There was no significant change in mean score between the first ten days and the last ten days of the six week study period in participants receiving inhaled salbutamol 200 mcg tds (Kraemer 1997). Prahl 1986 recorded cough, wheeze, recession, nasal flaring, auscultation and respiratory rate with all variables scored from zero to three points. They reported only the total group scores and showed no difference in change in score between the group treated with 0.15 mg nebulised salbutamol compared to placebo. They were able to show an effect in children over eighteen months of age (Prahl 1986). None of these papers presented this data in a suitable form for meta-analysis using the Cochrane software. No paper reported respiratory rate as an outcome variable.

Three studies reported the number of 'responders' or 'non-responders'. Overall, 38/49 participants in the treatment groups were classified as responders compared to 15/43 in the control groups (OR 0.12, 95% CI 0.04 to 0.33). The definition of response varied between studies; Kraemer used a definition of a > 2 SD change in either thoracic gas volume (TGV) or airway conductance (Gaw) (Kraemer 1991; Kraemer 1997). Fox used a definition of re-admission during or symptoms persisting through the fourteen day follow-up period (Fox 1996). Two studies were conducted at home, one with inhaled salbutamol, 200 mcg tds for six weeks (Kraemer 1997), the other with oral salbutamol, 1 mg tds for five days, then as required for nine days (Fox 1996). The third study was of a three doses of inhaled salbutamol, 200 mcg at five minute intervals in the pulmonary function laboratory (Kraemer 1991).

In the pulmonary function laboratory, inhaled salbutamol, 200 mcg administered three times daily over fifteen minutes, was shown to

lower functional residual capacity (FRC) difference -9.3 ml/kg (95% CI -13.32 to -5.28) in participants identified with hyperinflation, and improve conductance 0.9 L/s/H2O/kg (95% CI 0.21 to 1.59) in those with an airway obstruction. Overall there was an improvement in specific conductance in both groups (hyperinflated difference 23.7, 95% CI 3.08 to 44.32, obstructed difference 13.7, 95% CI -3.48 to 30.88) (Kraemer 1991). Kraemer also measured TGV and sGaw before and after six weeks of inhaled salbutamol, 200 mcg tds and found no significant change in either parameter (Kraemer 1997).

CROSSOVER STUDIES

One study followed 48 participants at home during two, four-week treatment periods of regular inhaled salbutamol, 200 mcg tds or placebo (Chavasse 1999a). There was no difference in the mean daily symptom score (difference 0.12, 95% CI -0.71 to 0.95) or number of symptom free days (difference -0.52, -3.12 to 2.08) between the treatment periods. The symptom score was recorded by the parents in a diary, twice each day with both wheeze and cough being scored from zero to three. There was no difference in requirement for additional bronchodilator therapy (difference 0.01, 95% CI -0.11 to 0.13) between the treatment periods. The parents were unable to identify which inhaler contained salbutamol by assessing which inhaler had seemed the most beneficial to their child (OR 1.29, 95% CI 0.57 to 2.9). Ten other participants withdrew from this study due to clinical deterioration and although there was a slight excess of participants withdrawing during the placebo phase (hence indicating a possible benefit of salbutamol) this did not achieve statistical significance.

Prendiville studied five, symptom free participants in the lung function laboratory, each participant having two sets of tests performed on different days. There was no significant change in maximum flow at functional residual capacity (V'maxFRC) following 2.5 mg nebulised salbutamol compared to placebo (WMD -14.4, 95% CI -72.14 to 42.94). All five participants showed a marked reduction in reactivity to histamine challenge following salbutamol (Prendiville 1987a). Clarke also demonstrated a marked improvement in bronchial hyper-reactivity following 800 mcg inhaled salbutamol with the median PC30 (methacholine) increasing from 3.8 g/L (range 1.6 to 6.1) to 12.8 g/L (4.9 to 31). They also confirmed the findings of (Prendiville 1987a) that there was no significant improvement in V'maxFRC following salbutamol (Clarke 1993).

DISCUSSION

Bronchodilators and in particular b2-agonists are frequently used for the treatment of young children presenting with wheeze (Chavasse 1999b). The benefits of b2-agonists have been clearly demonstrated in children and adults. Thirty-five studies investigating the response to b2-agonist challenge in infants with recurrent wheeze were identified. A further thirty studies relating to bronchodilators in acute bronchiolitis (Kellner 1999) and twelve studies of anticholinergic bronchodilators (Everard 1999) were considered and excluded. Data from only six of the thirty-seven identified studies could be included in this review. Two randomised controlled trials had no data that could be analysed appropriately and twenty nine papers were either not adequate randomised controlled trials or failed to fulfil the inclusion criteria.

The protocol sought to exclude participants with a diagnosis of acute bronchiolitis. Eight studies were excluded because a

proportion of the recruits were found to have respiratory syncytial virus (RSV) on testing or had clinical findings of acute bronchiolitis (crepitations +/- wheeze) at the time of the study. Despite this it is impossible to be certain that all the participants included in any of the accepted trials had not had RSV at some time and that their ongoing symptoms were not sequelae of bronchiolitis. Such a distinction would in any case be meaningless since most children have encountered RSV by age age, though most will not have had clinical bronchiolitis. In most of the included studies virus testing was not performed.

All of the studies included some participants with a positive history of atopy, but in only two trials did all the participants fulfil this criteria (Kraemer 1991; Chavasse 1999a). A proportion of participants in each study were exposed to passive cigarette smoke both ante- and post-natally and no study excluded infants exposed to passive smoke as a different subgroup. At present, different phenotypes of wheezing infants are recognised and specific therapies may be more or less efficacious depending on this. Although the two studies which selected infants with a predisposition to atopy were negative, these infants are more likely to have symptoms persisting through childhood (Martinez 1995) and might be expected to be more likely to respond.

The results from one of the parallel group studies showed a small benefit from salbutamol (in the emergency department), although the overall improvement may not have been clinically important. Conversely, generally no benefit was documented from the crossover studies. Direct comparison between studies was rarely possible due to the different settings, outcome variables or dose and drug delivery method (see Table 1).

RESPIRATORY RATE

Only one study of the five performed in hospital documented the effect of b2-agonists on respiratory rate, despite this being a fundamental part of the physical examination. Respiratory rate was found to fall significantly following nebulised salbutamol during an acute exacerbation of wheeze in the receiving room. It was not associated with a reduction in admission rate. As with many clinical signs, respiratory rate may be affected by the state of arousal of the subject which may be altered by therapeutic intervention, and may simply vary with time between observations without change in clinical status.

SYMPTOM SCORES

In the one study performed in the emergency department, an improvement was recorded in symptom score (wheeze, accessory muscle score and respiratory rate) but this was not associated with a reduction in admission rate. An earlier study by the same author had also shown an improvement in symptom score following three nebulisers in the emergency department (Bentur 1990) and a modest improvement in clinical score was also found following two nebulisers (Holmgren 1992). Prahl 1986 found no overall group change in symptom score in participants who had been admitted to hospital.

Symptom scores were also measured in the three home based studies with symptoms recorded by the participants in diaries. Symptoms were scored between zero (no symptoms) and three (maximum symptom). All three studies measured cough and wheeze with a variety of additional symptoms. Chavasse 1999a

reported no difference in mean daily symptom score or symptom free days over a four week period in a crossover trial. Kraemer 1997 showed no change in mean symptom score or any component following six weeks of regular inhaled salbutamol and Fox 1996 reported no change in median symptom scores following two weeks of oral salbutamol in parallel group studies.

There is no clear evidence that salbutamol or other b2-agonists offer relief from symptoms in early life. The improvements of acute wheeze treated in the emergency department did not have any impact outcome or admission rate. Regular inhaled or oral salbutamol does not seem to modify daily symptoms or offer protection against exacerbations.

There are a number of different symptom scores reported in the literature comprising a number of different variables. A good scoring system for either use in hospital by clinicians or at home by medically untrained carers has to be easily attainable, reproducible and clinically significant (Yung 1996). Validation and reliability of many scores reported have not been formally evaluated and therefore clinical significance is uncertain. One clinical score developed Tal 1983 has recently been evaluated in relation to oxygen saturation showing a high sensitivity and specificity to predict hypoxia but this score was not used in any of the studies reviewed here (Pavon 1999). Different symptom scores cannot be combined in a meta-analysis. Changes in symptoms and signs may also be related to the state of arousal of the subject and thus may not reflect clinical change.

OXYGENATION

There was a marginal improvement in oxygen saturation of 1.6% (Bentur 1992). Five other studies have also measured a change in oxygenation following a dose of salbutamol. Three studies showed an apparent fall in saturation or partial pressure of oxygen between five and one hundred and forty minutes following the dose of salbutamol, but only one of these studies was randomised and blind (Prendiville 1987c; Seidenberg 1991; Clarke 1993). One study showed no significant change in saturation between attendance in the emergency room and discharge or admission one and a half hours later (Bentur 1990). Only one other trial has shown an improvement in partial pressure of oxygen, measured half an hour after two nebulised doses of salbutamol. The study was not randomised and only had a small placebo group (Holmgren 1992). An overall change in oxygen saturation of 1.6% is probably not clinically relevant and there is no other strong evidence to indicate benefit in oxygenation from salbutamol in the short term.

RESPONDERS

Three studies categorised participants as responders or non-responders. Significantly more showed a response to salbutamol compared to placebo. Fox 1996 defined a group of patients as treatment failures if they either required readmission during the follow up or had symptoms at fourteen days. Kraemer used a definition of treatment response of a change in pulmonary function (TGV or Gaw) of greater than two standard deviations (Kraemer 1991; Kraemer 1997).

Chavasse used a parent defined measure of response. In this study, parents were unable to identify a response to salbutamol by their child as they were unable to identify the salbutamol inhaler, any

more frequently than the placebo inhaler, as the one offering the most benefit (Chavasse 1999a).

There were different definitions of response including clinical and physiological outcomes. Comparisons and meta-analysis of the different definitions of response are contentious.

PULMONARY FUNCTION

Prendiville 1987a was unable to show any improvement in V'maxFRC, measured by the rapid thoraco-abdominal compression technique, following salbutamol but this was in only five patients. There was a significant increase in bronchial protection against histamine challenge. Clarke 1993 demonstrated similar results with no change in V'maxFRC following salbutamol inhalation but protection against methacholine challenge in a randomised controlled trial.

A lack of improvement in V'maxFRC following salbutamol was noted in two open studies (Seidenberg 1991; Chavasse 1999a) with a deterioration recorded in further one (Prendiville 1987b). Potential reasons why no response could be measured using V'maxFRC include:

1. The measurement of V'maxFRC is based on the assessment of functional residual capacity (FRC). FRC is dynamic and may change between measurements, particularly in disease states and following therapy. Change in FRC may invalidate comparison of pre and post bronchodilator measurements as flow would be assessed at different lung volumes.
2. The airway tone in infants may be temporarily reduced following treatment causing airway collapse and a reduction in flow.
3. The requirement for sedation restricts the time period during which measurements can be taken. A response may be missed due to the short time period between measurements. The phase of sleep may also affect the measurement.

A preliminary study performed using the raised volume rapid thoracic compression technique, a recent modification of the standard rapid thoraco-abdominal compression technique to standardise lung volume and reduce intra-observation variation, also showed no benefit (Hayden 1998a). This study was not randomised and had only a small control group of healthy patients and a small sub-group of wheezy infants who received placebo.

The primary outcome in studies by Prendiville and Clarke was the change in bronchial reactivity following salbutamol. V'maxFRC was used as the measure of response. In both studies there was a decrease in bronchial reactivity following salbutamol (Prendiville 1987a; Clarke 1993). An improved recovery following carbacol challenge was also shown following salbutamol by Orlowski 1991. In this study a measure of resistance was used to define response but the randomisation methodology was unclear. These studies provide evidence that there is a capability for response to induced bronchospasm, and that the airways must have B2 receptors. The difference in response between these and more clinical studies suggests that the clinical condition of recurrent wheeze (i.e. usually viral induced) has a different mechanism, such as airway oedema, compared to bronchial reactivity.

Other parameters of pulmonary mechanics have been measured with mixed response. Kraemer (Kraemer 1991; Kraemer 1997) showed an increase (improvement) in conductance following

salbutamol. In four studies no change in resistance (the reciprocal of conductance) could be measured (Radford 1975; Lenney 1978; Prendiville 1987b; Seidenberg 1991) and in two others there was a tendency to an increase (deterioration) in resistance (O'Callaghan 1986; Chavasse 1999a). Resistance was measured by plethysmography in four studies and by forced oscillation (Lenney 1978) and single breath occlusion (Chavasse 1999a) in one study each. Two recent studies using high speed interrupter technique to obtain impedance measurements have partitioned the respiratory system into airway and tissue components. These studies both showed a positive effect of salbutamol on airway mechanics, but neither trial was formally randomised or controlled (Hayden 1998(b); Jackson 1999).

No clear evidence of response to B2-agonists has been demonstrated by the currently available pulmonary function tests, however there is evidence of bronchoprotection against a chemical challenge. Infant pulmonary function tests are beset by a number of technical difficulties and theoretical assumptions that make interpretation more difficult and results potentially invalid, particularly in the presence of small airways disease. There is the potential that benefit may be missed due to the requirements of the testing procedures. Pulmonary function tests have not always been performed in the presence of symptoms (due to concern about of sedation) and this may also reduce a measurable response.

AUTHORS' CONCLUSIONS

Implications for practice

There is no clear benefit of using b2-agonists in the management of patients with recurrent wheeze in the first two years of life although the evidence is conflicting.

Difficulties in defining clear groups (phenotypes) of patients and the transient nature of the symptoms which often resolve spontaneously have confounded many studies. There are no suitable objective outcome parameters by which a response can be adequately measured. Clinical symptoms and signs are usually subjective thus varying between observers and can be affected by short term changes in the patient (i.e. state of arousal). The standard available pulmonary function tests for infants are probably not suitable to measure a response to a single dose challenge due to technical and theoretical problems.

The moderate improvement in symptoms noted in the emergency department (one study) did not impact on the requirement for hospital admission. The changes in bronchial hyperreactivity are not reflected in clinical practice and suggest only the potential to respond to b2-agonists. Regular b2-agonist offers no relief from regular symptoms, nor protection from exacerbation.

Implications for research

Further evidence is required to clarify the efficacy of b2-agonists but further studies should only be performed if:

- (1) The patient group can be clearly defined with, if possible a differentiation between episodic viral wheezers and persistent wheezers, with attention to atopic tendency and other contributory factors. Acute RSV disease should also be differentiated and considered as a separate entity.
- (2) The outcome parameter is suitable and capable of measuring a response. Ideally it should be quick and non-invasive, without the requirement for the patient to be sedated.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bentur 1992

Methods	Randomised, double blind, placebo controlled trial. Parallel design. Randomisation: Not described. Blinding: described. Concealment : Unclear. Jadad's score 4.	
Participants	28 participants. 13 treatment group, 15 placebo group. No withdrawals or dropouts. Age 3 - 24 months. Acutely symptomatic attending emergency department. 3 previous episodes of wheeze. Exclusions include CF, BPD, neonatal ventilation, aspiration,bronchiolitis and cardiac disorders.	
Interventions	Salbutamol (Albuterol) nebuliser 0.15mg/kg. 2 doses 1 hour apart. Placebo - nebulised normal saline.	
Outcomes	Respiratory rate, wheeze score, accessory muscle score, total symptom score, oxygen saturation, hospital admission rate	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Chavasse 1999a

Methods	Randomised, double blind, placebo controlled trial. Crossover design. Randomisation: Computer generated (PACT). Blinding: Unmarked identical active and placebo inhalers, distributed from pharmacy with coded prescription. Allocation concealment: Sealed envelope.	
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Chavasse 1999a (Continued)

Jadad's score 5.

Participants	80 participants. 48 completers. 32 defaulters. Age 3 - 12 months. Persistent or recurrent symptoms referred from outpatients and general practitioner. All had personal and/or first degree family history of atopy. 40% had parents who smoked. Exclusion criteria included other chronic lung disease, prematurity and neonatal ventilation and cardiac disorders.
Interventions	Salbutamol 200mcg inhaled three times per day for 4 weeks. MDI plus Babyhaler and mask. Placebo inhaler was propellant only.
Outcomes	Mean daily symptom score, symptom free days, additional bronchodilator treatment requirements. Parental preference as identification of most beneficial inhaler.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Investigators not aware as to order of treatment group assignment (Cochrane Grade A)

Clarke 1993

Methods	Randomised, double blind, placebo controlled trial. Crossover design. Randomisation: Not described. Blinding: Not described. Concealment unclear. Jadad's score 3.
Participants	15 participants. Age 8 - 23 months. Recurrent wheezing of at least 1 month. 50% had family history of atopy, 50% had mother who smoked. Exclusion of congenital or systemic disorder or CF.
Interventions	Salbutamol 800mcg inhaled. Single dose. Patients sedated with Triclofos. Methacholine commenced at 0.5g/l to maximum 32g/l.
Outcomes	Maximum flow at functional residual capacity. (V'maxFRC). Methacholine challenge (PC30)
Notes	Data presented as medians therefore unable to extract

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Fox 1996

Methods	Randomised, double blind, placebo controlled trial.
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Short acting beta2-agonists for recurrent wheeze in children under two years of age (Review)

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Fox 1996 (Continued)

Parallel group design.
Randomisation: Not described. Blinding: Double dummy. Concealment: Unclear.
Jadad's score 4.

Participants	62 participants randomised (12 others considered but responded to nebuliser). 21 in each group. Age 2 - 14 months. Acute episode of wheeze with at least one previous episode. 75% with family history of atopy, 65 % parent who smoked. Exclusion if other significant cardiorespiratory illness (i.e. BPD).
Interventions	Salbutamol syrup 1mg tds (2mg for over 12 months old) for 5 days then as required for up to 9 days. Placebo - not described but looked identical.
Outcomes	Symptom score recorded for two weeks. Treatment failures (non-responders) defined as readmission within 2 weeks or still symptomatic at two weeks.
Notes	All participants had initially failed a single nebulised dose of salbutamol or ipratropium bromide. Three treatment groups. Prednisolone tablets plus salbutamol syrup, Placebo tablets and salbutamol syrup, and Placebo tablets and syrup. Comparing latter two groups in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Kraemer 1991

Methods	Randomised, double blind, placebo controlled trial. Parallel and crossover design. Randomisation: Not described. Blinding described. Concealment: Unclear. Jadad's score 3
Participants	40 participants. 36 completed, 4 defaulters. Age 1 - 25 months. Referrals with recurrent or persistent dyspnoea or wheeze. May have had bronchiolitis previously. All had family history of atopy. Parental smoking not documented. Exclusions included CF, cardiac and gastro-oesophageal reflux.
Interventions	Salbutamol 600mcg inhaled. Sedated with chloral hydrate 80-100mg/kg.
Outcomes	Change in conductance (sGaw) or functional residual capacity (TGV) by plethysmography. Number of responders defined as change in sGaw or TGV of > 2 SD.
Notes	Parallel data only included. All patients considered to have post-bronchiolitic wheeze on clinical grounds.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Kraemer 1997

Methods	Randomised, double blind placebo controlled trial. Parallel group design. Randomisation: Not described. Blinding: Not described. Concealment: Unclear. Jadad's score 3.
Participants	42 participants. 8 in treatment group, 6 in placebo. Age 2 - 25 months. Two previous documented episodes of wheeze and dyspnoea. 45% had family history of atopy, 16% had parent who smoked. Exclusions include recent URTI, previous corticosteroids or xanthines.
Interventions	Salbutamol 200mcg tds for six weeks. Placebo inhaler 2 puffs tds for six weeks.
Outcomes	Symptom score. Functional residual capacity (TGV), conductance (Gaw) and resistance (Raw) by plethysmography. Number of responders defined as change in Gaw or TGV of > 2 SD.
Notes	There were four groups studied. (1) Salbutamol plus becotide (Ventide combination inhaler), (2) Salbutamol, (3) Placebo, (4) Open group of withdrawals on Ventide. Comparisons of groups 2 & 3 in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Prahl 1986

Methods	Randomised, double blind, placebo controlled trial. Parallel design. Randomisation: Not described. Blinding: Not described. Concealment: Unclear. Jadad's score 2.
Participants	41 participants (28 included). 15/28 treatment, 13/28 placebo. Age < 18 months (13 between 18 - 36 months - not included in this review). Admission with wheezy bronchitis. Tested for viruses - results not reported. Family history of atopy and parental smoking habits not documented. Exclusion criteria not reported.
Interventions	Salbutamol (Albuterol) 0.15mg/kg nebulised in two parts. Placebo - normal saline.
Outcomes	Clinical score including cough, wheeze and retractions.
Notes	No suitable data extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Prahl 1986 *(Continued)*

Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)
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Prendiville 1987a

Methods	Randomised, double blind, placebo controlled trial. Crossover design. Randomisation: Not described. Blinding: Not described. Concealment: Unclear. Jadad's score 2.
Participants	5 participants. Age 3 - 12 months. Recurrent wheeze spanning 1 - 8 months. Studied when asymptomatic. 80% family history of atopy, 60% had eczema. 80 % had parent who smoked.
Interventions	Salbutamol 2.5 mg nebulised. Single dose. Sedation with chloral hydrate 100 mg/kg. Histamine challenge with doubling concentrations from 0.25 g/l.
Outcomes	Maximum flow at functional residual capacity. (V'maxFRC). Histamine challenge (PC30) measured by V'maxFRC
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

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

Study	Reason for exclusion
Bentur 1990	Not a randomised controlled trial. No control group.
Bremont 1992	Not a randomised controlled trial. Used infusion rather than inhaled medication.
Closa 1998	No placebo group. Comparison of nebuliser versus inhaler.
Connor 1989	Age range outside specified - up to 36 months. Author contacted for data < 24 months.
Daugbjerg 1993	Heterogenous patient group with recurrent wheeze and bronchiolitis.
De La Luz 1999	Age range beyond specified (0 to 72 months)
Hayden 1998(b)	Not a randomised controlled trial. Not randomised.
Hayden 1998a	Not a randomised controlled trial. Not randomised.
Henderson 1993	Included only healthy infants.
Hickey 1994	Heterogenous patient group with >= 50% having RSV.

Short acting beta2-agonists for recurrent wheeze in children under two years of age (Review)

Study	Reason for exclusion
Holmgren 1992	Not a randomised controlled trial. Not randomised.
Jackson 1999	Not a randomised controlled trial. No control group.
Lenney 1978	Not a randomised controlled trial. No control group.
Mallol 1987a	Heterogenous patient group with recurrent wheeze and bronchiolitis.
Mallol 1987b	Heterogenous patient group with recurrent wheeze and bronchiolitis.
Nasplitz 1992	No placebo group. Comparison of fenoterol plus or minus ipratropium bromide. Some patients on first episode of wheeze only.
O'Callaghan 1986	Not a randomised controlled trial. No control group.
O'Callaghan 1988	Not a randomised controlled trial. Not randomised and no control group.
Orlowski 1991	Not a randomised controlled trial.
Ploin 2000	Age range beyond specified (0 to 60 months)
Prendiville 1987b	Not a randomised controlled trial. Active and placebo treatments given in order.
Prendiville 1987c	Not a randomised controlled trial. Active and placebo treatments given in order.
Radford 1975	Not a randomised controlled trial. No contemporaneous control group.
Rubilar 2000	Heterogenous patient group with recurrent wheeze and bronchiolitis.
Rutter 1975	No a randomised controlled trial. Heterogenous patient group with recurrent wheeze and bronchiolitis.
Schweich 1992	Heterogenous patient group with $\geq 50\%$ having RSV.
Seidenberg 1991	Not a randomised controlled trial. Phase 1 not controlled. Phase 2 not randomised.
Spier 1985	Abstract only. Probable mixture of recurrent wheeze and bronchiolitis. Study during RSV season.
Tal 1983	Heterogenous patient group with recurrent wheeze and bronchiolitis.

DATA AND ANALYSES

Comparison 1. Salbutamol versus Placebo. Parallel Group Studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory Rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Symptom Score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Oxygen Saturation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Hospital Admission	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Non-Responders	3	92	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.04, 0.33]
6 Functional Residual Capacity (TGV ml/kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Conductance (Gaw L/s/ H2O/kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Specific Conductance % change (sGaw)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Hyperinflated	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Obstructed	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Salbutamol versus Placebo. Parallel Group Studies, Outcome 1 Respiratory Rate.

Study or subgroup	Treatment		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bentur 1992	13	-7.7 (5)	15	-2.6 (6.7)		-5.1[-9.45,-0.75]
					Favours treatment	Favours control

Analysis 1.2. Comparison 1 Salbutamol versus Placebo. Parallel Group Studies, Outcome 2 Symptom Score.

Study or subgroup	Treatment		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bentur 1992	13	-2.9 (1.9)	15	-0.4 (1.8)		-2.5[-3.88,-1.12]
					Favours treatment	Favours control

Analysis 1.3. Comparison 1 Salbutamol versus Placebo. Parallel Group Studies, Outcome 3 Oxygen Saturation.

Study or subgroup	Treatment		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bentur 1992	13	1.3 (1.8)	15	-0.3 (1.6)		1.6[0.33,2.87]
					Favours control	Favours treatment

Analysis 1.4. Comparison 1 Salbutamol versus Placebo. Parallel Group Studies, Outcome 4 Hospital Admission.

Analysis 1.5. Comparison 1 Salbutamol versus Placebo. Parallel Group Studies, Outcome 5 Non-Responders.

Analysis 1.6. Comparison 1 Salbutamol versus Placebo. Parallel Group Studies, Outcome 6 Functional Residual Capacity (TGV ml/kg).

Analysis 1.7. Comparison 1 Salbutamol versus Placebo. Parallel Group Studies, Outcome 7 Conductance (Gaw L/s/H2O/kg).

Analysis 1.8. Comparison 1 Salbutamol versus Placebo. Parallel Group Studies, Outcome 8 Specific Conductance % change (sGaw).

Comparison 2. Salbutamol versus Placebo. Crossover Studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom Score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Symptom Free Days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Additional Treatment Given per Day	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Parent identification of benefit from inhaler	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 V'maxFRC (ml/s)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Histamine Responsiveness (PC30 g/dl)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Salbutamol versus Placebo. Crossover Studies, Outcome 1 Symptom Score.

Analysis 2.2. Comparison 2 Salbutamol versus Placebo. Crossover Studies, Outcome 2 Symptom Free Days.

Analysis 2.3. Comparison 2 Salbutamol versus Placebo. Crossover Studies, Outcome 3 Additional Treatment Given per Day.

Analysis 2.4. Comparison 2 Salbutamol versus Placebo. Crossover Studies, Outcome 4 Parent identification of benefit from inhaler.

Analysis 2.5. Comparison 2 Salbutamol versus Placebo. Crossover Studies, Outcome 5 V'maxFRC (ml/s).

Analysis 2.6. Comparison 2 Salbutamol versus Placebo. Crossover Studies, Outcome 6 Histamine Responsiveness (PC30 g/dl).

ADDITIONAL TABLES

Table 1. Comparison of included studies

Study Design	Device	Home	Emergency Dept	Ward	Pulmonary Function
Parallel	Nebuliser		Bentur 1992	Prahl 1986	
	Metered Dose Inhaler/Spacer	Kraemer 1997			Kraemer 1991
	Oral	Fox 1996			
Crossover	Nebuliser				Prendaville 1987a

Table 1. Comparison of included studies *(Continued)*

Metered Dose Inhaler/Spacer	Chavasse 1999a	Clarke 1993
Oral		

WHAT'S NEW

Date	Event	Description
22 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 3, 2002

Date	Event	Description
12 February 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

The protocol was written by Dr. Chavasse and Dr. Seddon.

Review of papers for inclusion was performed by Dr. Chavasse and Dr. Seddon with additional input from A Bara.

Data extraction was performed by A Bara and Dr. Chavasse.

The text of the review was written by Dr. Chavasse and Dr. Seddon.

DECLARATIONS OF INTEREST

The authors who have been involved in this review have done so without any known conflict of interest. RC and PS were the co-investigators of one of the primary studies ([Chavasse 1999a](#)) however neither are paid consultants of any related pharmaceutical company.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [*therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Respiratory Sounds [*drug effects]

MeSH check words

Humans; Infant