Asthma and other wheezing disorders in children

Search date October 2005

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| ASTHMA UNCONTROLLED BY STANDARD DOSE INHALED CORTICOSTEROIDS                |
| ![Unknown effectiveness]                                                    | 20   |
| Adding leukotriene receptor antagonists (montelukast)                       |
| ![Unknown effectiveness]                                                    | 19   |
| Adding long acting beta2 agonist                                            |
| ![Unknown effectiveness]                                                    | 20   |
| Adding oral theophylline                                                    |
| ![Unknown effectiveness]                                                    | 18   |
| Increased dose of inhaled corticosteroid (beclomethasone)                  |

| ACUTE WHEEZE IN INFANTS                                                     |
| ![Likely to be beneficial]                                                  | 2    |
| Short acting beta2 agonists (salbutamol by nebuliser)                      |
| ![Likely to be beneficial]                                                  | 1    |
| Short acting beta2 agonists delivered by metered dose inhaler/spacer versus nebuliser |

| PROPHYLAXIS                                                                |
| ![Likely to be beneficial]                                                  | 17   |
| Leukotriene receptor antagonists (oral montelukast in children over 2 years of age) |
| ![Unknown effectiveness]                                                    | 14   |
| Nedocromil (inhaled)                                                       |
| ![Trade-off between benefits and harms]                                    | 25   |
| Corticosteroids (inhaled lower dose)                                       |
| ![Unknown effectiveness]                                                    | 24   |
| Ipratropium bromide (inhaled)                                               |
| ![Unlikely to be beneficial]                                               | 25   |
| Sodium cromoglycate (Inhaled)                                               |

Covered elsewhere in BMJ Clinical Evidence

Bronchiolitis
Key Points

- Childhood asthma can be difficult to distinguish from viral wheeze and can affect up to 20% of children.
- The consensus is that oxygen, high dose nebulised beta_2 agonists and systemic corticosteroids should be used to treat an acute asthma attack.
  - High dose beta_2 agonists may be equally effective when given intermittently or continuously via a nebuliser, or from a metered dose inhaler using a spacer, in children with an acute asthma attack.
  - Admission to hospital may be averted by adding ipratropium bromide to beta_2 agonists, or by using high dose nebulised or oral corticosteroids.
- Prophylactic inhaled corticosteroids improve symptoms and lung function in children with asthma. Their effect on final adult height is unclear.
  - Inhaled nedocromil, inhaled long acting beta_2 agonists, oral theophylline and oral leukotriene receptor antagonists are less effective than corticosteroids.
  - Inhaled sodium cromoglycate does not seem to improve symptoms.
- CAUTION: Monotherapy with long acting beta_2 agonists reduces the frequency of asthma episodes, but may increase the chance of severe asthma episodes and death when those episodes occur.
  - Intravenous theophylline may improve lung function in children with severe asthma, but can cause cardiac arrhythmias and convulsions.
- We don’t know whether adding higher doses of corticosteroids, long acting beta_2 agonists, oral leukotriene receptor antagonists or oral theophylline to standard treatment improves symptoms or lung function in children with uncontrolled asthma.
- In infants with acute wheeze, short acting beta_2 agonists via a nebuliser or a spacer may improve symptoms, but we don’t know whether high dose inhaled or oral corticosteroids or inhaled ipratropium bromide are beneficial.
- Oral short acting beta_2 agonists and inhaled high dose corticosteroids may prevent or improve wheeze in infants but can cause adverse effects.
  - We don’t know whether lower dose inhaled or oral corticosteroids, inhaled ipratropium bromide or inhaled short acting beta_2 agonists improve wheezing episodes in infants.

DEFINITION

Differentiation between asthma and non-asthmatic viral associated wheeze may be difficult; persistent symptoms and signs between acute attacks are suggestive of asthma, as are a personal or family history of atopic conditions such as eczema and hay fever. Childhood asthma is characterised by chronic or recurrent cough and wheeze. The diagnosis is confirmed by demonstrating reversible airway obstruction, preferably on several occasions over time, in children old enough to perform peak flow measurements or spirometry. Diagnosing asthma in children requires exclusion of other causes of recurrent respiratory symptoms. Acute asthma is a term used to describe a severe exacerbation of asthma symptoms accompanied by tachycardia and tachypnoea. The aim of prophylactic treatments in asthma is to minimise persistent symptoms and prevent acute exacerbations. Wheezing in infants is characterised by a high pitched purring or whistling sound produced mainly on the out breath, and is commonly associated with an acute viral infection such as bronchiolitis (see bronchiolitis) or asthma. These are not easy to distinguish clinically.

INCIDENCE/ PREVALENCE

Childhood asthma: Surveys have found an increase in the proportion of children diagnosed with asthma. The increase is higher than can be explained by an increased readiness to diagnose asthma. One questionnaire study from Aberdeen, Scotland, surveyed 2510 children aged 8–13 years in 1964 and 3403 children in 1989. Over the 25 years, the diagnosis of asthma rose from 4% to 10%. The increase in the prevalence of childhood asthma from the 1960s to 1980s was accompanied by an increase in hospital admissions over the same period. In England and Wales, this was a sixfold increase. Wheezing in infants is common and seems to be increasing, although the magnitude of any increase is not clear. One Scottish cross-sectional study (2510 children aged 8–13 years in 1964 and 3403 children in 1989) found that the prevalence of wheeze rose from 10% in 1964 to 20% in 1989, and episodes of shortness of breath rose from 5% to 10% over the same period. Difficulties in defining clear groups (phenotypes) and the transient nature of the symptoms, which often resolve spontaneously, have confounded many studies.
AETIOLOGY/RISK FACTORS

Childhood asthma: Asthma is more common in children with a personal or family history of atopy, increased severity and frequency of wheezing episodes, and presence of variable airway obstruction or bronchial hyperresponsiveness. Precipitating factors for symptoms and acute episodes include infection, house dust mites, allergens from pet animals, exposure to tobacco smoke, and anxiety. 

Wheezing in infants: Most wheezing episodes in infancy are precipitated by viral respiratory infections.

PROGNOSIS

Childhood asthma: A British longitudinal study of children born in 1970 found that 29% of 5 year olds wheezing in the past year were still wheezing at the age of 10 years. Another study followed a group of children in Melbourne, Australia from the age of 7 years (in 1964) into adulthood. The study found that a large proportion (73%) of 14 year olds with infrequent symptoms had few or no symptoms by the age of 28 years, whereas two thirds of those 14 year olds with frequent wheezing still had recurrent attacks at the age of 28 years. Wheezing in infants: One cohort study (826 infants followed from birth to 6 years) suggests that there may be at least three different prognostic categories for wheezing in infants: “persistent wheezers” (14% of total, with risk factors for atopic asthma such as elevated immunoglobulin E levels and a maternal history of asthma), who initially suffered wheeze during viral infections and in whom the wheezing persisted into school age; “transient wheezers” (20% of total, with reduced lung function as infants but no early markers of atopy), who also suffered wheeze during viral infections but stopped wheezing after the first 3 years of life; and “late onset wheezers” (15% of total), who did not wheeze when aged under 3 years but had developed wheeze by school age. Another retrospective cohort study found that 14% of children with one attack and 23% of children with four or more attacks in the first year of life had experienced at least one wheezing illness in the past year at the age of 10 years. Administering inhaled treatments to young children can be difficult. Inconsistencies in results could reflect the effects of the differences in the drugs used, delivery devices used, dosages used, and the differences in the pattern of wheezing illnesses and treatment responses among young children.

AIMS OF INTERVENTION

To reduce or abolish cough and wheeze; to attain best possible lung function; to reduce the risk of severe attacks; to minimise sleep disturbance and absence from school; to minimise adverse effects of treatment; and to allow normal growth.

OUTCOMES

Childhood asthma: Wheeze, cough, nights disturbed by asthma, days lost from school or normal activities, diary card symptom scores, frequency of use of short acting beta, agonists for symptom control, lung function tests (peak expiratory flow rates and forced expiratory volume in 1 second [FEV, ]), airway hyperresponsiveness (measured using methacholine challenge tests), rates of health service use (emergency consultations, casualty attendances, hospital admissions). In acute episodes — blood oxygen saturation, admission rate from casualty, duration of admission, need for intensive care or intubation, mortality. Wheezing in infants: There are no suitable objective outcome parameters by which a response can be adequately measured, as clinical assessment of an infant's lung function is impractical. Symptoms and signs are usually subjective, vary between observers, and can be affected by short term changes. The main outcomes used in trials include: respiratory rate, work of breathing (suprasternal/ternal/intercostal/subcostal recession, grunting, nasal flare, and head bobbing), agitation, and oxygen saturations. Parental preference is considered to be a relevant outcome.

METHODS

Clinical Evidence search and appraisal October 2005. We have excluded studies with heterogeneous groups of infants (those that included infants with bronchiolitis, episodic viral wheeze, and chronic, persistent wheeze). We have performed a GRADE evaluation of the quality of evidence for interventions in this review, see table, p 30 .

QUESTION

What are the effects of treatments for acute asthma in children?

OPTION

OXYGEN

We found no direct information about oxygen in the treatment of acute asthma in children.

Note

An RCT comparing oxygen versus no oxygen in acute severe asthma would be considered unethical. Clinical experience supports the need for oxygen in acute asthma.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30 .
Benefits: We found no systematic review or RCTs (see comment below). One double blind, prospective cohort study (280 children) found that decreased oxygen saturation upon entry to an emergency department was correlated with increased treatment with intravenous aminophylline and corticosteroids, and increased rates of hospital admission or subsequent readmission (arterial oxygen saturation less-than or equal to 91% v arterial oxygen saturation greater-than or equal to 96%; OR for hospital admission or readmission 35, 95% CI 11 to 150; for arterial oxygen saturation 92–95% v greater-than or equal to 96%; OR for hospital admission or readmission 4.2, 95% CI 2.2 to 8.8). [4]

Harms: We found no evidence about harms.

Comment: Clinical guide: An RCT comparing oxygen versus no oxygen treatment in acute severe asthma would be considered unethical. The cohort study reported above does not address directly whether oxygen should be given therapeutically but it does suggest, along with clinical experience, that oxygen should continue to be given promptly to children with acute asthma. [4]

OPTION BETA2 AGONISTS (HIGH DOSE NEBULISED)

Hospital admission / length of stay
Beta2 agonists We don't know whether intermittent nebulised salbutamol is more effective than continuous nebulised salbutamol for a maximum of 2 hours at reducing admission rates or the duration of emergency department stay in children aged 2-18 years treated for acute severe asthma in the emergency department (low-quality evidence).

Note
We found no direct evidence about whether or not nebulised beta2 agonists are better than no active treatment. High dose frequent nebulised beta2 agonists are a standard component of treatment for acute severe asthma, and placebo controlled trials would be unethical.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

Benefits: Beta2 agonists We found no systematic reviews or RCTs comparing nebulised beta2 agonists versus placebo in acute severe asthma. We found one systematic review (search date 2004) of continuous versus intermittent nebulised beta agonist administration. [5] The review found one RCT in children, which compared intermittent salbutamol (0.15 mg/kg/dose every 30 minutes) versus continuous salbutamol (0.30 mg/kg per hour) for a maximum of 2 hours. [6] It found no significant difference between treatments for admission rates or duration of emergency department stay (70 children aged 2–18 years treated for acute severe asthma in the emergency department; admissions: 9/35 [26%] with intermittent v 8/35 [23%] with continuous; P = 0.30; duration of emergency department stay: 123 minutes with intermittent v 124 minutes with continuous; P = 0.89).

Harms: Beta2 agonists The RCT identified by the systematic review [5] found no major adverse effects and found that no children relapsed during a 30 minute observation period or during the first 48 hours after treatment with either continuous or intermittent salbutamol. [5] It found that intermittent salbutamol significantly increased heart rate compared with continuous salbutamol (mean increase in heart rate: 30 beats/minute with intermittent v 18 beats/minute with continuous; P = 0.001). It found no significant difference in tremor between treatments (26% with intermittent v 14% with continuous; reported as not significant, figures not reported). Serum potassium monitoring, with supplementation as necessary, is recommended with prolonged intensive treatment with high dose beta agonists, particularly in children with co-morbidities. Delivery of nebulised beta2 agonists using air driven nebulisers may occasionally cause transient hypoxia.

Comment: Clinical Guide: High dose frequent nebulised beta2 agonists are a standard component of treatment for acute severe asthma, and placebo controlled trials would be unethical. In practice, doses of salbutamol given by nebuliser are generally 2.5 mg for children age 6 months to 5 years and 5 mg for children aged over 5 years.

OPTION SINGLE DOSE IPRATROPIUM BROMIDE (INHALED) ADDED TO BETA2 AGONISTS (IN EMERGENCY ROOM)

Symptom improvement
Single dose (in emergency room) Adding a single dose of inhaled ipratropium bromide to a beta₂ agonist (fenoterol, salbutamol, or terbutaline) may be more effective than beta₂ agonist alone at improving lung function (forced expiratory volume in 1 second) at 1 and 2 hours in children with mild to moderate asthma exacerbations presenting to an emergency department (low-quality evidence).

Hospital admissions / length of stay
Single dose (in emergency room) Adding a single dose of inhaled ipratropium bromide to a beta₂ agonist (fenoterol, salbutamol, or terbutaline) seems to be no more effective than beta₂ agonist alone at reducing hospital admissions in children with mild to moderate asthma exacerbations presenting to an emergency department (moderate-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

Benefits: Single dose (in emergency room):
We found one systematic review (search date 2000, 5 RCTs, 453 children aged 18 months to 17 years with acute asthma presenting to an emergency department). It found that, in children with mild to moderate exacerbations, adding a single dose of inhaled ipratropium bromide to inhaled beta₂ agonists (fenoterol, salbutamol, or terbutaline) versus the beta₂ agonist alone significantly improved forced expiratory volume in 1 second (FEV₁) at 1 hour (3 RCTs: standardised mean difference 0.57, 95% CI 0.21 to 0.93) and at 2 hours (3 RCTs: standardised mean difference 0.53, 95% CI 0.17 to 0.90), but found no significant reduction in hospital admission (3 RCTs: RR 0.93, 95% CI 0.65 to 1.32).

Harms: Single dose (in emergency room):
See multiple dose ipratropium bromide (inhaled) added to beta₂ agonists (in emergency room), p 5.

Comment: None.

OPTION MULTIPLE DOSE IPRATROPIUM BROMIDE (INHALED) ADDED TO BETA2 AGONISTS (IN EMERGENCY ROOM)

Symptom improvement
Multiple doses (in emergency room) Multiple doses of inhaled ipratropium bromide plus an inhaled beta₂ agonist (fenoterol or salbutamol) seem to be more effective than beta₂ agonist alone at improving lung function (forced expiratory volume in 1 second) in children with mild, moderate, or severe exacerbations of asthma presenting to an emergency department (moderate-quality evidence).

Hospital admission / length of stay
Multiple doses (in emergency room) Multiple doses of inhaled ipratropium bromide plus an inhaled beta₂ agonist (fenoterol or salbutamol) seem to be more effective than beta₂ agonist alone at reducing hospital admissions in children with mild, moderate, or severe exacerbations of asthma presenting to an emergency department (moderate-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

Benefits: Multiple doses (in emergency room):
We found one systematic review (search date 2000, 7 RCTs, 1045 children presenting to an emergency department) and one subsequent RCT. The systematic review found that, in children with mild, moderate, or severe exacerbations, adding multiple doses of inhaled ipratropium bromide to an inhaled beta₂ agonist (fenoterol or salbutamol) improved FEV₁ (4 RCTs: WMD 9.7% predicted FEV₁, 95% CI 5.7% to 13.7%, 1 hour after last ipratropium bromide inhalation) and reduced hospital admissions (6 RCTs: RR 0.75, 95% CI 0.62 to 0.89; NNT 13, 95% CI 8 to 32). Subgroup analysis found a significant reduction in hospital admissions in children with severe exacerbations (children with baseline FEV₁ < 50% predicted or change of 7–9 in baseline clinical score after last combined inhalation; RR of hospital admission 0.71, 95% CI 0.58 to 0.89; NNT 7, 95% CI 5 to 20).

Harms: Multiple doses (in emergency room):
The systematic review found no significant increase in the risk of nausea (3 RCTs: RR 0.59, 95% CI 0.30 to 1.14), vomiting (3 RCTs: RR 1.03, 95% CI 0.37 to 2.87), or tremor (4 RCTs: RR 1.01, 95% CI 0.63 to 1.63) in children treated with multiple doses of ipratropium bromide.
Asthma and other wheezing disorders in children

Comment: None.

**OPTION** IPRATROPiUM BROMiDE (INHALED) ADDED TO BETa2 AGONiSTS (AFTER INITIAL STABiLISATION)

Symptom improvement

*Multiple doses (after initial stabilisation)* We don't know whether adding nebulised ipratropium bromide to salbutamol (a beta₂ agonist) and corticosteroid (hydrocortisone or prednisolone) is more effective than adding placebo to salbutamol and corticosteroid at improving clinical asthma scores, oxygen saturation, or number of nebulisations needed, in children admitted to hospital with initial stabilisation (low-quality evidence).

Adverse effects

*Multiple doses (after initial stabilisation)* Adding nebulised ipratropium bromide to salbutamol (a beta₂ agonist) and corticosteroid (hydrocortisone or prednisolone) may increase heart rate compared with adding placebo to salbutamol and corticosteroid (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

**Benefits:** Multiple doses (after initial stabilisation): We found one RCT (80 children and adolescents aged 1–18 years admitted to hospital with moderate to severe asthma, FEV₁ 25–85% predicted or clinical asthma score of 3–9, initially stabilised in emergency department), which compared addition of nebulised ipratropium bromide 250 µg versus placebo (sodium chloride) to nebulised salbutamol and intravenous hydrocortisone or oral prednisolone. The RCT found no significant difference between groups during the first 36 hours in clinical asthma scores, oxygen saturation, or number of nebulisations needed.

**Harms:** Multiple doses (after initial stabilisation): The RCT found a significant increase in heart rate with ipratropium bromide compared with placebo (P = 0.01).

Comment: None

**OPTION** METERED DOSE INHALER PLUS SPACER DEVICES VERSUS NEbulISERS FOR DELIVERiNG BETa2 AGONiSTS

Symptom improvement

*Metered dose inhaler plus spacer devices versus nebulisers for delivering beta₂ agonists* We don't know whether salbutamol delivered by spacer is more effective than salbutamol delivered by jet nebuliser at improving clinical symptoms (score based on respiratory rate, air entry, chest retraction, wheezing) 30 minutes after treatment in children less than 5 years old admitted to hospital with acute wheeze, or whether beta₂ agonists (salbutamol or terbutaline) delivered through a spacer are more effective than a single nebulised treatment at reducing deterioration in blood gasses in children with acute asthma but excluding life threatening asthma (low-quality evidence).

Hospital admission / length of stay

*Metered dose inhaler plus spacer devices versus nebulisers for delivering beta₂ agonists* A metered dose inhaler plus a spacer may be more effective than nebulisation for delivery of beta₂ agonists at marginally reducing time spent in the emergency department, but we don't know whether metered dose inhaler plus a spacer is more effective than nebulisation for delivery of beta₂ agonists at reducing hospital admissions in children with acute asthma but excluding life threatening asthma (low-quality evidence).

Adverse effects

*Metered dose inhaler plus spacer devices versus nebulisers for delivering beta₂ agonists* Delivery of beta₂ agonists using nebulisation may increase heart rate compared with a metered dose inhaler plus a spacer, but we don't know whether there is any difference between delivery of beta₂ agonists using nebulisation compared with a metered dose inhaler in other adverse outcomes (not specified) in children with acute asthma but excluding life threatening asthma (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

**Benefits:** Metered dose inhaler plus spacer devices versus nebulisers for delivering beta₂ agonists: We found one systematic review (search date 2001) and one subsequent RCT. The systematic review (13 RCTs, 880 children with acute asthma but excluding life threatening asthma) compared a spacer/holding chamber attached to a metered dose inhaler versus single or multiple...
treatment with nebuliser for delivery of beta_2 agonists (fenoterol, salbutamol, or terbutaline) or beta agonist (oriprenaline). The review found no significant difference between spacer and multiple treatments with nebulisers in hospital admission rates (OR 0.65, 95% CI 0.40 to 1.06). The review found that children using metered dose inhaler plus spacer spent significantly less time in the emergency department than those having multiple treatment with a nebuliser (2 RCTs, WMD –0.47 hours, 95% CI –0.58 hours to –0.37 hours; see comment below). The review found that deterioration in blood gases was less common when beta_2 agonists (salbutamol or terbutaline) were delivered through a spacer compared with single nebulised treatment (first RCT, 33 children: RR 0.63, 95% CI 0.12 to 3.28; second RCT, 111 children: RR 0.49, 95% CI 0.28 to 0.85). The subsequent RCT found no significant difference between salbutamol 200 µg by spacer and salbutamol 0.15 mg/kg by jet nebuliser in clinical symptoms, 30 minutes after treatment (47 children < 5 years of age admitted to hospital with acute wheeze; clinical score based on respiratory rate, air entry, chest retraction and wheezing, score range 0 [no symptoms] to 12 [severe], mean score: 3.4 with spacer v 3.2 with nebuliser; reported as not significant; figures not reported). The systematic review (search date 2001) found a significant increase in pulse rate with nebulisers compared with spacers (WMD 7.6% from baseline, 95% CI 5.2% to 10.0%). The review found no significant deterioration in any other outcome measures with delivery of beta_2 agonists using metered dose inhaler plus a spacer versus nebulisation. The subsequent RCT found that nebulised salbutamol significantly increased heart rate 30 minutes after treatment compared with salbutamol by spacer (mean number of beats/minute: 133 with nebuliser v 127 with spacer; P=0.004. The findings from the review and the subsequent RCT suggest that, in children old enough to use a spacer, metered dose inhaler with spacer could be substituted for nebulisation in the treatment of acute asthma in emergency departments and hospital wards.

Harms: Metered dose inhaler plus spacer devices versus nebulisers for delivering beta_2 agonists: The systematic review (search date 2001) found a significant increase in pulse rate with nebulisers compared with spacers (WMD 7.6% from baseline, 95% CI 5.2% to 10.0%). The review found no significant deterioration in any other outcome measures with delivery of beta_2 agonists using metered dose inhaler plus a spacer versus nebulisation. The subsequent RCT found that nebulised salbutamol significantly increased heart rate 30 minutes after treatment compared with salbutamol by spacer (mean number of beats/minute: 133 with nebuliser v 127 with spacer; P=0.004. The findings from the review and the subsequent RCT suggest that, in children old enough to use a spacer, metered dose inhaler with spacer could be substituted for nebulisation in the treatment of acute asthma in emergency departments and hospital wards.

Comment: The findings from the review and the subsequent RCT suggest that, in children old enough to use a spacer, metered dose inhaler with spacer could be substituted for nebulisation in the treatment of acute asthma in emergency departments and hospital wards.

OPTION CORTICOSTEROIDS (SYSTEMIC)

Symptom improvement Systemic corticosteroids compared with placebo We don't know whether adding oral or intravenous corticosteroids to usual treatment (including salbutamol, terbutaline, or theophylline) is more effective than adding placebo to usual treatment at improving lung function measured by predicted peak expiratory flow rate in children admitted to hospital with acute asthma (low-quality evidence).

High dose inhaled corticosteroids compared with oral corticosteroids We don't know whether high dose inhaled corticosteroids are more effective than oral corticosteroids at improving symptom scores or lung function in addition to other usual treatment in children with asthma in hospital emergency departments or admitted to hospital (low-quality evidence).

Hospital admission / length of stay
Systemic corticosteroids compared with placebo Adding oral corticosteroids to usual treatment (including salbutamol, terbutaline, or theophylline) may be more effective than adding placebo to usual treatment at increasing the proportion of children discharged from hospital at the first review after 4 hours in children admitted to hospital with acute asthma. We don't know whether adding oral or intravenous corticosteroids to usual treatment (including salbutamol, terbutaline, or theophylline) is more effective than adding placebo to usual treatment at reducing mean length of hospital stay in children admitted to hospital with acute asthma (low-quality evidence).

High dose inhaled corticosteroids compared with oral corticosteroids We don't know whether high dose inhaled corticosteroids are more effective than oral corticosteroids at reducing hospital admission in addition to other usual treatment in children with asthma in hospital emergency departments (low-quality evidence).

Relapse rate Systemic corticosteroids compared with placebo Adding oral corticosteroids to usual treatment (including salbutamol, terbutaline, or theophylline) is more effective than adding placebo to usual treatment at decreasing the proportion of children with relapse within 1-3 months in children admitted to hospital with acute asthma (high-quality evidence).

Note The current consensus is that systemic corticosteroids are beneficial in children with severe acute asthma; therefore, placebo controlled trials in this population would be considered unethical.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.
Benefits: Systemic corticosteroids versus placebo:
We found one systematic review (search date 2002, 6 RCTs, 371 children, already receiving salbutamol, terbutaline, or theophylline) evaluating the effects of adding systemic corticosteroids versus adding placebo in children and adolescents with acute asthma. We found that adding oral corticosteroids significantly increased discharge from hospital at first review after 4 hours and reduced relapse within 3 months compared with usual care (2 RCTs, 210 children, mean age 5 years; discharge at first review after 4 hours: OR 7.00, 95% CI 2.98 to 16.45; NNT 3, 95% CI 2 to 7). The review found no significant difference between adding oral or intravenous corticosteroids and adding placebo in mean length of hospital stay (3 RCTs, 132 children, mean age range 4–10 years; mean length of hospital stay: WMD −8.75 hours, 95% CI −19.23 hours to +1.74 hours), pulmonary function (2 RCTs, 64 children, mean age range 4–10 years; pulmonary function, % predicted peak expiratory flow rate: WMD +7.21, 95% CI −7.01 to +21.25). The corticosteroids used in the studies were oral or intravenous prednisolone, intravenous hydrocortisone, or intravenous methylprednisolone.

Oral corticosteroids versus high dose inhaled corticosteroids:
See benefits of high dose inhaled corticosteroids, p 8.

Harms: Systemic corticosteroids versus placebo:
The studies included in the systematic review did not formally address the issue of harms. We found few reports of adverse effects with short courses of systemic corticosteroids.

Oral corticosteroids versus high dose inhaled corticosteroids:
See harms of high dose inhaled corticosteroids, p 9.

Varicella infection:
Several case reports have associated systemic corticosteroid treatment with severe varicella infection. One case control study (167 cases, 134 controls) in otherwise immunocompetent children with complicated and uncomplicated varicella infection did not find significant risk attributable to corticosteroid exposure (OR 1.6, 95% CI 0.2 to 17.0), but it was too small to exclude a clinically important risk.

Comment: Systemic corticosteroids versus placebo:
The studies included in the systematic review probably excluded the most severely ill children; this was explicitly stated in one study. The authors of the review comment on the surprising paucity of evidence from RCTs for this accepted standard intervention. RCTs of systemic corticosteroids versus placebo in severe acute asthma would now be considered unethical.

OPTION CORTICOSTEROIDS (HIGH DOSE INHALED)

Symptom improvement
High dose inhaled corticosteroids compared with oral corticosteroids: We don’t know whether high dose inhaled corticosteroids are more effective than oral corticosteroids at improving symptom scores or lung function in addition to other usual treatment in children with asthma in hospital emergency departments or admitted to hospital (low-quality evidence).

Hospital admission / length of stay
High dose inhaled corticosteroids compared with oral corticosteroids: We don’t know whether high dose inhaled corticosteroids are more effective than oral corticosteroids at reducing hospital admission in addition to other usual treatment in children with asthma in hospital emergency departments (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

Benefits: High dose inhaled corticosteroids versus oral corticosteroids:
We found one systematic review (search date 2003, 4 RCTs), one subsequent RCT, and one additional RCT. The systematic review compared the effects of initial treatment with high dose inhaled corticosteroids versus oral corticosteroids in hospital emergency departments on admission rates. The review did not pool results from the RCTs because of marked heterogeneity among the studies. One RCT (103 children with moderate to severe asthma, aged 5–16 years, mean initial forced expiratory volume in 1 second [FEV1], 45%) compared fluticasone (2 mg through metered dose inhaler with spacer) versus prednisolone 2 mg/kg orally. It found that prednisolone reduced hospital admission (31% with inhaled fluticasone vs 10% with oral prednisolone; P = 0.01) and increased mean FEV1 at 4 hours (9% with inhaled fluticasone vs 19% with oral prednisolone; P less-than or equal to 0.001). The second RCT (128 children with mild to moderate
Theophylline can cause serious adverse effects (cardiac arrhythmia or convulsions) if therapeutic blood concentrations are not maintained. A systematic review (search date 2004, 7 RCTs, 380 children with severe asthma, aged 1–17 years) found no significant difference between nebulised dexamethasone (1.5 mg/kg through nebuliser) versus prednisolone 2 mg orally. It found no significant difference between nebulised dexamethasone and oral prednisolone in rates of hospital admission (12/56 [21%] with nebulised dexamethasone v 17/55 [31%] with oral prednisolone; ARR +9.5%, 95% CI –8.0% to +21.0%; RR 0.69, 95% CI 0.36 to 1.27), but found fewer relapses with nebulised dexamethasone within 48 hours after discharge (0/44 [0%] with nebulised dexamethasone v 6/38 [16%] with oral prednisolone; ARR 16.0%, 95% CI 27.0% to 4.5%); however, all children in the RCT received a 5 day course of prednisolone (2 mg/kg/day) on discharge. In the remaining two RCTs (104 children with mild to moderate asthma, budesonide (800 µg through nebuliser at 1, 30, and 60 minutes; 1600 µg through turbohaler) was compared with prednisolone 2 mg/kg orally. One RCT found no significant difference between treatments in hospital admission (1/41 [2.4%] with inhaled corticosteroids v 5/39 [12.8%] with oral corticosteroids; OR 0.17, 95% CI 0.02 to 1.53). The other RCT reported no admissions. The subsequent RCT (321 children aged 4–16 years, peak expiratory flow rate 40–75% predicted) compared nebulised fluticasone (1 mg twice daily for 7 days) versus oral prednisolone (2 mg/kg for 4 days then 1 mg/kg for 3 days). It found that nebulised fluticasone significantly improved mean morning peak expiratory flow rate over 7 days compared with oral prednisolone (difference 9.5 L/minute, 95% CI 2.0 L/minute to 17.0 L/minute). No significant differences were found in symptom scores or withdrawals. The additional RCT (46 children, aged 5–16 years, admitted to hospital with severe exacerbations of asthma) compared nebulised budesonide (2 mg/hour) versus oral prednisolone 2 mg/kg at admission and after 24 hours. It found no significant difference between groups in FEV1, at 24 hours, or at 3 and 24 days after admission. All children in this trial were treated with budesonide 800 µg daily after discharge from hospital.

### Harms:

The systematic review found no significant adverse effects with inhaled corticosteroids. The subsequent RCT found no significant difference in the profile of adverse events between inhaled fluticasone and oral prednisolone, except for a slightly higher frequency of oral candidiasis with fluticasone (8% with fluticasone v 3% with prednisolone).

### Comment:

**High dose inhaled corticosteroids versus oral corticosteroids:**

The systematic review concluded that there was insufficient evidence to support the substitution of high dose inhaled corticosteroids for oral corticosteroids in the initial phase of treatment of moderately severe acute asthma. The subsequent RCT was funded by the manufacturers of fluticasone.

### Option

**THEOPHYLLINE (INTRAVENOUS)**

### Symptom improvement

**Intravenous theophylline versus placebo** In children admitted to hospital with severe asthma and receiving oxygen, bronchodilators, and glucocorticoids, adding intravenous theophylline may be more effective than adding placebo at improving lung function (measured by forced expiratory volume in 1 second) and symptom scores at 6–8 hours after treatment, but not at reducing the number of bronchodilator treatments required (low quality evidence).

### Hospital admission / length of stay

**Intravenous theophylline versus placebo** In children admitted to hospital with severe asthma and receiving oxygen, bronchodilators, and glucocorticoids, we don’t know whether adding intravenous theophylline is more effective than adding placebo at reducing the length of hospital stay (moderate-quality evidence).

### Note

Theophylline can cause serious adverse effects (cardiac arrhythmia or convulsions) if therapeutic blood concentrations are exceeded.

### For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

### Benefits:

**Intravenous theophylline versus placebo:**

We found one systematic review. The systematic review (search date 2004, 7 RCTs, 380 children and adolescents aged 1–19 years admitted to hospital with severe asthma, forced expiratory volume in 1 second 35–45% predicted, receiving oxygen, maximised inhaled bronchodilators, and oral/intravenous glucocorticoids) compared the effects of adding intravenous theophylline versus adding placebo on lung function (measured as change from baseline in forced expiratory volume in 1 second). The review found that at 6–8 hours, intravenous theophylline significantly improved lung function (2 RCTs; WMD in change in % predicted FEV1, 8.4%, 95% CI 0.8% to 15.9%) and clinical symptom scores (WMD –0.55, 95% CI –0.93 to –0.16) compared with placebo but found no significant difference in the number of nebulised bronchodilator treatments required (2 RCTs;
Harms: **Intravenous theophylline versus placebo:**
The systematic review found that adding theophylline significantly increased the risk of vomiting (5 RCTs; RR 3.69, 95% CI 2.15 to 6.33) compared with placebo, but found no significant differences for headache, tremor, seizures, and arrhythmia. No deaths were reported in the included studies. Theophylline can cause serious adverse effects (cardiac arrhythmia or convulsions) if therapeutic blood concentrations are exceeded.

Comment: None.

**QUESTION** What are the effects of single agent prophylaxis in children taking as needed inhaled beta agonists for asthma?

**OPTION** CORTICOSTEROIDS (INHALED)

**Symptom improvement**

*Inhaled corticosteroids compared with placebo* Prophylactic inhaled corticosteroids added to usual care seem to be more effective than placebo plus usual care at improving symptom scores and lung function (measured by peak expiratory flow rates) and decreasing the need for other asthma medications (reduced beta₂ agonist use, reduced oral corticosteroid use) and the need for urgent care (moderate quality evidence).

*Inhaled corticosteroids compared with theophylline* Inhaled beclomethasone added to usual care may be more effective than oral theophylline added to usual care at reducing the use of bronchodilators and oral corticosteroids, but not at improving mean asthma symptom scores in children aged 6-16 years (low-quality evidence).

*Inhaled corticosteroids compared with sodium cromoglycate* Inhaled beclomethasone added to usual care seems to be more effective than inhaled sodium cromoglycate at improving symptoms and lung function (measured by peak expiratory flow rate) and reducing bronchodilator use and asthma exacerbations, but not at reducing the need for relief medication (low-quality evidence).

*Inhaled corticosteroids compared with nedocromil* We don’t know whether inhaled budesonide is more effective than inhaled nedocromil at improving lung function, or the need for additional asthma medication or emergency care in children aged 5-12 years with mild-moderate asthma (low-quality evidence).

*Inhaled corticosteroids compared with inhaled long acting beta₂ agonists* Inhaled beclometasone may be more effective than inhaled salmeterol at reducing the use of rescue salbutamol, but we don’t know whether inhaled beclometasone is more effective than inhaled salmeterol at improving lung function measured by forced expiratory volume in 1 second (low-quality evidence).

*Inhaled corticosteroids compared with oral montelukast* Inhaled fluticasone may be more effective than oral montelukast at increasing lung function (measured by forced expiratory volume in 1 second, morning and evening peak expiratory flow rate), rescue medication-free days, and the proportion of parents and physicians “very satisfied” with treatment, and at reducing night time symptom scores in children aged 6-12 years with chronic asthma for at least 6 months. We don’t know whether high or low dose budesonide is more effective than oral montelukast at improving clinical score or lung function at 6 months in newly diagnosed mildly asthmatic children aged 6-18 years (low-quality evidence).

*Hospital admission / length of stay* Inhaled corticosteroids compared with placebo Prophylactic inhaled budesonide added to usual care seems to be more effective than placebo plus usual care at decreasing admissions to hospital in children aged 5-12 years with mild-moderate asthma (moderate quality evidence).

*Inhaled corticosteroids compared with nedocromil* We don’t know whether inhaled budesonide is more effective than inhaled nedocromil at reducing admission to hospital in children aged 5-12 years with mild-moderate asthma (low-quality evidence).

**Airway hyperresponsiveness / bronchial reactivity**

*Inhaled corticosteroids versus inhaled long acting beta₂ agonists* Inhaled beclometasone may be more effective than inhaled salmeterol at reducing airway hyperresponsiveness (measured using methacholine 36 hours after study medication) at 12 months (low-quality evidence).

**Note**
Several RCTs have found that inhaled corticosteroids slightly reduce growth rate compared with placebo, although one observational study with long term follow up suggested attainment of normal adult height. Inhaled corticosteroids have been associated with rare reports of adrenal suppression.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

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Benefits: Inhaled corticosteroids versus placebo:

We found one systematic review (search date 1996) and two subsequent RCTs. [21] [22] [23] The systematic review (search date 1996, 24 RCTs, 10/24 RCTs in preschool children, all receiving usual care, including as needed inhaled beta agonists, duration 4–88 weeks), which compared regular inhaled corticosteroids (betamethasone, beclometasone, budesonide, flunisolide, or fluticasone) versus placebo. [21] It found that corticosteroids plus usual care significantly improved symptom score, reduced beta2 agonist use, reduced oral corticosteroid use and improved peak expiratory flow rates (PEFR) compared with usual care alone (improvement in symptom score: 50%, 95% CI 49% to 51%; beta2 agonist use: RR 0.37, 95% CI 0.36 to 0.38; oral corticosteroid use: RR 0.68, 95% CI 0.66 to 0.70; weighted mean improvement in PEFR 11% predicted, 95% CI 9.5% to 12.5%). The first subsequent RCT (1041 children aged 5–12 years, with mild to moderate asthma, mean prestudy forced expiratory volume in 1 second (FEV1) 94% predicted, all using salbutamol for asthma symptoms) compared three treatments for 4–6 years: inhaled budesonide 200 µg twice daily, inhaled nedocromil 8 mg twice daily, and placebo. [24] It found that budesonide reduced the need for other asthma medications, admission to hospital, or emergency care compared with placebo (see table 1, p 29). Compared with placebo, budesonide significantly improved FEV1, before bronchodilator use, but not after bronchodilator use (see table 1, p 29). The second subsequent RCT (241 children aged 6–14 years) also compared three treatments: beclometasone (81 children), salmeterol (80 children), and placebo (80 children). [23] Compared with placebo, beclometasone significantly reduced rescue bronchodilator use (days and nights without need for salbutamol: 92% with beclometasone v 83% with placebo; P less-than or equal to 0.001) and treatment withdrawals because of exacerbations (5 with beclometasone v 15 with placebo; P = 0.03). Beclometasone improved FEV1 compared with placebo (10% with beclometasone v 5% with placebo).

Inhaled corticosteroids versus theophylline:

We found no systematic review. We found one RCT (195 children aged 6–16 years receiving usual care, including as needed inhaled beta agonists, followed for 12 months), which compared inhaled beclometasone 360 µg daily versus oral theophylline. [24] It found no significant difference between inhaled beclometasone and oral theophylline in the mean asthma symptom score (0 = no symptoms, 6 = incapacitating symptoms; scores were low and ranged from 0.5–0.8 for beclometasone v 0.6–0.9 for theophylline) but found less use of bronchodilators and oral corticosteroids with inhaled beclometasone. [24]

Inhaled corticosteroids versus sodium cromoglycate:

We found no systematic review. We found four RCTs comparing inhaled corticosteroids (betamethasone, budesonide, fluticasone) versus inhaled sodium cromoglycate. [25] [26] [27] [28] One RCT (20 children aged 6–14 years) found that betamethasone significantly improved symptoms and lung function compared with sodium cromoglycate (mean PEFRs; P < 0.001). [25] The second RCT (crossover, 75 children aged 5–15 years) found that budesonide or fluticasone significantly reduced bronchodilator use (P < 0.05) and lung function compared with sodium cromoglycate (FEV1; P < 0.01). [26] The third RCT (unblinded, 335 children aged 2–6 years) found that budesonide significantly reduced the rate of asthma exacerbations over 52 weeks (P less-than or equal to 0.001) compared with sodium cromoglycate. Asthma exacerbations were defined as use of systemic corticosteroids or additional maintenance treatment, emergency department or urgent care visit, or admission to hospital. [27] The fourth RCT (unblinded, multicentre, 225 children aged 4–12 years) found that fluticasone significantly improved mean percentage PEFR (at 6–8 weeks; P = 0.0001) and symptoms (at 6–8 weeks; P < 0.05) compared with sodium cromoglycate, but found no significant difference for relief medication use or FEV1. [28]

Inhaled corticosteroids versus nedocromil:

We found no systematic review. We found one RCT (1041 children aged 5–12 years, with mild to moderate asthma, mean prestudy FEV1 94% predicted, all using salbutamol for asthma symptoms), which compared inhaled budesonide 200 µg twice daily versus inhaled nedocromil (8 mg twice daily) versus placebo 4–6 years. [22] It found that budesonide improved FEV1, and reduced the need for additional asthma medication, admission to hospital, and emergency care more than nedocromil (see table 1, p 29), but the significance of these differences was not reported.

Inhaled corticosteroids versus inhaled long acting beta2 agonists:

We found no systematic review but found two RCTs of beclometasone 200 µg twice daily versus salmeterol 50 µg twice daily for 1 year. [25] [29] The first RCT (67 children aged 6–16 years) found that beclometasone was more effective than salmeterol in improving FEV1 (mean change of FEV1 = −4.5% predicted [95% CI −9.0% to +0.1%] with salmeterol v +10% [CI not reported] with beclometasone; mean difference beclometasone v salmeterol 14.2%, 95% CI 8.3% to 20.0%), reducing the use of rescue salbutamol (0.44 uses/day with salmeterol v 0.07 uses/day with beclometasone; P less-than or equal to 0.001). [29] Both treatments improved symptom scores (before trial 3% of children asymptomatic with salmeterol v 6% with beclometasone; at 1 year 36% with salmeterol v
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55% with beclometasone) and PEFR (improvement in morning PEFR 49 L/minute with salmeterol v 61 L/minute with beclometasone), and there was no significant difference between treatments at 1 year. There were two exacerbations in the beclometasone group compared with 17 in the salmeterol group. [29] The second RCT (241 children aged 6–14 years) compared beclometasone (81 children) versus salmeterol (80 children) versus placebo (80 children). [30] It found that beclometasone reduced airway hyperresponsiveness more than salmeterol (methacholine PC20 36 hours after study medication 12 months into the study: 2.1 mg/mL with beclometasone v 0.9 mg/mL with salmeterol; P = 0.009). Salmeterol and beclometasone did not differ in improvement of FEV1 (10% with beclometasone v 10% with salmeterol).

Inhaled corticosteroids versus oral montelukast:

We found two RCTs. [31] [32] The first double blind RCT compared fluticasone propionate (50 µg twice daily by multi-dose powder inhaler) versus oral montelukast (5 mg chewable tablet once daily) for 12 weeks. [31] It found that fluticasone significantly increased FEV1, morning and evening PEFRs, and rescue medication-free days compared with montelukast (double blind RCT, 342 children aged 6–12 years with chronic asthma for at least 6 months and FEV1, 60–80% of predicted; proportion with > 5% increase in FEV1: 63% with fluticasone v 43% with montelukast; P = 0.002; mean change in morning PEFR: 39.9 L/minute with fluticasone v 23.0 L/minute with montelukast; P = 0.004; mean change in evening PEFR: 35.5 L/minute with fluticasone v 20.4 L/minute with montelukast; P = 0.02; rescue-free days: 45.1% with fluticasone v 35.0% with montelukast; P = 0.002). It found that fluticasone significantly reduced night time symptom scores and salbutamol use compared with montelukast (asthma symptom score, scale 0 to 3, higher score = worse symptoms, mean change in night time symptom score: –0.40 with fluticasone v –0.19 with montelukast; P < 0.001; mean change in daily puffs of salbutamol: –1.43 with fluticasone v –1.23 with montelukast; P = 0.18). It found that fluticasone significantly increased the proportion of parents and physicians who were very satisfied with study treatment at 12 weeks compared with montelukast (satisfaction measured on a scale of 0 to 6, unclear what score represented “very satisfied”; proportion of parents “very satisfied”: 58% with fluticasone v 42% with montelukast; P = 0.006; proportion of physicians “very satisfied”: 48% with fluticasone v 29% with montelukast; P = 0.016). It found that montelukast increased withdrawal due to asthma exacerbation compared with fluticasone (14/170 [8%] with montelukast v 9/172 [5%] with fluticasone, statistical assessment not performed). [32]

The second RCT compared three treatments for 6 months: low dose budesonide (400 µg daily by dry powder inhaler), high dose budesonide (800 µg/day by dry powder inhaler), and oral montelukast (5 mg/day for children aged 6–14 years, 10 mg/day for older children). [33] It found no significant difference between high or low dose budesonide and montelukast in clinical score, or FEV1, at 6 months (51 newly diagnosed mildly asthmatic children aged 6–18 years who were sensitive to house dust mite; clinical score based on day time and night time symptoms, score range 0 [no symptoms or beta2 agonist use] to 9 [severe day and night symptoms plus > 3 uses of beta2 agonist]; mean symptom score: 2.2 with high dose budesonide v 1.9 with low dose budesonide v 1.9 with montelukast; P > 0.12 for each dose of budesonide v montelukast; FEV1, as per cent predicted: 93.0% with high dose budesonide v 93.4% with low dose budesonide v 90.9% with montelukast; P > 0.07 for each dose of budesonide v montelukast).

Harms:

Inhaled corticosteroids versus placebo:

The systematic review (search date 1996) found no significant difference between inhaled corticosteroids (betamethasone, budesonide, flunisolide, or fluticasone) and placebo in adrenal function (12 RCTs), and found clinical cases of oral candidiasis (4 RCTs). [21] The first subsequent RCT (1041 children with mild to moderate asthma) compared budesonide 400 µg daily versus nedocromil versus placebo with 4–6 years of follow up. [22] The mean increase in height in the budesonide group was 1.1 cm less than in the placebo group (22.7 cm with budesonide v 23.8 cm with placebo; P = 0.005); the difference occurred mainly within the first year of treatment. [22] The second subsequent RCT found that the mean increase in height in the beclometasone group was significantly less than in the placebo group (mean increase: 3.96 cm with beclometasone v 5.04 cm with placebo; P = 0.018). [22] One large RCT in adults and children (7221 people with mild persistent asthma for less than 2 years, including 3210 children aged 17 years or under) compared once daily budesonide (200 µg once daily from dry powder inhaler if aged < 11 years and 400 µg once daily if < 11 years) versus placebo over 3 years. [22] It found that oral candidiasis was reported more frequently with budesonide (1.2%) than with placebo (0.5%), but no difference was found between groups in any other adverse event. Case reports [33] and a national survey of paediatricians and endocrinologists [34] have indicated the possibility of adrenal suppression leading to adrenal crisis associated with hypoglycaemia in children on high dose inhaled corticosteroids. Most cases involved fluticasone in daily doses of 500–2000 µg. Observational studies have found little or no biochemical evidence of change in bone metabolism with inhaled corticosteroids. [33] [34] Two cross-sectional studies using a slit lamp to screen for lenticular changes in children taking long term inhaled corticosteroids (beclometasone, budesonide) found no posterior subcapsular cataracts. [35] [36] The systematic review identified eight RCTs reporting growth velocity and found no significant difference between inhaled corticosteroids and placebo. [21] Another systematic review (search
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de date 1993, 21 studies) reported height for age in 810 children with asthma treated with oral or inhaled corticosteroids. It found no evidence of growth impairment with inhaled beclometasone (12 studies, 331 children). [39] A third systematic review (search date 1999, 3 RCTs) identified one RCT (94 children, aged 7–9 years) comparing the effect of inhaled beclometasone 400 µg daily versus placebo on growth as a primary outcome measure in children with recurrent viral induced wheeze. [40] It found a significant decrease in growth with beclometasone compared with placebo (mean difference in growth at end of 7 month treatment period: −1 cm, 95% CI −1.4 cm to −0.6 cm; P < 0.0001) and found no significant catch up growth during a follow up 4 month washout period. [41] We found one large subsequent RCT that evaluated the effects of inhaled budesonide on growth in children with mild asthma. [42] The RCT found that children receiving budesonide grew less than children receiving placebo over 3 years (1 RCT, 3195 children aged 5–17 years; mean difference in growth per year: −0.43 cm, 95% CI −0.54 cm to −0.32 cm; P < 0.0001). The differences in growth rate were similar between children under 11 years treated with budesonide 200 µg daily (−0.45 cm/year, 95% CI −0.56 cm/year to −0.34 cm/year; P < 0.0001) and children over 11 years being treated with budesonide 400 µg daily (−0.40 cm/year, 95% CI −0.66 cm/year to −0.14 cm/year; P = 0.003). In children less than 11 years being treated with 200 µg daily, the effect was more pronounced during the first year (−0.58 cm/year, 95% CI −0.76 cm/year to −0.40 cm/year; P < 0.0001) than during the third year (−0.33 cm/year, 95% CI −0.52 cm/year to −0.14 cm/year; P = 0.0005). [42]

**Inhaled corticosteroids versus theophylline or sodium cromoglycate:**
The RCT comparing inhaled beclometasone 360 µg daily versus oral theophylline for 1 year found a significantly higher rate of growth (more notable in boys) in the theophylline group (195 children; mean rate of growth in prepubescent boys 4.3 cm/year with beclometasone v 6.2 cm/year with theophylline), [23] This effect was not sufficient to be noticed by the children or by their parents, and no child was withdrawn from the study on this account. [24] One controlled, prospective study compared 216 children treated with budesonide 400–600 µg daily versus 82 children treated with theophylline or sodium cromoglycate over 3–5 years of follow up. [43] No significant changes in growth velocity were found at doses up to 400 µg daily (5.5 cm/year with budesonide v 5.6 cm/year with controls). The adult height of 142 of these budesonide treated children (mean treatment period 9.2 years, mean dosage 412 µg/day) was compared with 18 controls never treated with inhaled corticosteroids and 51 healthy siblings. No significant differences were found. Children in all groups attained their target adult height (mean difference between measured and target adult height: +0.3 cm, 95% CI −0.6 cm to +1.2 cm for budesonide treated children; −0.2 cm, 95% CI −2.4 cm to +2.1 cm for control children with asthma; +0.9 cm, 95% CI −0.4 cm to +2.2 cm for healthy siblings). [44] Two RCTs found no clinically relevant differences between inhaled corticosteroids (betamethasone, budesonide) and sodium cromoglycate. [25] [27] One RCT found that budesonide significantly reduced growth compared with fluticasone or sodium cromoglycate (decrease in height standard deviation score > 2 standard deviations compared with mean height standard deviation score change during preceding year; P < 0.05). [26] Another RCT found that a higher proportion of children taking sodium cromoglycate withdrew because of adverse events (breathlessness and wheeze, burning sensation in chest, sore throat, sickness) compared with fluticasone. [28]

**Inhaled corticosteroids versus nedocromil:**
The RCT (1041 children with mild to moderate asthma) comparing budesonide 400 µg daily versus nedocromil versus placebo found that the mean increase in height over 4–6 years of follow up was less with budesonide than with nedocromil, but the significance of this difference was not reported (22.7 cm with budesonide v 23.7 cm with nedocromil; significance assessment not performed). [29]

**Inhaled corticosteroids versus inhaled long acting beta agonists:**
Two RCTs comparing beclometasone versus salmeterol found slowing in linear growth with beclometasone (growth over year of treatment 5.4 cm [29] and 6.1 cm [23] in the salmeterol groups; 4.0 cm [29] and 4.7 cm [23] in the beclometasone groups; P = 0.004; [29] P = 0.007 [23]). One RCT comparing inhaled beclometasone versus salmeterol found that symptom improvement in the salmeterol group was accompanied by significant deterioration in bronchial reactivity, indicating a failure to control underlying bronchial inflammation. [29] See harms of long acting beta agonists, p 15.

**Inhaled corticosteroids versus montelukast:**
The first RCT (342 children) found that treatment related adverse events and withdrawal due to treatment related adverse events were similar with fluticasone and montelukast (adverse events: 7% with fluticasone v 6% with montelukast; assessment not performed; withdrawals due to adverse effect: 2% with both treatments; statistical assessment not performed). [30] The second RCT gave no information on adverse events. [31]
Comment: Inhaled corticosteroids versus placebo post exercise:
We found one crossover RCT that only assessed post-exercise symptoms. It compared low dose (50 or 100 µg) hydrofluoroalkalane beclometasone dipropionate once in the evening by autohaler versus placebo. Treatment periods lasted 4 weeks with a 1 week washout period between. The RCT did not report pre-crossover results, but found no evidence of a carryover or period effect. It found that both doses of beclometasone significantly reduced the percentage fall in FEV$_1$ after exercise compared with placebo (25 children aged 5–14 years; fall in FEV$_1$: 20.8% with beclometasone 50 µg v 20.9% with beclometasone 100 µg v 27.9% with placebo; P < 0.05). It found few adverse effects during treatment with low dose (50 or 100 µg) hydrofluoroalkalane beclometasone dipropionate by autohaler or placebo (AR: 1/25 [4%] with beclometasone 50 µg v 4/25 [16%] with beclometasone 100 µg v 3/25 [12%] with placebo).

Treatment with inhaled corticosteroids should be reviewed regularly and the dose gradually reduced to the lowest that is compatible with good symptom control. Regular measurement of height and plotting on height centile charts should ideally be undertaken in children receiving continuing treatment with inhaled corticosteroids. Children requiring long term use of high dose (off licence) inhaled corticosteroids should be referred to a specialist.

SODIUM CROMOGLYCATE (INHALED)

Symptom improvement
Inhaled sodium cromoglycate versus placebo: Adding inhaled sodium cromoglycate to usual treatment may be no more effective than adding placebo to usual treatment in improving the number of symptom free days or cough in children with moderate to severe asthma. Adding inhaled sodium cromoglycate to usual treatment may be marginally more effective than adding placebo to usual treatment in improving wheeze and overall symptom scores in children with moderate to severe asthma (very low-quality evidence).

Inhaled sodium cromoglycate compared with inhaled corticosteroids: Inhaled sodium cromoglycate may be less effective than inhaled corticosteroids at improving symptoms and lung function (measured by peak expiratory flow rate) and reducing bronchodilator use and asthma exacerbations, but not at reducing the need for relief medication use (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

Benefits: Inhaled sodium cromoglycate versus placebo:
We found one systematic review (search date 2002, 24 RCTs, about 1000 children aged 0–18 years with moderate to severe asthma, receiving usual care, including as needed inhaled beta agonists) comparing inhaled sodium cromoglycate versus placebo. The RCTs differed in design, severity of asthma, number of children included, age of children, duration of intervention, and follow up period. The review found no difference between sodium cromoglycate and placebo treatment groups in the number of symptom free days (4 RCTs: WMD +6.76, 95% CI −2.18 to +15.70) or cough (9 RCTs: WMD −0.18, 95% CI −0.32 to +0.04). There were small differences favouring cromoglycate for wheeze (WMD −0.11, 95% CI −0.19 to −0.03) and overall symptom scores (WMD −0.19, 95% CI −0.07 to −0.32). The review found significant publication bias by the absence of small, negative trials (P = 0.01 for cough and wheeze). The review concluded that there is insufficient evidence that sodium cromoglycate is an effective prophylactic treatment in children with asthma.

Inhaled sodium cromoglycate versus inhaled corticosteroids:
See benefits of inhaled corticosteroids, p 10.

Harms: Inhaled sodium cromoglycate versus placebo:
Fifteen RCTs included in the systematic review reported adverse effects described as minor and of low incidence, including cough, bitter taste, wheezing, sneezing, throat irritation, and perioral eczema. Fifteen RCTs included in the systematic review reported adverse effects described as minor and of low incidence, including cough, bitter taste, wheezing, sneezing, throat irritation, and perioral eczema. Fifteen RCTs included in the systematic review reported adverse effects described as minor and of low incidence, including cough, bitter taste, wheezing, sneezing, throat irritation, and perioral eczema.

Inhaled sodium cromoglycate versus inhaled corticosteroids:
See harms of inhaled corticosteroids, p 10.

Comment: None.

NEDOCROMIL (INHALED)

Symptom improvement
Inhaled nedocromil compared with placebo: Adding inhaled nedocromil to usual medication may be more effective than adding placebo to usual medication at improving asthma symptom scores, clinician assessed asthma severity,
and the need for prednisolone or emergency care, but not for improving lung function or the need for other asthma medications (low-quality evidence).

**Inhaled nedocromil compared with inhaled corticosteroids** We don't know whether inhaled nedocromil is more effective than inhaled budesonide at improving lung function, or the need for additional asthma medication or emergency care in children aged 5-12 years with mild-moderate asthma (low-quality evidence).

**Admission to hospital / length of stay**

**Inhaled nedocromil compared with inhaled corticosteroids** We don't know whether inhaled nedocromil is more effective than inhaled budesonide at reducing admission to hospital in children aged 5-12 years with mild-moderate asthma (low-quality evidence).

**Benefits:**

**Inhaled nedocromil versus placebo:**

We found no systematic review. We found three RCTs. The first RCT (209 children and adolescents aged 6–7 years allowed to continue using usual medication) compared inhaled nedocromil (4 mg 4 times/day) versus placebo for 12 weeks. Symptoms were recorded by the children in daily diary cards, including scoring day and night time asthma and cough severity, use of all medication, and morning and evening peak expiratory flow rates (PEFR). The RCT found that inhaled nedocromil significantly reduced total symptom scores, clinician assessed asthma severity, beta_{2} agonist use, and improved lung function (forced expiratory volume in 1 second) compared with placebo.

The second RCT (parallel group study, 79 children aged 6–12 years recovering from acute asthma and allowed to use inhaled bronchodilators) compared inhaled nedocromil (2 mg 3 times/day) versus placebo for 12 weeks. Symptoms were recorded by the children in daily diary cards, including day and night time asthma severity, morning and evening PEFR, and usage of bronchodilators. The RCT found that, after 6 weeks, inhaled nedocromil significantly improved (from baseline) the morning PEFR (difference, 20 L/minute; \( P = 0.036 \)), evening PEFR (difference, 22 L/minute; \( P = 0.033 \)), night time asthma score (difference on a 5 point scale, 0.48; \( P = 0.001 \)), and day time asthma score (difference on a 5 point scale, 0.38; \( P = 0.03 \)) compared with placebo. The RCT found no significant difference before 6 weeks of treatment. The third RCT (1041 children aged 5–12 years, with mild to moderate asthma, mean prestudy FEV_{1} 94% predicted, all using salbutamol for asthma symptoms) compared three treatments for 4–6 years: inhaled nedocromil (8 mg twice daily), inhaled budesonide 200 µg twice daily, and placebo. It found that nedocromil reduced the need for prednisolone and emergency care visits compared with placebo (see table 1, p 29). However, it found no significant difference between nedocromil and placebo in admissions to hospital, need for beclometasone or other asthma medications, or FEV_{1} (see table 1, p 29).

**Inhaled nedocromil versus inhaled corticosteroids:**

See benefits of inhaled corticosteroids, p 10.

**Harms:**

**Inhaled nedocromil versus placebo:**

Sore throat and headache were reported marginally more often with nedocromil than with placebo in the first RCT. The second RCT found no significant difference between nedocromil and placebo in adverse event rates, except for more frequent respiratory adverse events with placebo.

**Inhaled nedocromil versus inhaled corticosteroids:**

See harms of inhaled corticosteroids, p 10.

**Comment:**

None.
is more effective than inhaled beclometasone at improving lung function measured by forced expiratory volume in 1 second (low-quality evidence).

Airway hyperresponsiveness / bronchial reactivity

Inhaled long acting beta₂ agonists compared with inhaled corticosteroids

Inhaled salmeterol may be less effective than inhaled beclometasone at reducing airway hyperresponsiveness (measured using methacholine 36 hours after study medication) at 12 months (low-quality evidence).

Note

Although monotherapy with long acting beta₂ adrenergic agonists decreases the frequency of asthma episodes, they may increase the chance of severe asthma episodes and death when those episodes occur.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30.

Benefits: Inhaled long acting beta₂ agonist versus placebo:

We found no systematic review. We found two RCTs. The first RCT (241 children aged 6–14 years with clinically stable asthma and < 1 month of prior glucocorticoid use) compared inhaled salmeterol (80 children) versus beclometasone (81 children) versus placebo (80 children) for 1 year. The RCT found that salmeterol significantly improved lung function (mean change in forced expiratory volume in 1 second as a percentage of predicted, 10% with salmeterol v 5% with placebo; P < 0.001) but found no significant difference in the use of rescue salbutamol (days and nights without need for salbutamol: 88% with salmeterol v 83% with placebo; P = 0.09) or withdrawals because of exacerbations (15 with salmeterol v 15 with placebo; P = 0.55) compared with placebo. The second RCT (parallel group study, 207 children aged 4–11 years with asthma diagnosed according to American Thoracic Society guidelines, receiving usual care, including as needed inhaled beta agonists, FEV₁ [without medication] 50–80% predicted) compared inhaled salmeterol 50 µg twice daily versus placebo for 12 weeks. The RCT found that salmeterol significantly improved lung function compared with placebo (change in mean morning peak expiratory flow rate 25 L/minute with salmeterol v 13.2 L/minute with placebo; P < 0.001; change in mean evening peak expiratory flow rate 20 L/minute with salmeterol v 10.1 L/minute with placebo; P = 0.01) and reduced salbutamol use (–0.8 with salmeterol v –0.3 with placebo; P = 0.004). It found no significant difference in the number of nights without awakenings between salmeterol and placebo.

Inhaled long acting beta₂ agonist versus inhaled corticosteroids:

See benefits of inhaled corticosteroids, p 10.

Harms:

The American Food and Drug Administration have issued a warning that, although monotherapy with long acting beta₂ adrenergic agonists decreases the frequency of asthma episodes, they may increase the chance of severe asthma episodes and death when those episodes occur. Long acting beta₂ agonists occasionally cause tremor or tachycardia.

Inhaled long acting beta₂ agonist versus placebo:

One RCT found no evidence of adverse effects from salmeterol over 1 year. The second RCT found no significant difference between salmeterol and placebo for adverse effects.

Inhaled long acting beta₂ agonist versus inhaled corticosteroids:

See harms of inhaled corticosteroids, p 10.

Comment:

Clinical guide:

Monotherapy with long acting beta₂ agonists is not advised because of the possibility of significant deterioration in bronchial reactivity, indicating a failure to control underlying bronchial inflammation (see harms of inhaled corticosteroids, p 10).

OPTION THEOPHYLLINE (ORAL)

Symptom improvement

Oral theophylline compared with placebo

Oral theophylline added to usual care seems to be more effective than adding placebo to usual care at increasing mean morning peak expiratory flow rate and reducing the mean number of acute night time attacks and doses of bronchodilator used in children aged 6-15 years experiencing at least 2 night awakenings per week (moderate-quality evidence).

Oral theophylline versus inhaled corticosteroids

Oral theophylline added to usual care may be less effective than inhaled beclomethasone added to usual care at reducing the use of bronchodilators and oral corticosteroids, but not at improving mean asthma symptom scores in children aged 6-16 years (low-quality evidence).

Note

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Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30

Benefits: Oral theophylline versus placebo:
We found no systematic review. We found one RCT (crossover study, 24 children aged 6–15 years experiencing at least 2 night awakenings/week, receiving usual care, including as needed inhaled beta₂ agonists) comparing once daily oral sustained release theophylline (mean theophylline level of 11.2 mg/L) versus placebo for 6 weeks. The RCT found that theophylline significantly increased mean morning peak expiratory flow rate (244 L/minute with theophylline v 207 L/minute with placebo; P < 0.001) and significantly reduced the mean number of acute night time attacks (3.2 with theophylline v 10.7 with placebo; P < 0.001) and the mean number of doses of bronchodilator used (6.5 with theophylline v 23.7 with placebo; P < 0.001) compared with placebo.

Oral theophylline versus inhaled corticosteroids:
See benefits of inhaled corticosteroids, p 10.

Harms: Oral theophylline versus placebo:
The RCT found significantly higher rates of gastric symptoms, including dyspepsia, nausea, and vomiting with oral sustained release theophylline versus placebo (30% with theophylline v 6% with placebo; P < 0.001). One systematic review (search date not reported, 12 studies, 340 children) of the behavioural and cognitive effects of theophylline found no evidence of significant adverse effects. Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded.

Oral theophylline versus inhaled corticosteroids:
See harms of inhaled corticosteroids, p 10.

Comment: None.

LEUKOTRIENE RECEPTOR ANTAGONISTS (ORAL)

Symptom improvement
Oral leukotriene receptor antagonists compared with placebo Oral montelukast (a leukotriene receptor antagonist) added to usual care may be more effective than placebo added to usual care at increasing mean morning lung function (measured by forced expiratory volume in 1 second) and decreasing daily beta₂ agonist use, but not in reducing the number of days without beta agonist use, the proportion of children with worsening asthma, the proportion of children having at least one asthma attack, and nocturnal awakenings with asthma (very low-quality evidence).

Oral montelukast compared with inhaled corticosteroids Oral montelukast may be less effective than inhaled fluticasone at increasing lung function (measured by forced expiratory volume in 1 second, morning and evening peak expiratory flow rate), rescue medication-free days, and the proportion of parents and physicians "very satisfied" with treatment, and at reducing night time symptom scores in children aged 6–12 years with chronic asthma for at least 6 months. We don't know whether oral montelukast is more effective than high or low dose budesonide at improving clinical score or lung function at 6 months in newly diagnosed mildly asthmatic children aged 6–18 years (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30

Benefits: Oral leukotriene receptor antagonists versus placebo:
We found no systematic review. We found four RCTs. The first RCT (parallel group study, 336 children aged 6–16 years with mean forced expiratory volume in 1 second [FEV₁] 72% predicted, concomitant inhaled steroid treatment in 33% of placebo group and 39% of montelukast group) compared oral montelukast 5 mg daily versus placebo for 8 weeks. The RCT found that montelukast significantly increased the mean morning FEV₁ (8.2% with montelukast v 3.6% with placebo; P < 0.001) and significantly reduced the total daily beta₂ agonist use (reduced by 13% with montelukast and increased by 9.5% with placebo; P = 0.01) compared with placebo. The RCT found no significant difference between montelukast and placebo in day time asthma symptom score or in nocturnal awakenings with asthma. The second RCT (parallel group study, 689 children aged 2–5 years, concomitant inhaled steroid treatment in 29% of the placebo group, 27% of the montelukast group, 2:1 ratio montelukast : placebo group) compared oral montelukast (4 mg/day) versus placebo for 12 weeks. The RCT found that montelukast significantly improved average day time symptom scores (improved by 0.37 with montelukast v 0.26 with placebo on a 6 point scale; P = 0.003) and reduced the need for rescue oral steroid courses (needed in 19%
with montelukast v 28% with placebo; P = 0.008) compared with placebo. The RCT found no significant difference between montelukast and placebo in average overnight asthma symptom scores. The third small RCT compared montelukast (4 mg) versus placebo, but did not provide statistical comparisons between treatments. It found that there was a significant improvement from baseline in forced expiratory volume in 0.5 seconds (FEV0.5) and symptom score with montelukast but not with placebo (24 children aged 10–26 months with probable early childhood asthma, defined as recurrent wheeze, atopy on skin testing, elevated exhaled nitric oxide and a positive family history of asthma; mean FEV0.5 : 189 mL at baseline to 214 mL after treatment with montelukast; P = 0.038; v 161 mL at baseline to 166 mL after treatment with placebo; P = 0.26; symptom score based on cough wheeze and shortness of breath, scores range 0 [no symptoms] to 18 [severe symptoms], median score: 5.5 at baseline to 1.5 after treatment with montelukast; P = 0.04; v 3.0 at baseline to 4.0 after treatment with placebo; P = 0.35). The fourth double blind RCT compared montelukast (4 mg oral granules) versus placebo for 6 weeks.

Oral leukotriene receptor antagonists versus inhaled corticosteroids:
See benefits of inhaled corticosteroids, p 10.

Harms:
Oral leukotriene receptor antagonists versus placebo:
The first two RCTs found no significant difference in the incidence of adverse effects with montelukast versus placebo. The third small RCT gave no information on adverse effects. The fourth RCT (256 children aged 6–24 months with mild asthma) found no significant difference between montelukast and placebo at 6 weeks for overall treatment related adverse effects (reported as no significant difference, figures not reported), upper respiratory tract infection (mean difference +11.0%, 95% CI –1% to +21%), fever (–0.4%, 95% CI –11% to +8%), diarrhoea (–2%, 95% CI –11% to +6%), or vomiting (–3%, 95% CI –12% to +5%).

Oral leukotriene receptor antagonists versus inhaled corticosteroids:
See harms of inhaled corticosteroids, p 10.

Comment:
None.

QUESTION What are the effects of additional prophylactic treatments in childhood asthma inadequately controlled by standard dose inhaled corticosteroids?

OPTION INCREASED DOSE OF INHALED CORTICOSTEROID

Symptom improvement
*Increased dose of inhaled corticosteroid* In children already taking inhaled beclomethasone twice daily, adding a further dose of inhaled beclomethasone twice daily may be no more effective than adding placebo at improving lung function, symptom scores, or exacerbation rates at 1 year in children aged 6-16 years whose compliance with existing medication is good (low-quality evidence).

Airway hyperresponsiveness / bronchial reactivity
*Increased dose of inhaled corticosteroid* In children already taking inhaled beclomethasone twice daily, adding a further dose of inhaled beclomethasone twice daily may be no more effective than adding placebo at improving bronchial reactivity or airway responsiveness at 1 year, in children aged 6-16 years whose compliance with existing medication is good (low-quality evidence).

Adverse effects
*Increased dose of inhaled corticosteroid* In children already taking inhaled beclomethasone twice daily, adding a further dose of inhaled beclomethasone twice daily may reduce growth compared with adding placebo in children aged 6-16 years whose compliance with existing medication is good (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30.
Benefits: Increased dose of inhaled corticosteroid:
We found no systematic review. We found one RCT (177 children aged 6–16 years, already taking beclometasone 200 µg twice daily, mean pre-bronchodilator forced expiratory volume in 1 second [FEV₁] 86% predicted) found that at 3 months adding salmeterol to beclometasone 200 µg twice daily versus salmeterol 50 µg twice daily versus placebo. [59] No significant differences were found at 1 year in lung function (mean change in forced expiratory volume in 1 second 5.8% predicted, 95% CI 2.9% to 8.7% with double dose beclometasone v 4.3%, 95% CI 2.1% to 6.5% with placebo), symptom scores, exacerbation rates, bronchial reactivity, or changes in airway responsiveness (1.30 units of methacholine, 95% CI 0.73 units to 1.87 units with salmeterol v 0.80 units of methacholine, 95% CI 0.33 units to 1.27 units with placebo). No benefit of either adding salmeterol or a second dose of beclometasone was found in this group of children, whose compliance with pre-existing medication was good.

Harms: Increased dose of inhaled corticosteroid:
Growth was significantly slower in children receiving higher dose inhaled corticosteroids at 1 year follow up (3.6 cm, 95% CI 3.0 cm to 4.2 cm with double dose beclometasone v 5.1 cm, 95% CI 4.5 cm to 5.7 cm with salmeterol v 4.5 cm, 95% CI 3.8 cm to 5.2 cm with placebo). There have been case reports of serious adrenal crisis in children receiving high doses of inhaler steroid, principally fluticasone in doses above 500 µg daily. [34]

Comment: Higher dose inhaled corticosteroids are frequently used, despite lack of evidence of benefit. In some children, higher prescribed doses may compensate for poor compliance or incorrect inhaler technique.

**OPTION** ADDITION OF REGULAR (DAILY) LONG ACTING BETA2 AGONIST

**Symptom improvement**
Addition of regular (daily) long acting beta₂ agonist The addition of inhaled salmeterol (a long acting beta₂ agonist) to inhaled beclometasone may be more effective than inhaled beclometasone alone at increasing mean morning peak expiratory flow rates at 3 months, but not in improving lung function, exacerbation rates, or symptom scores, at 1 year in children aged 6-16 years. The addition of inhaled salmeterol to inhaled corticosteroids may be more effective than the addition of placebo at increasing mean morning peak expiratory flow rates and symptom free days at 3 months, but not in increasing mean evening peak expiratory flow rates in children aged 4-16 years. The addition of formoterol to inhaled corticosteroids may be more effective than adding placebo at improving lung function at 12 weeks, but not at improving symptom scores, the use of rescue medication, or quality of life in children aged 6-11 years (low-quality evidence).

**Airway hyperresponsiveness / bronchial reactivity**
Addition of regular (daily) long acting beta₂ agonist The addition of inhaled salmeterol (a long acting beta₂ agonist) to inhaled beclometasone may be no more effective than inhaled beclometasone alone at improving airway responsiveness or bronchial reactivity at 1 year in children aged 6-16 years (low-quality evidence).

**Note**
Long acting beta₂ adrenergic agonists may increase the chance of severe asthma episodes and death when those episodes occur.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

Benefits: Addition of regular (daily) long acting beta₂ agonist:
We found no systematic review. We found three RCTs. [59] [60] [61] The first RCT (177 children aged 6–16 years, 1 year follow up, mean pre-bronchodilator forced expiratory volume in 1 second [FEV₁] 86% predicted) found that at 3 months adding salmeterol to beclometasone 200 µg twice daily increased mean morning peak expiratory flow rates (PEFR) compared with beclometasone alone (difference: +12 L/minute; P value not reported). [59] At 1 year of follow up there were no significant differences were found in symptom scores at any time. The second RCT (210 children aged 4–16 years, 12 weeks of follow up, mean morning PEFR 79% predicted; P < 0.05) The median proportion of symptom free days improved more with addition of salmeterol than without (60% with salmeterol v 30% with placebo for the third month of treatment; P < 0.05). The third RCT (302 children aged 6–11 years, 14 weeks of follow up, mean morning FEV₁ 78% predicted) compared addition of formoterol 4.5 or 9 µg twice daily versus placebo in children inadequately controlled on inhaled corticosteroids (average dose 750 µg/day). [60] At 12 weeks, mean morning PEFR (relative to the predicted PEFR) was 4% higher in the salmeterol group (P < 0.05). Mean evening PEFR was not significantly different. The median proportion of symptom free days improved more with addition of salmeterol than without (60% with salmeterol v 30% with placebo for the third month of treatment; P < 0.05) The third RCT (302 children aged 6–11 years, 14 weeks of follow up, mean morning FEV₁ 78% predicted) compared addition of formoterol 4.5 or 9 µg twice daily versus placebo in children inadequately controlled on inhaled corticosteroids (average dose 450 µg/day). [61] Formoterol significantly increased mean morning PEFR compared with placebo over 12 weeks (increase in PEFR compared with placebo: 7.8 L/minute, 95% CI 0.6 L/minute to 15.0 L/minute with formoterol 4.5 µg;
At 12 weeks, formoterol significantly increased FEV₁ compared with placebo (increase in % predicted FEV₁ compared with placebo: 4.01%, 95% CI 1.22% to 6.81% with formoterol 4.5 µg; 3.63%, 95% CI 0.72% to 6.55% with formoterol 9 µg). At 12 weeks, the RCT found no significant differences between formoterol and placebo in symptoms scores, use of rescue medication, or quality of life (P values not reported).

Harms: Addition of regular (daily) long acting beta₂ agonist:
Three RCTs found no significant adverse effects associated with salmeterol or formoterol. The American Food and Drug Administration have issued a warning that, although monotherapy with long acting beta₂ adrenergic agonists decreases the frequency of asthma episodes, they may increase the chance of severe asthma episodes and death when those episodes occur.

Comment: The second RCT was organised and funded by the manufacturer of salmeterol. Studies of adults with poor control on low dose inhaled corticosteroids have found greater benefit with additional long acting beta₂ agonists than with higher doses of inhaled steroid (see salmeterol versus high dose inhaled corticosteroids in the topic on asthma in adults).

**OPTION ADDITION OF ORAL THEOPHYLLINE**

**Symptom improvement**

Addition of oral theophylline: The addition of oral theophylline to existing treatment may be more effective than the addition of placebo at increasing the mean number of symptom free days and reducing the use of additional beta agonist (orciprenaline) and additional corticosteroid (beclometasone or prednisolone) at 4 weeks, but not in improving symptoms (as recorded on diary cards) or in decreasing the use of rescue medication (very low-quality evidence).

Note: Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

**Benefits:**
We found no systematic review and two RCTs. The first RCT (double blind, crossover trial; 33 children aged 6–19 years, recruited from a hospital asthma clinic, 22 children using inhaled beclometasone [mean 533 µg/day], 11 using oral prednisolone [mean 30 mg alternate days]) found that the addition for 4 weeks of oral theophylline (serum concentration 10–20 µg/mL) increased the mean number of symptom free days (63% with theophylline v 42% with placebo; P less-than or equal to 0.01) compared with placebo. Inhaled beta agonist (orciprenaline) was needed twice as often with placebo (0.5 doses/day with theophylline v 1.0 doses/day with placebo; P less-than or equal to 0.01). Additional daily prednisolone was needed by fewer children with theophylline than with placebo (3/32 [9%] with theophylline v 10/32 [31%] with placebo; P = 0.02). The second RCT (36 children, parallel groups, mean age 12.5 years, using inhaled steroids for at least 6 months before study entry) found that adding theophylline (to a mean serum theophylline level of 7.1 µg/mL) did not significantly improve symptoms (as recorded on diary cards) or use of rescue medication (P value not reported; see comment below).

**Harms:**
In the first RCT, short term adverse effects included mild transient headache and nausea in six children after the crossover from placebo to the theophylline dose that they had previously tolerated.

The RCTs were too small and brief to comprehensively assess harms. Theophylline has serious adverse effects (cardiac arrhythmia, convulsions) if therapeutic blood concentrations are exceeded.

**Comment:**
In the first RCT, one child was excluded from the analysis because of poor compliance. The second RCT did not present between group comparisons for lung function but found that, at 12 weeks of follow up, addition of oral theophylline significantly improved peak expiratory flow rate (P = 0.02) compared with baseline, although forced expiratory volume in 1 second (FEV₁) remained unchanged (P = 0.5).

**OPTION ADDITION OF ORAL LEUKOTRIENE RECEPTOR ANTAGONISTS**

**Symptom improvement**
Addition of oral leukotriene receptor antagonists: In children aged 6–14 years with persistent asthma who had been taking inhaled budesonide for at least 6 weeks, adding oral montelukast to inhaled budesonide may be more effective than adding placebo to inhaled budesonide at modestly reducing asthma exacerbation days at 4 weeks, but not in improving global evaluations or reducing asthma attacks requiring unscheduled medical intervention or treatment with oral corticosteroid (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

Benefits: Addition of oral leukotriene receptor antagonists:
We found no systematic review but found one crossover RCT (279 children aged 6–14 years previously treated with inhaled corticosteroid for at least 6 weeks, with mean forced expiratory volume in 1 second (FEV₁) 78% predicted after 1 month run-in with budesonide 200 µg), which compared adding oral montelukast versus adding placebo to inhaled budesonide over 4 weeks. It found fewer asthma exacerbation days (decrease from baseline peak flow of > 20%, or increase from baseline of beta₂ agonist use of > 70%) with montelukast compared with placebo (12.2% with montelukast v 15.9% with placebo; P < 0.001). No significant differences were found in quality of life measurements, global evaluations, or asthma attacks requiring unscheduled medical intervention or treatment with oral corticosteroid.

Harms: Addition of oral leukotriene receptor antagonists:
The RCT found no significant difference with montelukast versus placebo in asthma exacerbation, upper respiratory tract infection, headache, cough, pharyngitis, and fever.

Comment: The RCT in children was brief (4 weeks of treatment). We found one large RCT of montelukast added to beclometasone in adults with inadequately controlled asthma, which found benefit over a 16 week period. Both RCTs were funded by the manufacturers of montelukast.

QUESTION What are the effects of treatments for acute wheezing in infants?

OPTION SHORT ACTING BETA2 AGONISTS VERSUS PLACEBO

Symptom improvement
Nebulised salbutamol compared with placebo: Nebulised salbutamol may be more effective than placebo at improving respiratory rate in infants aged 3 months to 2 years with acute exacerbation of wheeze in hospital emergency room settings. We don’t know whether nebulised salbutamol is more effective than placebo at improving clinical symptom scores in infants with acute exacerbation of wheeze in hospital emergency room settings (very low-quality evidence).

Hospital admission / length of stay
Nebulised salbutamol compared with placebo: Nebulised salbutamol seems to be no more effective than placebo at reducing hospital admission in infants aged 3 months to 2 years with acute exacerbation of wheeze in hospital emergency room settings (low-quality evidence).

Note
Nebulised beta₂ agonists may cause tachycardia, tremor, and hypokalaemia.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

Benefits: Nebulised salbutamol versus placebo:
We found one systematic review (search date not reported, 2 RCTs, children with an acute exacerbation of wheeze in hospital emergency room settings). The first RCT (28 infants, aged 3 months to 2 years) compared nebulised salbutamol (0.3 mg/kg in 2 doses over 1 hour) versus placebo for respiratory rate and symptom score (assessment of heart rate, respiratory rate, wheeze, and accessory muscle score). The RCT found that nebulised salbutamol significantly improved respiratory rate (WMD −5.10 breaths/minute, 95% CI −9.45 breaths/minute to −0.75 breaths/minute) and total clinical symptom score for heart rate, respiratory rate, wheezing, and accessory muscle use (clinical symptom score scale 0 [none] to 3 [severe], WMD −2.50, 95% CI −3.88 to −1.12) compared with placebo but found no significant difference in hospital admission (OR 1.95, 95% CI 0.27 to 13.98). The second RCT (28 infants aged < 18 months and 13 infants aged 18–36 months with acute wheeze) found no significant difference in change from baseline in clinical symptom scores with nebulised salbutamol (2 doses of 0.15 mg/kg) versus placebo. Some improvement was observed in children aged over 18 months, but this was not statistically significant (P not reported).
Harms: **Nebulised salbutamol versus placebo:**

The systematic review did not comment on any adverse effects of nebulised salbutamol in infants with acute wheezing. Nebulised beta\(_2\) agonists may cause tachycardia, tremor, and hypokalaemia.

**Comment:** None.

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### SHORT ACTING BETA\(_2\) AGONISTS DELIVERED BY METERED DOSE INHALER/SPACER VERSUS NEBULISER

#### Symptom improvement

**Delivery through metered dose inhaler compared with nebuliser**

We don't know whether delivery of terbutaline through a metered dose inhaler plus spacer is more effective than delivery of terbutaline through a nebuliser at improving clinical score (assessing respiratory rate, wheezing, retractions, degree of cyanosis, colour, and pulse oximetry data) in infants aged 1–24 months (low-quality evidence).

#### Hospital admission / length of stay

**Delivery through metered dose inhaler compared with nebuliser**

We don't know whether delivery of salbutamol through a metered dose inhaler plus spacer is more effective than delivery of salbutamol through a nebuliser in reducing hospital admissions in infants less than 2 years with acute wheezing or in children aged 1-5 years with acute recurrent wheezing (low-quality evidence).

**Note**

Nebulised beta\(_2\) agonists may cause tachycardia, tremor, and hypokalaemia.

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30

#### Benefits

**Delivery through metered dose inhaler versus nebuliser:**

We found no systematic review. We found three RCTs comparing delivery of short acting beta\(_2\) agonists through metered dose inhaler versus nebuliser. The first RCT (64 children aged 1–5 years with acute recurrent wheezing) found no significant difference in hospital admissions with delivery of salbutamol 50 µg/kg through a metered dose inhaler plus spacer versus nebulised salbutamol 150 µg/kg. The second RCT (42 infants, mean age < 2 years with acute wheezing) found no significant difference in hospital admissions with delivery of salbutamol 400 µg through a metered dose inhaler plus spacer versus nebulised salbutamol 2.5 mg. The third RCT (34 infants aged 1–24 months) found no significant difference in the rate of improvement from baseline of a clinical score (assessing respiratory rate, wheezing, retractions, degree of cyanosis, colour, and pulse oximetry data) with delivery of terbutaline 500 µg through a metered dose inhaler plus spacer versus nebulised terbutaline 4 mg.

**Harms:**

**Delivery through metered dose inhaler versus nebuliser:**

Three RCTs found no clinically significant adverse events.

**Comment:** None.

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### IPRATROPIUM BROMIDE (INHALED)

#### Symptom improvement

**Addition of inhaled ipratropium bromide to short acting beta\(_2\) agonist**

The addition of ipratropium bromide to beta\(_2\) agonist may be more effective than beta\(_2\) agonist alone at reducing the need for further drug treatment at 45 minutes in infants presenting to emergency departments, but not at improving "excellent" clinical response (very low-quality evidence).

#### Hospital admission / length of stay

**Inhaled ipratropium bromide compared with placebo**

Inhaled ipratropium bromide may be no more effective than placebo at reducing duration of hospital stay in infants aged 2-24 months admitted to hospital for acute wheeze (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table, p 30

#### Benefits

**Inhaled ipratropium bromide versus placebo:**

We found one systematic review (search date 2001, 1 RCT, 31 infants aged 2–24 months, admitted to hospital for acute wheeze). The RCT included in the review found no significant difference in duration of hospital stay between ipratropium bromide (125–250 µg depending on age) and placebo (WMD = –0.4 days, 95% CI –1.4 days to +0.61 days).
Addition of inhaled ipratropium bromide to short acting beta₂ agonist:
We found one systematic review (search date 2001, 2 RCTs, 130 infants presenting to emergency department). The first RCT (69 infants) included in the review compared addition of ipratropium bromide beta₂ agonist versus beta₂ agonist alone and found that combined treatment significantly reduced the need for further drug treatment after 45 minutes compared with beta₂ agonist alone (OR 0.22, 95% CI 0.08 to 0.61). The second RCT (61 infants) included in the review compared addition of ipratropium bromide to albuterol 0.15 mg/kg versus addition of placebo and found no significant difference in the frequency of “excellent” clinical response (OR 0.96, 95% CI 0.37 to 2.47). Two further RCTs included in the review compared ipratropium bromide in addition to beta₂ agonist versus placebo in infants admitted to hospital for acute wheezing, although quality and design issues limit the conclusions that can be drawn from these studies.

Harms: The systematic review did not report on adverse events during treatment with ipratropium bromide.

Comment: The results of the review do not support the widespread, indiscriminate use of anticholinergic agents in the treatment of children under the age of 2 years with airflow obstruction and wheeze. It is possible that infants did obtain symptomatic relief but that this was not always identified by the outcomes chosen.

OPTION CORTICOSTEROIDS (ORAL)

Symptom improvement
Oral corticosteroids compared with placebo: We don’t know whether oral corticosteroids are more effective than placebo (any other treatments given not specified) at improving daily symptom scores (cough, wheeze, or breathlessness) in acutely wheezing infants aged 3–17 months (very low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

Benefits: Oral corticosteroids versus placebo: We found no systematic review. We found one RCT (38 acutely wheezing infants aged 3–17 months with wheezing episode lasting greater than or equal to 48 hours, including 30 infants who had previously been admitted to hospital with wheeze) comparing oral prednisolone (2 mg/kg/day) versus placebo given for 5 days during an acute wheezing episode. It found no significant difference in daily symptom score (cough, wheeze, or breathlessness; P = 0.64) between treatment and placebo groups.

Harms: Oral corticosteroids versus placebo: No adverse effects were reported by parents in this RCT.

Comment: None.

OPTION CORTICOSTEROIDS (HIGH DOSE INHALED)

Symptom improvement
Corticosteroids (high dose inhaled): Episodic high dose inhaled corticosteroids given at the onset of upper respiratory tract symptoms may be more effective than placebo at increasing parental preference (the clinical importance of which is unclear), but not at reducing the need for oral corticosteroids in infants with acute viral wheeze. We don’t know whether high dose inhaled budesonide is more effective than placebo at increasing symptom free days or increasing improvement on a physician rated global assessment of health status measure in children aged 6-12 months with mild to moderate recurrent wheeze (very low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

Benefits: Corticosteroids (high dose inhaled): We found one systematic review (search date 1999, 3 RCTs, 122 infants with acute viral wheeze) and one subsequent RCT. The primary outcome for the review was wheeze episodes requiring oral corticosteroids. The review found that episodic high dose inhaled corticosteroids (budesonide, beclometasone) given at onset of upper respiratory tract symptoms reduced the need for oral corticosteroids compared with placebo, but the difference was not statistically significant (2 crossover RCTs, 67 infants; RR 0.53, 95% CI 0.27 to 1.04). A third RCT (55 infants, parallel study), not included in the meta-analysis due to heterogeneity, also found that inhaled corticosteroid given at onset of upper respiratory tract symptoms reduced episodes requiring oral corticosteroids, although the difference was not statistically significant (RR 0.82, 95% CI 0.52 to 1.29).
review also found a clear parental preference for the inhaled corticosteroids over placebo (2 crossover RCTs, 67 infants; RR 0.64, 95% CI 0.48 to 0.87). The subsequent RCT compared high dose inhaled budesonide 0.5 or 1.0 mg daily versus placebo over 12 weeks, and its primary outcome was safety (see harms below). It found that budesonide increased symptom free days, but the significance of this difference was not assessed (141 children aged 6–12 months with mild to moderate recurrent wheeze; mean % symptom free days: 43.4% with budesonide 1 mg v 48.8% with budesonide 0.5 mg v 37.5% with placebo; significance assessment not performed). It found no significant difference in the improvement on a physician rated global assessment of health status (AR for a rating of a “great deal better” or “somewhat better”: 85% with budesonide 1 mg v 90% with budesonide 0.5 mg v 67% with placebo; reported as not significant, figures not reported).

Harms: Corticosteroids (high dose inhaled):
One participant withdrew from one RCT included in the review because of suspected adverse effects of budesonide (no further details reported). The systematic review did not report specifically on adverse events. The subsequent RCT found that more people receiving budesonide had abnormal adrenal function on low dose postcosyntropin test than with placebo, but this difference did not reach significance (AR for abnormal adrenal function: 11.8% with budesonide 1 mg v 14.3% with budesonide 0.5 mg v 3.2% with placebo; difference reported as not significant; figures not reported).

Comment:
Most of the RCTs included in the systematic review were carried out before the 1990s, when it was commonly thought that wheeze was synonymous with asthma, and different patterns of wheeze in young children were seldom recognised. Although there is some evidence to support the use of high dose inhaled corticosteroids in acute episodes of viral wheeze, the practicalities of delivering treatment may limit applicability.

QUESTION
What are the effects of prophylactic treatments for wheezing in infants?

OPTION IPRATROPIUM BROMIDE (INHALED)

Symptom improvement
*Inhaled ipratropium bromide* Nebulised ipratropium bromide may be no more effective than placebo at improving relief of symptoms (as defined by diary cards) in infants aged 4–23 months with recurrent episodes of wheeze managed at home (low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

Benefits: *Inhaled ipratropium bromide:*
We found one systematic review (search date 2001, 1 RCT). The RCT (crossover, 23 infants aged 4–23 months with recurrent episodes of wheeze managed at home) included in the review compared nebulised ipratropium bromide versus placebo or sodium cromoglycate. The RCT found no significant difference in relief of symptoms, as defined by diary cards, for ipratropium bromide versus placebo (OR 0.60, 95% CI 0.19 to 1.88).

Harms: *Inhaled ipratropium bromide:*
The RCT reported no significant adverse effects with ipratropium bromide.

Comment:
The study may have lacked power to detect a clinically important difference between treatments. We found insufficient data to support the use of ipratropium bromide as a prophylactic agent for wheezing in infants.

OPTION SHORT ACTING BETA2 AGONISTS (ORAL)

Symptom improvement
*Oral short acting beta2 agonists* Oral salbutamol may be more effective than placebo at reducing treatment failures (not further defined) in infants aged 3–14 months with at least 1 previous wheezy episode (very low-quality evidence).

For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30

Benefits: *Oral short acting beta2 agonists:*
We found one systematic review (search date not reported, 1 RCT). The RCT (59 infants aged 3–14 months with at least 1 previous wheezy episode) compared oral salbutamol plus placebo, placebo plus prednisolone, and placebo plus placebo for 14 days. It found that oral salbutamol
Asthma and other wheezing disorders in children

(syrup 1 mg 3 times/day) significantly reduced treatment failures (RR 2.51, 95% CI 1.09 to 5.79) compared with placebo and found no significant difference between salbutamol alone and the combination of salbutamol plus prednisolone (RR 0.71, 95% CI 0.18 to 2.80). [79]

**Harms:**

**Oral short acting beta\(_2\) agonists:**

The systematic review (as above) did not report on adverse events. [66]

**Comment:**

None.

**OPTION**

| SHORT ACTING BETA\(_2\) AGONISTS (INHALED) |

**Symptom improvement**

**Inhaled short acting beta\(_2\) agonists**

Inhaled salbutamol may be no more effective than placebo at improving symptoms (measured in a diary card or including cough, wheezing, sleep problems, expectorations) or lung function (measurement not defined) in infants under 2 years with recurrent wheeze but no apparent history of acute viral bronchiolitis (very low-quality evidence).

**For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30**

**Benefits:**

**Inhaled short acting beta\(_2\) agonists:**

We found one systematic review (search date not reported, 2 RCTs, infants under 2 years with recurrent wheeze but no apparent history of acute viral bronchiolitis). [66] One RCT (crossover, 80 infants aged < 1 year with persistent or recurrent wheeze and a personal or family history of atopy) included in the review compared inhaled salbutamol (200 µg 3 times/day) versus placebo for 4 weeks. It found no significant difference between salbutamol and placebo in symptoms (recorded in a diary) or lung function (WMD +0.12, 95% CI −0.71 to +0.95). [85] Another RCT (29 infants aged 2–18 months with a history of recurrent wheeze) compared inhaled salbutamol 600 µg plus inhaled beclometasone 300 µg versus inhaled salbutamol 600 µg alone or placebo for 6 weeks. It found no significant improvement in symptoms (cough, wheezing, sleep problems, expectorations) with salbutamol compared with placebo (change in symptom score from baseline: −0.2 with salbutamol vs +0.3 with placebo; P > 0.05).

**Harms:**

**Inhaled short acting beta\(_2\) agonists:**

The systematic review did not report on adverse events. [66]

**Comment:**

None.

**OPTION**

| CORTICOSTEROIDS (INHALED) LOWER DOSE |

**Symptom improvement**

**Lower dose inhaled corticosteroids compared with placebo** We don’t know whether lower dose inhaled corticosteroids are more effective than placebo at improving symptoms in infants with wheeze (very low-quality evidence).

**Addition of inhaled corticosteroid to short acting beta\(_2\) agonist**

Inhaled beclometasone plus inhaled salbutamol may be more effective than placebo at improving symptom scores in infants aged 2-18 months with a history of recurrent wheeze (very low-quality evidence).

**For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30**

**Benefits:**

**Lower dose inhaled corticosteroids versus placebo:**

We found one systematic review (search date 1999, 1 RCT, 41 children aged 7 months to 6 years), [75] two additional RCTs [82] [83] and three subsequent RCTs. [84] [85] [86] The RCT included in the review (41 children) found no significant difference after 4 months in acute episodes of wheeze with inhaled budesonide (400 µg/day through metered dose inhaler) compared with placebo. [87] The RCT did not analyse infants separately. The first additional RCT (29 infants aged 4–17 months with recurrent wheeze) found that inhaled budesonide (150 µg through a metered dose inhaler) significantly improved breathlessness, day time wheeze, and day time cough compared with placebo, but not night time wheeze and cough (breathlessness: SMD 0.21, 95% CI 0.05 to 0.37; P = 0.02; day time wheeze: SMD 0.53, 95% CI 0.10 to 0.96; P = 0.03; day time cough: SMD 0.35, 95% CI 0.05 to 0.65; P = 0.04; night time wheeze and cough: P > 0.05, no further data reported). It found no significant difference in the need for bronchodilators between inhaled budesonide (150 µg through a metered dose inhaler) and placebo (SMD +0.27, 95% CI −0.06 to +0.60; P = 0.12). [82] The second additional RCT (30 infants aged 7–24 months with wheeze and a family history of asthma or atopy) compared fluticasone propionate 50 µg twice daily versus fluticasone propionate 125 µg twice daily versus placebo given for 6 months (10 infants in each group). [83] The RCT
found that fluticasone significantly reduced wheezing episodes compared with placebo (mean number of episodes: 1.9 with fluticasone 50 µg v 2.8 with fluticasone 125 µg v 6.0 with placebo; P < 0.01). The first subsequent RCT (31 infants aged 13–18 months with recurrent wheeze, already taking salbutamol on an as needed basis) compared inhaled beclometasone 200 µg twice daily versus inhaled placebo administered for 8 weeks. [84] It found no significant difference between beclometasone and placebo in clinical score (data not reported), number of salbutamol doses, sleep disturbance, or number of symptom free days (mean daily doses of salbutamol in the last 2 weeks were 2.1, 95% CI 1.5 to 2.7 v 0.8, 95% CI 0.6 to 1.0; sleep disturbance, mean night wakings were 1.4, 95% CI 1 to 1.8 v 1.6, 95% CI 1.1 to 2.1; mean number of symptom free days in the last 2 weeks were 4.0, 95% CI 3.2 to 4.8 v 3.7, 95% CI 2.3 to 5.1). [84] The second subsequent double blind RCT compared fluticasone propionate 200 µg daily versus placebo. [85] It found that fluticasone significantly increased the proportion of symptom free days at 6 weeks compared with placebo but found no significant difference between treatments in the percentage of symptom free days or nocturnal symptom scores at 3 months (65 children aged 4–24 months with at least 3 episodes of wheeze or one prolonged period of persistent wheeze lasting longer than 2 months; difference in symptom free days at 6 weeks: 23%, 95% CI 9% to 43%; difference in symptom free days at 3 months: +12%, 95% CI −11% to +34%; difference in nocturnal symptom score: reported as not significant, figures not reported). The third subsequent RCT compared fluticasone propionate (125 µg twice daily by spacer) versus placebo over 6 months. [86] It found that fluticasone significantly increased symptom free days and significantly reduced the number of respiratory exacerbations and days on albuterol compared with placebo (26 children aged 6–20 months with 3 or more episodes of wheeze with a positive response to bronchodilators together with a family history of asthma or atopy in parents; symptom free days: 91.7% with fluticasone v 83.9% with placebo; P = 0.05; respiratory exacerbations: 2.1 with fluticasone v 4.1 with placebo; P = 0.04; days on albuterol: 8.6 with fluticasone v 16.3 with placebo; P = 0.028).

Addition of inhaled corticosteroid to short acting beta₂ agonist:
We found no systematic review but found one small RCT. [81] The RCT (29 infants aged 2–18 months with a history of recurrent wheeze) compared inhaled beclometasone 300 µg plus inhaled salbutamol 600 µg versus inhaled beclometasone 600 µg alone or placebo for 6 weeks. It found that beclometasone plus salbutamol improved symptom score (cough, wheezing, sleep problems, expectations) compared with placebo (P < 0.05).

Harms:
Lower dose inhaled corticosteroids versus placebo:
The first subsequent double blind RCT (65 children aged 4–24 months) reported no difference at 3 months between fluticasone propionate and placebo for non-serious adverse effects (figures or significance assessment not reported) and that there were no cases of oral candidiasis. [86] The second subsequent RCT found no similar growth rate over 6 months with fluticasone propionate (125 µg twice daily by spacer) versus placebo (14.2 cm/year with fluticasone v 12.2 cm/year with placebo; statistical assessment not performed). [86] The other RCTs did not report any adverse events. [82] [84] [87]

Comment:
None.

**OPTION**

CORTICOSTEROIDS (INHALED) HIGHER DOSE

**Symptom improvement**

Higher dose intermittent inhaled corticosteroids compared with placebo: Higher dose inhaled corticosteroids may be more effective than placebo at improving symptom scores, acute wheezing episodes, and reducing the proportion of days requiring oral prednisolone, but not at improving the number of exacerbations per child, cough, or restriction in physical activity because of coughing or wheezing (low-quality evidence).

**Note**

Higher doses of inhaled corticosteroids have the potential for adverse effects.

**For GRADE evaluation of interventions for asthma and other wheezing disorders in children, see table., p 30**

**Benefits:**

Higher dose intermittent inhaled corticosteroids versus placebo:
We found one systematic review (as above, search date 1999, 3 RCTs, high doses of inhaled corticosteroids) [75] and two additional RCTs. [88] [89] All three RCTs included in the review found that high dose inhaled corticosteroids (1600µg/day budesonide, 2250 µg/day beclometasone dipropionate, or 1600 µg twice daily budesonide) significantly improved symptom scores, although a meta-analysis was not possible for this outcome. Two of the included RCTs found a parental preference for high dose inhaled corticosteroids. The first additional RCT (40 infants aged 6–30 months with “severe infantile asthma” defined as recurrent or persistent wheeze) compared nebulised budesonide 1 mg twice daily versus placebo for 12 weeks. [86] The RCT found that, compared with
placebo, nebulised budesonide significantly reduced the proportion of children with acute wheezing episodes (40% with budesonide v 83% with placebo; \( P < 0.01 \)), incidence of day time wheezing (2.2% with budesonide v 11.6% with placebo; \( P < 0.05 \)), and incidence of night time wheezing (0.6% with budesonide v 6.5% with placebo; \( P < 0.01 \)) but did not significantly reduce the number of exacerbations per child (0 with budesonide v 1 with placebo; \( P = 0.13 \)). The second additional RCT (77 infants aged 11–36 months with moderate to severe recurrent wheezing) compared inhaled budesonide 400 \( \mu \)g twice daily versus placebo for 12 weeks. \(^{89}\) The RCT found that budesonide significantly improved symptom scores from baseline for wheezing and sleep disturbance compared with placebo (\( P < 0.05 \) for both symptoms) but found no significant difference for cough or for restriction in physical activity because of coughing or wheezing. It also found that inhaled budesonide versus placebo significantly reduced the proportion of days requiring oral prednisolone. \(^{89}\)

**Harms:**

**Higher dose inhaled corticosteroids versus placebo:** The RCTs did not report any adverse events. \(^{81}\) \(^{79}\) Higher doses of inhaled corticosteroids have the potential for adverse effects. See harms of inhaled corticosteroids, p 23 .

**Comment:**

None.

**GLOSSARY**

**Aminophylline:** A stable combination of theophylline and ethylenediamine; the ethylenediamine is added to increase the solubility of theophylline in water.

**Clinical asthma score:** is used to assess asthma severity. It involves five clinical variables (respiratory rate, wheezing, inspiratory–expiratory ratio, indrawing, dyspnoea), which are scored 0, 1, or 2. The scores for each variable are added together, with a possible total score of 10. (Parkin PC, Macarthur C, Saunders NR, et al. Development of clinical asthma score for use in hospitalized children between 1 and 5 years of age. J Clin Epidemial 1996;49:821–825.)

**Forced expiratory volume in 1 second (FEV\(_1\):** The volume breathed out in the first second of forceful blowing into a spirometer, measured in litres.

**Orciprenaline:** is known as metaproterenol in USA; it is a non-selective beta agonist.

**Peak expiratory flow rate (PEFR):** The maximum rate that gas is expired from the lungs when blowing into a peak flow meter or a spirometer. It is measured at an instant, but the units are expressed as litres a minute.

**Salbutamol:** is known as albuterol in USA; it is a short acting selective beta\(_2\) agonist.

**Viral wheeze:** is defined as wheeze in association with nasal congestion and discharge but minimal or no intermittent lower respiratory tract symptoms.

**SUBSTANTIVE CHANGES**

**High dose inhaled corticosteroids** One RCT added; \(^{76}\) categorisation unchanged (unknown effectiveness).

**Inhaled corticosteroids (lower dose)** Two RCTs added; \(^{85}\) \(^{86}\) categorisation unchanged (unknown effectiveness).

**Inhaled corticosteroids** Three RCTs added; \(^{30}\) \(^{31}\) \(^{32}\) categorisation unchanged (beneficial).

**Metered dose inhaler plus spacer devices for delivery of beta\(_2\) agonists** One RCT added; \(^{10}\) categorisation unchanged (beneficial).

**Oral leukotriene receptor antagonists (montelukast)** Two RCTs added; \(^{57}\) \(^{58}\) categorisation changed from Beneficial to Likely to be beneficial.
### TABLE 1
Comparison of inhaled budesonide, nedocromil, and placebo over 4–6 years on several measures of asthma symptoms and morbidity (%) [22].

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Budesonide (311 children)</th>
<th>Nedocromil (312 children)</th>
<th>Placebo (418 children)</th>
<th>Budesonide vs placebo</th>
<th>Nedocromil vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone courses per 100 person years</td>
<td>70</td>
<td>102</td>
<td>122</td>
<td>P &lt; 0.001</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Urgent care visits due to asthma per 100 person years</td>
<td>12</td>
<td>16</td>
<td>22</td>
<td>P &lt; 0.001</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Hospital admissions due to asthma per 100 person years</td>
<td>2.5</td>
<td>4.3</td>
<td>4.4</td>
<td>P = 0.04</td>
<td>P = 0.99</td>
</tr>
<tr>
<td>Beclomethasone or other asthma medications added (% of days)</td>
<td>6.6%</td>
<td>17.1%</td>
<td>18.7%</td>
<td>P &lt; 0.001</td>
<td>P = 0.53</td>
</tr>
<tr>
<td>Change in FEV1 (% of predicted) from baseline: before bronchodilator use</td>
<td>2.9</td>
<td>0.4</td>
<td>0.9</td>
<td>P = 0.02</td>
<td>P = 0.57</td>
</tr>
<tr>
<td>Changes in FEV1 (% of predicted) from baseline: after bronchodilator use</td>
<td>+0.6</td>
<td>-0.5</td>
<td>-0.1</td>
<td>P = 0.36</td>
<td>P = 0.56</td>
</tr>
</tbody>
</table>


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What are the effects of single agent prophylaxis in children taking as needed inhaled beta agonists for asthma?

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality of consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (70) [6]</td>
<td>Hospital admission / length of stay</td>
<td>Beta2 agonists</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality point deducted for sparse data. Directness point deducted for small number of comparisons</td>
</tr>
<tr>
<td>3 (not reported)</td>
<td>Symptom improvement</td>
<td>Single dose (in emergency room)</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality point deducted for incomplete reporting of results. Directness point deducted for unclear clinical relevance</td>
</tr>
<tr>
<td>3 (not reported)</td>
<td>Hospital admission / length of stay</td>
<td>Single dose (in emergency room)</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Quality point deducted for incomplete reporting of results</td>
</tr>
<tr>
<td>4 (not reported)</td>
<td>Symptom improvement</td>
<td>Multiple doses (in emergency room)</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Quality point deducted for incomplete reporting of results</td>
</tr>
<tr>
<td>6 (not reported)</td>
<td>Hospital admission / length of stay</td>
<td>Multiple doses (in emergency room)</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Quality point deducted for incomplete reporting of results</td>
</tr>
<tr>
<td>1 (80) [8]</td>
<td>Symptom improvement</td>
<td>Multiple doses (after initial stabilisation)</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality points deducted for sparse data and incomplete reporting of results</td>
</tr>
<tr>
<td>1 (80) [8]</td>
<td>Adverse effects</td>
<td>Multiple doses (after initial stabilisation)</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality points deducted for sparse data and incomplete reporting of results</td>
</tr>
<tr>
<td>3 (191) [9]</td>
<td>Symptom improvement</td>
<td>Metered dose inhaler plus spacer devices v nebulisers for delivering beta2 agonists</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality points deducted for sparse data and incomplete reporting of results</td>
</tr>
<tr>
<td>13 (880) [9]</td>
<td>Hospital admission / length of stay</td>
<td>Metered dose inhaler plus spacer devices v nebulisers for delivering beta2 agonists</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality points deducted for incomplete reporting of results. Directness point deducted for unclear clinical relevance of one outcome</td>
</tr>
<tr>
<td>14 (927) [9]</td>
<td>Adverse effects</td>
<td>Metered dose inhaler plus spacer devices v nebulisers for delivering beta2 agonists</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality points deducted for incomplete reporting of results, and unclear outcome measures</td>
</tr>
<tr>
<td>2 (64) [11]</td>
<td>Symptom improvement</td>
<td>Systemic corticosteroids v placebo</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality points deducted for sparse data and incomplete reporting of results</td>
</tr>
<tr>
<td>5 (342) [11]</td>
<td>Hospital admission / length of stay</td>
<td>Systemic corticosteroids v placebo</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcome measures</td>
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<tr>
<td>2 (210) [11]</td>
<td>Relapse rate</td>
<td>Systemic corticosteroids v placebo</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>High</td>
<td>Quality point deducted for incomplete reporting of results. Effect size point added for RR less than 0.5</td>
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<tr>
<td>3 (470) [13]</td>
<td>Symptom improvement</td>
<td>High dose inhaled corticosteroids v oral corticosteroids</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes</td>
</tr>
<tr>
<td>4 (335) [13]</td>
<td>Hospital admission / length of stay</td>
<td>High dose inhaled corticosteroids v oral corticosteroids</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality points deducted for incomplete reporting of results and heterogeneity between RCTs</td>
</tr>
<tr>
<td>At least 4 (not clear, less than 380) [20]</td>
<td>Symptom improvement</td>
<td>Intravenous theophylline v placebo</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Low</td>
<td>Quality points deducted for incomplete reporting of results and unclear outcome assessment</td>
</tr>
<tr>
<td>3 (not clear, less than 380) [20]</td>
<td>Hospital admission / length of stay</td>
<td>Intravenous theophylline v placebo</td>
<td>Low</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Quality points deducted for incomplete reporting of results</td>
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</table>

What are the effects of treatments for acute asthma in children?
### Important outcomes

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>Grade</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>26</td>
<td>Symptom improvement</td>
<td>Inhaled corticosteroids v placebo</td>
<td>4</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Quality point deducted for incomplete reporting of results</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital admission / length of stay</td>
<td>Inhaled corticosteroids v placebo</td>
<td>4</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Quality point deducted for incomplete reporting of results</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptom improvement</td>
<td>Inhaled corticosteroids v theophylline</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality points deducted for sparse data, and incomplete reporting of results</td>
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<tr>
<td></td>
<td>Symptom improvement</td>
<td>Inhaled corticosteroids v sodium cromoglycate</td>
<td>4</td>
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<tr>
<td></td>
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<td>Inhaled corticosteroids v nedocromil</td>
<td>4</td>
<td>-1</td>
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<td>-1</td>
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<td>Quality points deducted for incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups</td>
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<td></td>
<td>Hospital admission / length of stay</td>
<td>Inhaled corticosteroids v nedocromil</td>
<td>4</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>Low</td>
<td>Quality points deducted for incomplete reporting of results. Directness point deducted for no direct statistical comparison between groups</td>
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<tr>
<td></td>
<td>Symptom improvement</td>
<td>Inhaled corticosteroids v inhaled long acting beta2 agonists</td>
<td>4</td>
<td>-1</td>
<td>-1</td>
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<td>Low</td>
<td>Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results between studies</td>
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<td></td>
<td>Airway hyperresponsiveness / bronchial reactivity</td>
<td>Inhaled corticosteroids v inhaled long acting beta2 agonists</td>
<td>4</td>
<td>-1</td>
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<td>Low</td>
<td>Quality point deducted for incomplete reporting of results for small number of comparisons</td>
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<td></td>
<td>Symptom improvement</td>
<td>Inhaled corticosteroids v oral montelukast</td>
<td>4</td>
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<td>0</td>
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<td>Quality points deducted for incomplete reporting of results and unclear outcome assessment</td>
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<tr>
<td></td>
<td>Symptom improvement</td>
<td>Inhaled sodium cromoglycate v placebo</td>
<td>4</td>
<td>-2</td>
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<td>Quality points deducted for incomplete reporting of results and heterogeneity among RCTs. Directness point deducted for publication bias</td>
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<td>Inhaled nedocromil v placebo</td>
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<td>0</td>
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<td>Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results</td>
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<td></td>
<td>Hospital admission / length of stay</td>
<td>Inhaled nedocromil v placebo</td>
<td>4</td>
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<tr>
<td></td>
<td>Symptom improvement</td>
<td>Inhaled long acting beta2 agonist v placebo</td>
<td>4</td>
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<td>Symptom improvement</td>
<td>Oral theophylline v placebo</td>
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<td>-1</td>
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<td>0</td>
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<td>Quality point deducted for sparse data</td>
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<tr>
<td></td>
<td>Symptom improvement</td>
<td>Oral leukotriene receptor antagonists v placebo</td>
<td>4</td>
<td>-1</td>
<td>-1</td>
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<td>Very low</td>
<td>Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes. Directness point deducted for no direct statistical comparison between groups in 1 RCT</td>
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What are the effects of additional prophylactic treatments in childhood asthma inadequately controlled by standard dose inhaled corticosteroids?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>Grade</th>
<th>Comment</th>
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<tr>
<td>1 (177)</td>
<td>Symptom improvement</td>
<td>Increased dose of inhaled corticosteroid</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality points deducted for sparse data and incomplete reporting of results</td>
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## Important outcomes

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
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</thead>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (177) [59]</td>
<td>Airway hyperresponsiveness / bronchial reactivity</td>
<td>Increased dose of inhaled corticosteroid</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality points deducted for sparse data and incomplete reporting of results</td>
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<tr>
<td>1 (177) [59]</td>
<td>Adverse effects</td>
<td>Increased dose of inhaled corticosteroid</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality points deducted for sparse data and incomplete reporting of results</td>
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<tr>
<td>3 (689) [60] [61]</td>
<td>Symptom improvement</td>
<td>Addition of regular (daily) long acting beta2 agonist</td>
<td>4</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes</td>
</tr>
<tr>
<td>1 (177) [59]</td>
<td>Airway hyperresponsiveness / bronchial reactivity</td>
<td>Addition of regular (daily) long acting beta2 agonist</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>Quality points deducted for sparse data and incomplete reporting of results</td>
</tr>
<tr>
<td>2 (69) [62]</td>
<td>Symptom improvement</td>
<td>Addition of oral theophylline</td>
<td>4</td>
<td>-3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Very low</td>
<td>Quality points deducted for sparse data, no direct statistical comparison between groups in 1 RCT, and incomplete reporting of results</td>
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<tr>
<td>1 (279) [64]</td>
<td>Symptom improvement</td>
<td>Addition of oral leukotriene receptor antagonists</td>
<td>4</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
<td>Quality point deducted for incomplete reporting of results. Directness point deducted for no long term results</td>
</tr>
</tbody>
</table>

### What are the effects of treatments for acute wheezing in infants?

| 2 (69) [67] | Symptom improvement | Nebulised salbutamol v placebo | 4       | -2       | -1          | 0           | 0           | Very low | Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results between studies |
| 1 (28) [67] | Hospital admission / length of stay | Nebulised salbutamol v placebo | 4       | -2       | 0           | 0           | 0           | Low    | Quality points deducted for sparse data and incomplete reporting of results |
| 1 (34) [70] | Symptom improvement | Delivery through metered dose inhaler v nebuliser | 4       | -2       | 0           | 0           | 0           | Low    | Quality points deducted for sparse data and incomplete reporting of results |
| 2 (106) [68] | Hospital admission / length of stay | Delivery through metered dose inhaler v nebuliser | 4       | -2       | 0           | 0           | 0           | Low    | Quality points deducted for sparse data and incomplete reporting of results |
| 1 (31) [71] | Hospital admission / length of stay | Inhaled ipratropium bromide v placebo | 4       | -2       | 0           | 0           | 0           | Low    | Quality points deducted for sparse data and small number of comparisons |
| 2 (130) [71] | Symptom improvement | Addition of inhaled ipratropium bromide to short acting beta2 agonist | 4       | -2       | 0           | -1          | 0           | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for unclear outcome assessment |
| 1 (38) [74] | Symptom improvement | Oral corticosteroids v placebo | 4       | -2       | 0           | -1          | 0           | Very low | Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for unclear intervention |
| 4 (263) [75] | Symptom improvement | Corticosteroids (high dose inhaled) | 4       | -3       | 0           | 0           | 0           | Very low | Quality points deducted for incomplete reporting of results, no direct statistical comparison between groups in 1 RCT, heterogeneity among RCTs, and subjective outcome |

### What are the effects of prophylactic treatments for wheezing in infants?

| 1 (23) [71] | Symptom improvement | Inhaled ipratropium bromide | 4       | -2       | 0           | 0           | 0           | Low    | Quality points deducted for sparse data, and incomplete reporting of results |
| 1 (59) [79] | Symptom improvement | Oral short acting beta2 agonists | 4       | -2       | 0           | -1          | 0           | Very low | Quality points deducted for sparse data, and incomplete reporting of results. Directness point deducted for unclear outcome assessment |
## Important outcomes

<table>
<thead>
<tr>
<th>Number of studies (participants)</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Type of evidence</th>
<th>Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Effect size</th>
<th>GRADE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (109) [66] [67]</td>
<td>Symptom improvement</td>
<td>Inhaled short acting beta2 agonists</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>6 (222) [82] [83] [84] [85]</td>
<td>Symptom improvement</td>
<td>Lower dose inhaled corticosteroids v placebo</td>
<td>4</td>
<td>-2</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>1 (29) [81]</td>
<td>Symptom improvement</td>
<td>Addition of inhaled corticosteroid to short acting beta2 agonist</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>5 (not clear, at least 117) [75] [86]</td>
<td>Symptom improvement</td>
<td>Higher dose intermittent inhaled corticosteroids v placebo</td>
<td>4</td>
<td>-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

Type of evidence: 4 = RCT; 2 = Observational. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes. Effect size: based on relative risk or odds ratio.

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