ERS TASK FORCE

Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach


ABSTRACT: There is poor agreement on definitions of different phenotypes of preschool wheezing disorders. The present Task Force proposes to use the terms episodic (viral) wheeze to describe children who wheeze intermittently and are well between episodes, and multiple-trigger wheeze for children who wheeze both during and outside discrete episodes. Investigations are only needed when in doubt about the diagnosis.

Based on the limited evidence available, inhaled short-acting β2-agonists by metered-dose inhaler/spacer combination are recommended for symptomatic relief. Educating parents regarding causative factors and treatment is useful. Exposure to tobacco smoke should be avoided; allergen avoidance may be considered when sensitisation has been established. Maintenance treatment with inhaled corticosteroids is recommended for multiple-trigger wheeze; benefits are often small. Montelukast is recommended for the treatment of episodic (viral) wheeze and can be started when symptoms of a viral cold develop.

Given the large overlap in phenotypes, and the fact that patients can move from one phenotype to another, inhaled corticosteroids and montelukast may be considered on a trial basis in almost any preschool child with recurrent wheeze, but should be discontinued if there is no clear clinical benefit.

Large well-designed randomised controlled trials with clear descriptions of patients are needed to improve the present recommendations on the treatment of these common syndromes.

KEYWORDS: Asthma, episodic viral wheeze, inhaled corticosteroids, montelukast, multiple-trigger wheeze

CONTENTS

Methods ................................................................. 1097
Results ................................................................. 1097
Definitions ............................................................. 1097
  Definitions of temporal pattern of wheeze ......................... 1098
  Retrospective epidemiological description of duration of wheeze 1099
  Long-term outcome ............................................... 1099
  Recommendations: definitions of phenotypes (based on low-level evidence) 1099
Assessment .......................................................... 1099
  History and physical examination .................................. 1099
  Investigations ..................................................... 1100
  Recommendations: assessment (based on very low-level evidence) 1101
Population studies have shown that approximately one in three children has at least one episode of wheezing prior to their third birthday, and the cumulative prevalence of wheeze is almost 50% at the age of 6 yrs [1, 2]. Most wheeze in preschool children is associated with viral upper respiratory tract infections, which recur frequently in this age group. As a result, recurrent wheeze is a very common clinical problem facing practitioners throughout the world. It has been estimated that the problem of preschool wheeze utilises 0.15% of the total healthcare budget in the UK [3]. Despite its high prevalence, there is a lack of evidence regarding the pathophysiology and treatment of preschool wheeze.

The understanding of preschool wheezing illness has been enhanced by a number of birth cohort studies, in particular by highlighting the existence of different phenotypes [1, 4, 5]. However, the possible implications of these different phenotypes for treatment are poorly acknowledged in current international guidelines on the diagnosis and management of asthma [6–8]. Indeed, although two paediatric societies recently published guidelines on preschool wheezing disorders [9, 10], comprehensive evidence-based guidelines on the diagnosis and management of wheezing disorders in preschool children have not been published to date. The present ERS Task Force was instituted for exactly that purpose. The Task Force defined a phenotype as a cluster of associated features that are useful in some way, such as in managing the child or understanding the mechanisms of disease. Given the multifactorial nature of all wheezing disorders (including asthma) in general, and preschool wheezing disorders in particular, it is highly likely that clinical phenotypes described in the literature are the extremes of a broad spectrum of wheezing disorders [11, 12]. The Task Force therefore realises that the phenotypes defined in the present report are not exhaustive, and that many individual patients may not fit into the categories described. There may be overlap between phenotypes and they may change over time.

The purpose of the present Task Force was to produce guidelines for the treatment of wheezing in children aged <6 yrs based on all of the available evidence.

METHODS

Literature searches were performed in order to identify material relating to preschool wheeze. Eleven relevant study areas were identified, and, for each area, a literature search was carried out based on a predefined series of key clinical questions and keywords by a single clinical librarian. Search strategies were constructed by the clinical librarian in collaboration with a representative of each group in the Task Force. Searching included the Cochrane library, PubMed and EMBASE, and the strategies included filters to limit the results by study type (reviews, randomised controlled trials and other types of experimental research) and age range (0–5 yrs). The details of the search strategies are available on request. In most cases, the results were limited to English language material. No date limits were applied.

Each subgroup, consisting of at least three people, reviewed the retrieved references for relevant papers, adding additional papers from personal files if required. The evidence from the retrieved relevant papers was graded, according to recent recommendations [13], as high-, moderate-, low- or very low-grade evidence based on the following criteria: study design and quality (systematic reviews and randomised controlled trials: high quality; observational studies: low quality; any other type of article: very low quality), consistency of the data and relevance. A draft report was prepared by each subgroup. This was submitted to the whole Task Force for comments. The individual reports were then combined by the Task Force chairs (P.L.P. Brand and A. Bush), and the present manuscript was organised into three main sections: Definitions, Assessment and Treatment. Based on the evidence reviewed and graded by each subgroup, the Task Force chairs put together a list of recommendations that were graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [13]. Instead of the usual system of grading the strength of recommendations as A, B, C or D, the GRADE working group proposal to use a different, and more readily interpretable, system of categorising recommendations in four groups was followed: should (or should not) be done, or possibly should (or should not) be done. Recommendations could only be categorised as should (or should not) be done when the entire Task Force unanimously endorsed this recommendation.

RESULTS

One of the main findings of the present Task Force was that the evidence on which to base recommendations is limited in this age group. When no evidence was available from original studies, narrative reviews and published expert opinions were considered for inclusion in the present report. All of the evidence presented is of low quality unless specifically stated otherwise. The present recommendations are likely to change when more evidence becomes available.

DEFINITIONS

Definitions used in children aged <6 yrs are often confusing. Although many individuals later diagnosed with asthma exhibit their first symptoms during the preschool age period, making a diagnosis of asthma in preschool children is difficult. According to the latest edition of the Global Initiative for Asthma (GINA) guidelines, asthma is a syndrome with a highly variable clinical spectrum, characterised by airway inflammation [6]. Inflammation, however, has been poorly studied in preschool children, and may be absent in very young children who wheeze [14]. Therefore, a symptoms-only descriptive approach, outlined in table I, was adopted.
The majority of the Task Force agreed not to use the term asthma to describe preschool wheezing illness since there is insufficient evidence showing that the pathophysiology of preschool wheezing illness is similar to that of asthma in older children and adults.

Wheeze is defined as a continuous high-pitched sound with musical quality emitting from the chest during expiration. It is one of a number of forms of noisy breathing in preschool children [15]. Parents differ widely in their understanding and definition of wheeze; some think it is a sound such as whistling, squeaking or gasping, whereas others define it as a different rate or style of breathing, or think it is the same as cough [15–19]. If based on parental report alone, therefore, children may be labelled as having wheeze when they do not. If possible, therefore, wheeze should be confirmed by a health professional, bearing in mind that not all healthcare workers are equally accurate in estimating the severity of wheeze [20].

By definition, the present Task Force has not addressed the clinical problem of isolated cough without wheeze. Guidelines on the diagnosis and management of chronic cough in childhood are available elsewhere [21]. Since wheeze is the end result of narrowing of intrathoracic airways and expiratory flow limitation, irrespective of the underlying mechanism, there are numerous reasons for a child to wheeze, including anatomical abnormalities of the airways, cystic fibrosis and bronchomalacia. The Task Force unanimously agreed that the differential diagnosis of wheeze in preschool children should not be discussed in detail in the present report for a number of reasons. First, there is very little, if any, evidence to support recommendations regarding the diagnostic approach to a wheezing infant. Secondly, the differential diagnosis of wheeze in preschool children should not be discussed in detail in the present report for a number of reasons. First, there is very little, if any, evidence to support recommendations regarding the diagnostic approach to a wheezing infant. Secondly, the differential diagnosis of wheeze in preschool children has been discussed in detail in textbooks [22, 23]. Thirdly, it was felt that most clinicians and researchers would recognise the clinical problem of recurrent wheezing in preschool children without an in-depth discussion of its differential diagnosis.

Causative factors for recurrent wheeze may vary from child to child and within a child over time, due to a large number of interactions between genetic factors and the environment [24]. As in adults [25], specific combinations of genetic and environmental factors determine the individual patient's phenotype. In clinical practice, however, most of these factors are unknown.

The phenotypes used in epidemiological studies (transient versus persistent wheeze) can only be applied retrospectively [1, 4, 5]. Although the use of these phenotypes has improved mechanistic understanding, they are of little use to the clinician. Although the epidemiological phenotype of transient wheeze is often assumed to be equivalent to the clinical phenotype of episodic wheeze, this has never been demonstrated. Therefore, definitions of temporal pattern of wheeze (which are useful to clinicians) were distinguished from the retrospective definitions of duration of wheeze (which are used in epidemiological studies; table 1).

### Definitions of temporal pattern of wheeze

**Episodic (viral) wheeze**

Episodic (viral) wheeze is defined as wheeze in discrete episodes, with the child being well between episodes. Although not unique to the preschool age group [26, 27], this phenotype appears to be most common in preschool children [1, 4, 5]. It is usually associated with clinical evidence of a viral respiratory tract infection, although microbiological diagnostic studies are rarely performed in clinical practice. The most common causative agents include rhinovirus, respiratory syncytial virus (RSV), coronavirus, human metapneumovirus, parainfluenza virus and adenovirus [28]. Repeated episodes tend to occur seasonally.

Factors underlying the frequency and severity of episodes are only partially understood, but the severity of the first episode (which is, in turn, related to pre-existent impaired lung function and younger age), atopy, prematurity and exposure to tobacco smoke have been implicated [29–35]. Whether or not

### Definitions of temporal pattern of wheeze

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temporal pattern of wheeze</strong></td>
<td></td>
</tr>
<tr>
<td>Episodic (viral) wheeze</td>
<td>Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes</td>
</tr>
<tr>
<td>Multiple-trigger wheeze</td>
<td>Wheezing that shows discrete exacerbations, but also symptoms between episodes</td>
</tr>
<tr>
<td><strong>Duration of wheeze</strong></td>
<td></td>
</tr>
<tr>
<td>Transient wheeze</td>
<td>Symptoms that commenced before the age of 3 yrs and are found (retrospectively) to have disappeared by the age of 6 yrs; transient wheeze may be episodic or multiple-trigger wheeze</td>
</tr>
<tr>
<td>Persistent wheeze</td>
<td>Symptoms that are found (retrospectively) to have continued until the age of ≥6 yrs; persistent wheeze may be episodic or multiple-trigger wheeze</td>
</tr>
<tr>
<td>Late-onset wheeze</td>
<td>Symptoms that start after the age of 3 yrs; late-onset wheeze may be episodic or multiple-trigger wheeze</td>
</tr>
</tbody>
</table>
WHEEZING DISORDERS IN PRESCHOOL CHILDREN

the initial episode is classified as bronchiolitis is irrelevant. Similarly, it is not known whether or not the causative agent of the initial episode plays a major role in determining long-term outcome. Both RSV and rhinovirus have been linked to an increased risk of persistent wheezing over time [36–38]. In the case of RSV, most studies show that this has disappeared by the age of 11 yrs, and is not associated with an increased risk of atopy [37]. For rhinovirus, such long-term data are lacking.

Episodic (viral) wheeze most commonly declines over time, disappearing by the age of 6 yrs, but can continue as episodic wheeze into school age, change into multiple-trigger wheeze or disappear at an older age [1, 26].

Multiple-trigger wheeze

Although a viral respiratory tract infection is the most common trigger factor for wheeze in preschool children, some young children also wheeze in response to other triggers (multiple-trigger wheeze; table 1). Others have used the term persistent wheeze for this syndrome, but this is confusing because this term is also used to describe the long-term temporal outcome of wheeze (discussed further later).

Systematic studies of other such triggers are lacking. A textbook, written by two experts in the field, suggests that tobacco smoke and allergen exposure are important triggers, and that some children may also wheeze in response to mist, crying, laughter or exercise [23]. Although many believe that multiple-trigger wheeze in preschool children reflects chronic allergic airway inflammation (and could, therefore, be classified as asthma), there is little evidence to support this (see Investigations section).

Retrospective epidemiological description of duration of wheeze

The outcome and related characteristics of preschool wheeze have been determined by prospective birth cohort studies; however, in individuals, these categories can only be recognised retrospectively [1, 4, 5]. Therefore, these phenotypes can only be used in epidemiological studies and are of no value in clinical practice. Three groups have been recognised (table 1) but it should be stressed that the overlap between these groups is considerable and that the age limits applied are arbitrary.

In the Tucson birth cohort, 34% of children wheezed during the first 3 yrs of life but 60% of these had ceased to wheeze by the age of 6 yrs. As a group, these infants with transient wheeze show reduced lung function prior to the first respiratory illness, are exposed to maternal smoking, and are not characterised by a personal history of eczema or a family history of asthma [1]. In an attempt to predict which preschool wheezers continue to wheeze beyond the age of 6 yrs, these history data have been combined with characteristics such as blood eosinophilia into an asthma predictive index [39]. Although groups of children with a positive asthma predictive index respond to inhaled corticosteroid (ICS) therapy [40, 41], the predictive value of this index for the disappearance or persistence of wheeze over time in individual patients is of only modest clinical value [39].

The 15% of children who started wheezing after the age of 3 yrs and were still wheezing at the age of 6 yrs were defined as having late-onset wheeze. This was associated with maternal asthma, male sex and a history of rhinitis [1]. This group tended to be atopic and show normal lung function at birth and through the teenage years [42].

Children who wheezed in the first 3 yrs and continued beyond the age of 6 yrs were termed persistent wheezers [1]. This was associated with normal lung function during the first year of life, but reduced lung function from the preschool age period and through adulthood (in most but not all cohort studies), with atopy and a family history of asthma [1, 4, 5].

Long-term outcome

Long-term studies have shown that ~25% of children with persistent asthma had started to wheeze by the age of 6 months and 75% by the age of 3 yrs [1, 4, 5, 43]. Although the long-term outcome of asthma in school-age children has been extensively studied, both at the general population level and in patients with more severe disease, little evidence regarding the outcome of preschool wheezing into adulthood is available. Ongoing birth cohort studies should be able to provide information on the outcome in general populations during the 2010s. Considering more severe early wheeze, half of the children hospitalised with acute wheeze before the age of 2 yrs were symptom-free by the age of 5 yrs and 70% by 10 yrs, but only 57% by 17–20 yrs [44–46], illustrating the tendency for relapse during adolescence. Female sex, passive smoking during infancy and early sensitisation to allergens were risk factors for symptoms continuing into early adulthood, but type of virus and premature birth were not.

Recommendations: definitions of phenotypes (based on low-level evidence)

1) For clinical purposes, wheeze should be described in terms of its temporal pattern and classified as episodic (viral) or multiple-trigger wheeze.

2) Use of the terms transient, late-onset and persistent wheeze should probably be limited to population-based cohort studies and should not be used clinically.

3) The term asthma should probably not be used in preschool children because data regarding underlying inflammation are lacking.

ASSESSMENT

History and physical examination

The purpose of history-taking and physical examination is to confirm that the preschool child has a wheezing disorder, to identify the pattern of symptoms, the severity of the condition and any possible trigger factors, and to look for features suggestive of another diagnosis or associated condition. The detailed diagnostic tests for these conditions are beyond the scope of the present report and have been discussed by others [23].

History

History-taking is the main diagnostic instrument in the assessment of preschool wheeze in those who are not wheezing during the consultation. Accurately identifying wheeze from the history can be difficult since the term is used by parents and healthcare workers to describe a variety of symptoms [15, 17–19]. Children with doctor-confirmed wheeze exhibit greater airways resistance than children with only reported wheeze [47], even though interobserver agreement between doctors is poor [48]. A video questionnaire may help
parents to distinguish wheeze from upper airway noises [49]. Symptom scoring systems have been insufficiently validated to justify general use, and validated questionnaires for this purpose in this particular age group are needed. Noisy breathing is common among infants aged <6 months but only a small proportion have wheeze [15]. Reported noisy breathing that responds to bronchodilator therapy is likely to be genuine wheeze and to be caused, at least in part, by constriction of airway smooth muscle [50].

Physical examination
No evidence is available regarding the usefulness of physical examination in wheeze assessment. A textbook states that the degree of airway narrowing can only be estimated crudely and indirectly, by assessing work of breathing (chest retractions, nasal flaring and use of accessory respiratory muscles) and by auscultation of the chest to assess the ratio of expiration to inspiration and the degree of wheeze [23]. Upper airway obstruction (in particular, nasal congestion) can contribute to respiratory distress. The aim of further physical examination is the identification of unusual or atypical features that would suggest another underlying condition [23].

Investigations
The diagnosis of a preschool wheezing disorder can be made by history-taking alone. The type, invasiveness and number of any investigation largely depends upon the degree of morbidity and the doubt about the diagnosis [23]. This is a matter of clinical judgement. Most clinicians would agree that investigations are only justified when symptoms are present from birth, airway obstruction is abnormally severe, recovery is very slow or incomplete (resulting in prolonged or repeated hospital admission in the first few years of life), episodes continue in the absence of a viral infection or, sometimes, in cases when parents are very anxious [22, 23]. There is little research evidence to guide the choice of investigations. Among infants and preschool children with severe persistent symptoms who were investigated according to a fixed diagnostic protocol, a considerable number of pathological findings were observed suggesting that invasive investigations are justified in this category [51, 52].

Microbiological investigations
With current viral culture and PCR technology, a wide range of respiratory viruses can be identified, including the most common causative viruses [28]. There is no evidence, however, that this contributes to management, either in the short term (the acute episode) or in the long term, and it is recommended only for research purposes.

Tests of sensitisation to allergens
The reported prevalence of sensitisation in preschool children with wheeze in population studies varies widely [1, 4, 5]. Limited evidence is available regarding the prevalence of sensitisation in preschool children presenting to healthcare workers with wheeze. One study comparing children aged 2–5 yrs with doctor-confirmed wheeze who were responding favourably to a bronchodilator to healthy non-wheezing children found that 32% of wheezy children gave positive skin-prick test results to one or more aeroallergens, compared to 11% of healthy children (likelihood ratio 2.9) [53]. Sensitisation to inhalant allergens in 1–4-yr-old children from general practice increases the likelihood of the presence of asthma at the age of 6 yrs by a factor of two to three [54]. Sensitisation to hen’s egg at the age of 1 yr is a reasonable marker for allergic sensitisation to aeroallergens at the age of 3 yrs, with a specificity of >90% and sensitivity of >30% [55].

Total serum immunoglobulin E measurements in early life are not predictive of outcome [56]. Although elevated eosinophilic cationic protein levels in preschool wheezers are associated with symptom persistence [57], the degree of overlap between groups renders such measurements useless for clinical purposes. Blood eosinophilia can be used as part of an asthma predictive index, but the predictive value of this index (in particular, that of a positive result) is low [39].

Radiological examinations
There is no evidence that chest radiographs help in the diagnosis or treatment of preschool children with acute or recurrent wheezing [58]. Improvements in diagnostic imaging techniques may improve understanding of the mechanisms and long-term outcome of early childhood wheezing disorders by providing details about airway structure, airway wall thickness and airway calibre. At present, however, specialised imaging should be restricted to unusual or severe disease [22].

Measurement of gastro-oesophageal reflux
Although gastro-oesophageal reflux is common among infants and preschool children with chronic or recurrent respiratory symptoms [59], a beneficial effect of demonstrating and treating gastro-oesophageal reflux in infants with wheeze has not been shown.

Lung function tests
Studies have shown reduced forced expiratory flows associated with wheeze [50, 52, 60, 61]. Low lung function in school-age children [62–64] and infants [65] appears to track into early adulthood. It is not known, therefore, whether lung function deficits in school-age children with wheezing reflect developmental characteristics of the lung and airways in wheezy children, disease activity while symptomatic or remodelling secondary to airway inflammation. The presence of airway reactivity in infancy is associated with lower childhood lung function and increased risk of asthma in later childhood [66], but the mechanisms of airway reactivity in this age group are poorly understood and probably include factors other than inflammation [67]. There are no studies supporting the usefulness of pulmonary function tests in children with nonspecific symptoms, or in distinguishing between episodic and multiple-trigger wheeze. In the individual patient, however, determination of lung function (and bronchodilator response) in preschool children can help in the discrimination of common wheezing disorders from other conditions [68, 69].

Exhaled nitric oxide and other assessments of airways inflammation
Elevated exhaled nitric oxide fractions (FeNO) have been found in wheezing infants, especially when they are atopic [70, 71], and these normalise during treatment with ICSs [72] and montelukast [73, 74]. FeNO in infants are affected by environmental exposures
and genetic predisposition to atopy [75]. Reference values for FeNO are only available for children aged ≥4 yrs [76]. For uncooperative children aged <4 yrs, measurement of FeNO has not been standardised and there is no evidence supporting the usefulness of measuring or monitoring FeNO in this age group. Other tests of inflammation, such as analysis of induced sputum, have not been studied at all in preschool children.

Airway wall biopsy and bronchoalveolar lavage
Few studies have applied bronchoalveolar lavage or bronchial biopsy in preschool wheezing disorders. Most such investigations have been performed in children with severe or unusual clinical features, limiting the generalisability of findings. Both the degree of inflammation and the composition of the infiltrate have been variable, with neutrophils dominating in some studies, eosinophils in others and no evidence of either in others [77]. The only consistent finding was thickening of the reticular basement membrane in wheezy children [77], but not in infants (median age 12 months), even when reversible airflow obstruction and atopy were demonstrated [14]. A recent study showed that, by a median age of 29 months, some children with confirmed wheeze exhibit eosinophilic airway inflammation and reticular basement membrane thickening, implying an age window at 12–30 months during which interventions aimed at preventing established airway inflammation might be possible [78]. Further studies of airway inflammation using bronchoalveolar lavage and bronchial biopsy in large groups of representative patients with episodic and multiple-trigger wheeze are urgently needed in order to improve understanding of the pathophysiology of preschool wheezing disorders. Unfortunately, such studies are hindered by ethical and practical constraints. At present, such invasive investigations should only be used in unusual cases in specialised centres.

Recommendations: assessment (based on very low-level evidence)
1) The pattern and triggers of wheeze, personal and family history of atopy, and household smoking should be assessed by history-taking.
2) Parentally reported wheeze should be confirmed by a health professional whenever possible.
3) Tests of allergic sensitisation should be performed in patients requiring long-term treatment and follow-up.
4) Other investigations should probably not be carried out unless wheeze is unusually severe, therapy-resistant or accompanied by unusual clinical features.

TREATMENT
Environmental manipulation
Reducing tobacco smoke exposure
There is consistent strong evidence that passive exposure to environmental tobacco smoke is harmful, in terms of both induction and exacerbation of preschool wheeze [79], and should be firmly discouraged.

Allergen avoidance
Allergen avoidance to prevent the development of symptoms, in either the population as a whole or high-risk subgroups (primary prevention), is not discussed here. The rationale for using environmental control in the treatment of preschool age wheezing to reduce existing symptoms (secondary prevention) is the notion that allergen exposure contributes to the severity of symptoms [80]. There is some evidence that exposure to allergens in early life increases the risk of wheezing, but this is dependent upon the allergen, the population and other environmental factors [81]. The combination of sensitisation and high exposure to sensitising allergen in early life is associated with significantly poorer lung function at the age of 3 yrs [82]. Sensitisation to perennial allergens during the first 3 yrs of life is associated with reduced lung function at school age, with concomitant high exposure to perennial allergens early in life aggravating this [83]. High allergen exposure during preschool age enhances the development of airway hyper-responsiveness in sensitised children with wheeze (with later-life sensitisation and exposure having much weaker effects) [83].

Moving school-age atopic asthmatic children from their homes to the low-allergen environment of high-altitude sanatoria temporarily improves levels of markers of airway inflammation and asthma severity [84]. Some studies suggest that allergen avoidance at home may also be of some benefit amongst children of this age range [85, 86]. It remains unclear, however, whether the required major reduction in exposure can be achieved in normal life and whether it would be of beneficial effect in young children since no studies on the effects of allergen avoidance have been performed in preschool children with wheeze [87].

Parent and patient education
Parental knowledge and understanding of wheezing disorders in preschool children and their treatment is often inadequate (especially with respect to medication and the preceding signs and preventive actions) [88]; however, few educational studies in wheezy children have explicitly focused on the preschool age group.

Many educational studies have included children aged as young as 2 yrs, but the age range of the study group is frequently not described, and there is rarely an analysis of whether outcomes are different in younger children. For example, the Cochrane Review on educational interventions in children and adolescents aged 2–18 yrs with asthma included no separate analysis of outcomes in younger children [89]. Indeed, of the 32 studies included in the review, only one studied preschool children exclusively [90]; two other studies that included children aged <2 yrs were excluded.

Of the few studies in preschool children, those that have utilised multiple teaching sessions have shown improvements in morbidity, with more symptom-free days and better caregiver quality of life [90, 91], as well as improved knowledge and improved self-efficacy [92], and outcomes similar to those in older children. These studies all used different formats: reading of a home booklet followed by practitioner review on next consultation [92], small group teaching by nurses [90] and home-based education [91]. One other large randomised controlled trial in preschool children with acute wheeze found no effect of an education programme upon subsequent healthcare utilisation, disability score, parent’s quality of life and parental knowledge of asthma [93]. This study included two structured 20-min one-to-one sessions, the
first during hospital attendance and the other 1 month later. This raises the possibility that multiple educational sessions of longer duration might be more effective in preschool children.

Virtually all studies in preschool children have targeted education at parents or carers. However, young children themselves may benefit from asthma education and practical training in skills. One study found that children aged 2–5 yrs who were exposed to a developmentally appropriate educational intervention that included a picture book and video tape showed improved asthma knowledge, as well as better compliance and health, compared to controls [94].

Therefore, although educating parents of preschool children with wheeze (and perhaps also the children themselves) appears effective, and is advised, more work is needed before specific educational approaches can be recommended.

**Pharmacological therapy**

**Short-acting β₂-agonists**

Inhaled rapidly acting β₂-agonists are the most effective bronchodilators available, and, therefore, the drugs of choice for acute symptoms of wheeze. Double-blind placebo-controlled studies have demonstrated significant bronchodilatory effects [95–98] and protective effects against bronchoconstrictor agents [99, 100] in infants and preschool children treated with rapidly acting inhaled β₂-agonist. Thus, infants possess functional β₂-receptors from birth, and stimulation of these receptors can produce the same effects as in older children, although paradoxical responses to inhaled β₂-agonists have been reported in infants [50, 101]. Oral administration of β₂-agonist is also effective but is limited by systemic side-effects [102]. Intravenous infusion of β₂-agonists has only shown an advantage over hourly inhaled treatment in very severe acute wheeze in young children [103].

After inhalation, β₂-agonists are usually well tolerated. Side-effects, such as muscle tremor, headache, palpitations, agitation and hypokalaemia, are only seen when high doses are used [104].

Single-isomer R-albuterol is theoretically preferable (although much more expensive) to the racemic mixture of albuterol since the S-isomer is therapeutically inactive [104]. There is, however, no evidence regarding the clinical effectiveness or superiority of the use of R-albuterol compared to the racemic mixture in this age group.

**Long-acting inhaled β₂-agonists**

Formoterol and salmeterol have shown long-lasting bronchodilatory and bronchoprotective effects in preschool children [99, 105]. There are no published double-blind randomised placebo-controlled trials in preschool children on the addition of long-acting inhaled β₂-adrenergic agents to ICSs.

**Inhaled corticosteroids**

Treatment with ICSs may be considered for the treatment of current symptoms, or possibly for the prevention of progression of symptoms (disease modification). Each is considered in turn, as follows.

**Inhaled corticosteroids in treatment of symptoms of multiple-trigger wheeze**

A systematic review of randomised double-blind controlled trials of inhaled glucocorticosteroids in preschool children with multiple-trigger wheeze has shown significant improvements in important health outcomes, including symptoms, exacerbation rates, lung function and airway hyperresponsiveness [106]. The treatment effect appears to be smaller than that seen in school-age children and adults. For example, studies of ICSs in preschool children with multiple-trigger wheeze have reported a reduction in exacerbations by ~50% [107, 108]. Compared to placebo, children using 200 μg·day⁻¹ fluticasone exhibit a mean of 5% fewer days with symptoms [106].

The dose–response relationship of ICSs in preschool children is not entirely clear. Dose-related effects have been shown for exacerbation rate on treatment with daily ICS doses of up to 400 μg·day⁻¹ beclometasone equivalent (or 200 μg·day⁻¹ fluticasone) via pressurised metered-dose inhaler (pMDI) with spacer (pMDI-S) [107], without any further benefit from higher doses. Comparison of 0.25, 0.5 and 1.0 mg nebulised budesonide daily, however, showed similar improvement to that with placebo in one study [109], whereas another suggested a dose relation in the range 0.25–1.0 mg nebulised budesonide b.i.d. [110]. Marked individual variations in response are seen between patients. In a post hoc analysis of two large randomised controlled trials in young children (aged 12–47 months), those with frequent symptoms, aged >2 yrs and/or with a family history of asthma showed the best response to treatment with fluticasone (200 μg·day⁻¹), whereas those with less frequent symptoms, without a family history of asthma and aged <2 yrs showed no significant treatment effect [111]. Two recent studies using inhaled fluticasone to treat wheezy infants and preschool children failed to find any improvement in lung function [112, 113]. Atopic markers, such as a history of atopic dermatitis or allergic rhinitis, did not improve the chance of responding to ICSs [111]. However, preschool children with wheeze, selected based on the asthma predictive index for the prediction of persistent wheeze (including atopic dermatitis, allergic rhinitis and eosinophilia), respond to ICSs as a group [40, 41].

Local side-effects, such as hoarseness and candidiasis, are rare in preschool children [114], probably because medication is usually delivered by metered-dose inhaler with spacer (MDI-S) combination. Studies on the systemic side-effects of inhaled steroids have yielded inconsistent results. In a 1-yr study of 200 μg·day⁻¹ fluticasone in preschool children, height growth was similar in the fluticasone-treated children to that in the cromoglycate-treated children [114]. In another study, however, height growth was reduced by 1.1 cm after 2 yrs of inhaled 200 μg·day⁻¹ fluticasone compared with placebo [41]. The long-term consequences of inhaled steroid therapy on growth in preschool children have not been studied. Clinically relevant effects on adrenal function have only been observed in children receiving high doses of ICSs (>400 μg·day⁻¹ beclometasone equivalent) [106]. The risk of cataract was not increased in a study of 358 children aged 1–3 yrs receiving daily treatment with ICSs for ≥1 yr [114]. No other potential systemic side-effects have been studied in preschool children.

Thus ICSs are effective in preschool children with multiple-trigger wheeze, but the effect is smaller than that in older
children, and there is some concern about the effect on height. This justifies a more critical approach to long-term ICS use in preschool children with multiple-trigger wheeze than in older children and adults with asthma. Many clinicians tend first to give a trial of ICS for a period of ~3 months. If there is no improvement, the treatment should not be stepped up but stopped, and further investigations should be carried out in order to identify the cause of symptoms. If preschool children with multiple-trigger wheeze respond well to ICS therapy, it is unclear whether this is due to treatment or the natural resolution of symptoms. It is recommended, therefore, that treatment be withdrawn in children who become (almost) completely free of wheeze after ICS therapy. There are also clinicians who only continue treatment with ICSs in multiple-trigger wheeze if symptoms recur after withdrawal, and respond to reintroduction of the medication.

**Inhaled corticosteroids in treatment of symptoms of episodic (viral) wheeze**

The clinical benefits of ICSs for episodic (viral) wheeze are controversial [106]. Systematic reviews have concluded that episodic high-dose inhaled glucocorticosteroids (1,600–3,200 µg·day⁻¹ budesonide) provide some benefit in episodic (viral) wheeze (with a 50% reduction in the requirement for oral steroids, but no effect on hospitalisation rates or duration of symptoms), but that maintenance treatment with 400 µg·day⁻¹ beclometasone equivalent does not reduce the number or the severity of wheezing episodes in episodic (viral) wheeze [106, 115]. It should be emphasised that the available evidence is based on a few small trials that may be underpowered for the detection of a treatment effect. For example, the study on the effect of maintenance treatment with ICSs in episodic (viral) wheeze analysed only 41 patients [116]. The most recent study, published only in abstract form, showed that intermittent treatment with 1.5 mg·day⁻¹ fluticasone for ≤10 days for episodic (viral) wheeze reduced the severity and duration of symptoms but at a cost of slightly reduced height [117]. Thus, the use of high-dose intermittent steroids in this age group requires careful consideration.

**Nasal corticosteroids to reduce episodic (viral) wheeze**

Although treatment of allergic rhinitis may help to ameliorate asthma in school-age children and adolescents, a randomised controlled trial of nasal corticosteroids in preschool children with recurrent wheeze failed to demonstrate any benefit [118].

**Treatment of episodic (viral) wheeze in preschool children to reduce risk of persistent wheeze during later childhood**

Three randomised controlled trials (two on daily ICSs and one on intermittent use when the child was wheezy) have shown that use of ICSs in preschool children with episodic (viral) wheeze does not reduce the risk of persistent wheeze at the age of 6 yrs, and that symptoms return when steroid therapy is discontinued [41, 119, 120].

**Systemic glucocorticosteroids**

A systematic review of systemic corticosteroids in hospitalised children with acute asthma found that corticosteroid-treated children were seven times more likely to be discharged early than placebo-treated children, and five times less likely to relapse within 1–3 months following discharge (number needed to treat 3) [121]. Although that review included several studies in preschool children, they were not analysed separately. A systematic review of two studies found no evidence that parent-initiated oral corticosteroids are associated with a benefit in terms of hospital admissions, unscheduled medical reviews, symptoms scores, bronchodilator use, parent and patient impressions, physician assessment, or days lost from work or school [122].

**Leukotriene modifiers**

Montelukast is the only cysteiny1 leukotriene receptor antagonist licensed for the treatment of young children, at a dosage of 4 mg orally once daily. No clinically relevant side-effects have been reported [123].

**Montelukast in multiple-trigger wheeze**

In two studies, montelukast provided protection against bronchoconstriction induced by hyperventilation with cold dry air, and improved airways hyperresponsiveness by one doubling dose after 4 weeks, compared to placebo [124, 125]. The bronchoprotective effect was independent of concurrent steroid treatment. In a multicentric study of 689 young children with multiple-trigger wheeze, montelukast improved symptoms and achieved a 30% reduction in exacerbations [123]. One recent study showed that nebulised budesonide was more effective at reducing exacerbation rates in 2–8-yr-old children with multiple-trigger wheeze than oral montelukast [126]. Since preschool children were not analysed separately, it is not known whether this difference in efficacy also applies to this age range.

**Montelukast in episodic (viral) wheeze**

Daily use of montelukast over a 1-yr period reduced the rate of wheezing episodes in 549 children with episodic (viral) wheeze by 32% compared to placebo (number needed to treat 12) [127]. A trial of intermittent montelukast, started when patients developed signs of a common cold, compared with placebo in 220 children with episodic wheeze showed a 30% reduction in unscheduled health visits (number needed to treat 11), but no effect on hospitalisations, duration of episode, and β-agonist and prednisolone use [128].

**Cromones**

Clinical documentation regarding sodium cromoglycate use in preschool children is sparse and there are no reports on infants. The Cochrane Review concluded that a beneficial effect of cromolyn therapy in preschool children with multiple-trigger wheeze could not be proven [129]. Most studies were of poor quality, but one well-designed randomised controlled trial found no effect on symptom scores or exacerbation frequency in children aged 1–4 yrs with multiple-trigger wheeze [130]. No studies have been performed with nedocromil in preschool children.

**Xanthines**

The Cochrane Review on the effects of xanthines (theophylline and aminophylline) in the chronic treatment of children with asthma, the effects on symptoms and exacerbations of wheeze in preschool children were small and mostly nonsignificant [131]. The studies were all small however. There have been no good studies comparing xanthines to other medications in preschool wheeze.
Anticholinergic agents
In the Cochrane Review it was concluded that inhaled ipratropium may be beneficial in older children [132], but there is no good evidence in preschool children [133]. There are no important side-effects when ipratropium is inhaled by MDI-S combination.

Antihistamines
The antihistamines ketotifen and cetirizine have been studied in preschool wheeze. In the Cochrane Review it was concluded that children treated with ketotifen were 2.4 times as likely to be able to reduce or stop bronchodilator treatment than those treated with placebo. There were also less consistent benefits with respect to asthma symptoms and exacerbations [134]. The interpretation of these studies, however, is hampered by the fact that the description of patients is insufficient to classify them as having episodic (viral) wheeze or multiple-trigger wheeze. In addition, the initial favourable reports in the 1980s were never confirmed in later studies. There are no good studies comparing ketotifen to other asthma medications.

Cetirizine was compared to placebo in a randomised trial in infants with atopic dermatitis, with the aim of preventing the development of asthma. At the age of 3 yrs, there was no difference in wheeze prevalence between the two groups. In a post-hoc analysis in a subgroup of patients radioallergosorbent test-positive for cat, house dust mite or grass pollen, there appeared to be a protective effect of cetirizine [135]. This needs to be confirmed in further studies. There are no studies of cetirizine in preschool children with wheeze.

Other treatment options
No studies have been performed on the effects of immunotherapy or influenza immunisation in preschool children with wheeze.

Delivery devices
As a general principle, inhaled drug delivery is preferable to the oral and parenteral routes, in order to provide rapid relief of symptoms and minimise systemic side-effects. Inhalation therapy in preschool children is hampered by numerous factors, including narrower airways, increased turbulence, deposition high in the respiratory tree, and lack of cooperation and coordination. Although there is anecdotal evidence suggesting that some preschool children may be able to use dry powder inhalers effectively and reliably [136], there is consensus among experts that these devices should not be used in preschool children because they lack the ability to generate sufficiently high inspiratory flows [137]. Similarly, pMDIs cannot be used by preschool children without the use of a spacer device because of difficulties in the appropriate timing of the inspiratory effort. The two inhalation systems to be considered, therefore, are pMDI-S and nebuliser.

A systematic review has shown that the delivery of inhaled β2-agonists by pMDI-S in acutely wheezy infants and preschool children is more effective than by nebuliser; recovery was quicker and the risk of hospital admission was reduced by 60% [138]. There are no studies comparing the two delivery devices for long-term management. The economic, practical and hygienic advantages of pMDI-S over nebulisers support the use of pMDI-S as the preferred means of delivery of inhaled drugs in preschool children.

Although there is no formal evidence to support this, there is consensus that cooperative children should use a spacer device with a mouthpiece wherever possible [137]. Noncooperative children aged <3 yrs should use a spacer with a face mask; a tight face mask seal is considered important for optimal drug delivery. Crying children are unlikely to receive any drug to the lower airways [139].

Filter studies have shown high day-to-day variability in delivered doses in preschool children [140]. This should be borne in mind when prescribing therapy and judging its effects.

If a spacer is used, it should be noted that electrostatic charge reduces MDI-S delivery. New unwashed and unprimed plastic spacers are electrostatically charged, and, therefore, yield reduced drug delivery [141]. This can be overcome by washing the plastic spacer in detergent and allowing it to drip dry, priming it with 5–10 puffs of aerosol or using a metal spacer. There are no data on the safety of the detergent washing method however. Since priming with aerosol is the most expensive and wasteful method of the three, it is not recommended.

Methodological considerations
In accordance with others [106], the Task Force found it difficult to synthesise the evidence on the efficacy of treatment in preschool wheeze for a number of reasons. First, inclusion criteria were commonly unclear. Studies have included children with asthma or wheeze without further specification. Even when inclusion criteria were specified, pooling such studies was frequently impossible because of clinical heterogeneity or the lack of distinction of different phenotypes. Secondly, treatment (agents, dosages and delivery devices) differed considerably between studies. Thirdly, different outcome parameters have been studied, most of which were neither standardised nor validated. Fourthly, the number of studies and the number of patients enrolled was generally quite low, especially for studies on ICSs in episodic wheeze. Fifthly, given the fact that symptoms of wheeze in preschool children tend to resolve spontaneously and that the most troublesome symptoms occur episodically, adherence to treatment by parents and caregivers is probably low, although few studies have examined this. The one study specifically addressing this found that parents of preschool children with troublesome wheeze would not give their child a bronchodilator on 40% of the occasions when the child was wheezy, even though they knew their adherence was monitored and even though they were instructed to administer inhaled bronchodilator when their child was wheezing [142]. Finally, age appears to be an important effect modifier, in that the younger the child is, the poorer the response to any treatment.

Recommendations for treatment (based on low-level evidence unless otherwise specified)
1) Passive smoking is deleterious to preschool children with wheeze, as at all ages (high-level evidence), and should be firmly discouraged.
2) There is insufficient evidence on which to base recommendations for the reduction of exposure to environmental allergens in the treatment of preschool wheezing.
3) An educational programme using multiple teaching sessions on causes of wheeze, recognising warning signals and treatment should be provided to parents of wheezy preschool children.

4) A pMDI-S combination should be used as the preferred delivery device for inhalation therapy in preschool children (high-level evidence).

5) In cooperative children, spacers with a mouthpiece should probably be used.

6) In uncooperative young children, spacers with a tight-fitting face mask should probably be used.

7) Plastic spacers should be treated with detergent before use in order to reduce their electrostatic charge.

Acute wheezing episode

1) Inhaled short-acting β2-agonists on an as-needed basis should be used for the symptomatic treatment of acute wheezing in preschool children. These drugs should be used cautiously in infants since paradoxical responses have been reported in this age group.

2) Alternative routes of administration (oral and intravenous) should not be used.

3) Single-isomer salbutamol should not be used.

4) Addition of ipratropium bromide to short-acting β2-agonists may be considered in patients with severe wheeze.

5) A trial of oral corticosteroids should probably be given to preschool children with acute wheeze of such severity that they need to be admitted to hospital.

6) Parent-initiated treatment with a short course of oral corticosteroids should not be given.

7) Although high-dose ICS therapy appears to have a small beneficial effect in the treatment of acute wheezing in preschool children, this treatment is not recommended because of high cost and lack of comparison to bronchodilator therapy.

Maintenance treatment of multiple-trigger wheeze

1) ICSs at a daily dose of up to 400 μg·day⁻¹ beclometasone equivalent should be given for the treatment of preschool children with multiple-trigger wheeze.

2) When the response to this treatment is poor, patients should not be treated with higher doses but should probably be referred to a specialist for further evaluation and investigations.

3) If response to inhaled steroids is favourable, treatment should probably be discontinued after several weeks or months, in order to judge whether symptoms have resolved or whether ongoing treatment is needed.

4) Linear growth should be measured in preschool children using ICSs.

5) Infants younger than 1 yr should probably not be prescribed ICSs.

6) Infants aged 1–2 yrs should only be prescribed ICSs if their symptoms are troublesome and they show a clear-cut response to treatment.

7) A trial of montelukast may be considered in preschool children with multiple-trigger wheeze.

8) Cromones, ketotifen and xanthines are not recommended for use in preschool children with wheeze.

9) Immunotherapy is not recommended for preschool children with wheeze outside the setting of a randomised controlled trial.

10) Influenza immunisation is not recommended for preschool children with wheeze.

Maintenance treatment of episodic (viral) wheeze

1) Montelukast 4 mg once daily should probably be given for the treatment of episodic (viral) wheeze.

2) A trial of inhaled corticosteroids may be considered in preschool children with episodic (viral) wheeze, in particular when episodes occur frequently or if the family history of asthma is positive.

ACKNOWLEDGEMENTS

The affiliation details of the present study’s authors are as follows. P.L.P. Brand: Princess Amalia Children’s Clinic, Isala Clinics, Zwolle; J.C. de Jongste: Dept of Paediatric Respiratory Medicine, Erasmus Medical Centre/Sophia Children’s Hospital, Rotterdam; P.J.F.M. Merkus: Dept of Paediatrics, Division of Respiratory Medicine, Children’s Hospital, Radboud Medical Centre Nijmegen, Nijmegen; and W.M.C. van Aalderen: Dept of Paediatric Pulmonology, Emma Children’s Hospital, Academic Medical Centre, Amsterdam (all the Netherlands). E. Baraldi: Dept of Paediatrics, Unit of Respiratory Medicine and Allergy, Unit of Neonatal Intensive Care, University of Padua School of Medicine, Padua; A.L. Boner and G. Piacentini: Dept of Paediatrics, G.B. Rossi Polyclinic, Verona; F. Midulla: Dept of Paediatric Emergency, University of Rome La Sapienza, Rome; and G.A. Rossi: Pulmonary Disease Unit, G. Gaslini Institute, Genoa (all Italy). H. Bisgaard: Danish Paediatric Asthma Centre, Copenhagen University Hospital, Copenhagen, Denmark; J.A. Castro-Rodriguez: School of Medicine, Pontifical Catholic University of Chile, Santiago, Chile; A. Custovic: North West Lung Research Centre, Wythenshawe Hospital, Manchester; M.L. Everard: University Division of Child Health, Sheffield Children’s Hospital, Sheffield; J. Grigg: Academic Unit of Paediatrics, Institute of Cell and Molecular Science, Barts and The London Medical School, London; S. McKenzie: Fielden House, Royal London Hospital, Barts and The London NHS Trust, London; N. Wilson: Dept of Paediatrics, Royal Brompton Hospital, London; A. Bush: Dept of Paediatric Respiratory Medicine, National Heart and Lung Institute, Royal Brompton Hospital and Imperial College, London; W. Lenney: Academic Dept of Child Health, University Hospital of North Staffordshire, Stoke-on-Trent; J.Y. Paton: University Division of Developmental Medicine, Yorkhill Hospitals, Glasgow; P. Seddon: Royal Alexandra Children’s Hospital, Brighten; and M. Silverman: Dept of Infection, Inflammation and Immunology, University of Leicester, Leicester (all UK). J. de Blic: Paediatric Pneumology and Allergology Service, Paris Public Assistance Hospitals, Necker Hospital for Sick Children, Paris, France. E. Eber: Respiratory and Allergic Disease Division, Dept of Paediatrics and Adolescent Medicine Division, Children’s Hospital, Academic Medical Centre, Amsterdam (all the Netherlands).
REFERENCES


65 Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function


Randomized controlled trial of intermittent high dose fluticasone versus placebo in young children with viral-induced asthma. Am J Respir Crit Care Med 2007; 175: Suppl. 1, A958.


DISCUSSION PAPER

Setting the standard for routine asthma consultations: a discussion of the aims, process and outcomes of reviewing people with asthma in primary care

*Hilary Pinnock*, Monica Fletcher, Steve Holmes, Duncan Keeley, Jane Leyshon, David Price, Richard Russell, Jenny Versne, Bronwen Wagstaff

---

**Abstract**

Globally, asthma morbidity remains unacceptably high. If outcomes are to be improved, it is crucial that routine review consultations in primary care are performed to a high standard. Key components of a review include:

- Assessment of control using specific morbidity questions to elucidate the presence of symptoms, in conjunction with the frequency of use of short-acting bronchodilators and any recent history of acute attacks
- After consideration of the diagnosis, and an assessment of compliance, inhaler technique, smoking status, triggers, and rhinitis, identification of poor control should result in a step-up of treatment in accordance with evidence-based guideline recommendations
- Discussion should address understanding of the condition, patient-centred management goals and attitudes to regular treatment, and should include personalised self-management education

Regular review of people with asthma coupled with provision of self-management education improves outcomes. Underpinned by a theoretical framework integrating professional reviews and patient self-care we discuss the practical barriers to implementing guided self-management in routine clinical practice.

---

**Keywords** asthma, primary care, guided self-management, monitoring long-term conditions, asthma action plan

---

**Introduction: the burden of asthma**

Worldwide, asthma is an important cause of morbidity, economic cost, and mortality. It is estimated that about 300 million people have asthma, with the highest prevalence in the UK, Australasia and North America.1 In England, data from general practice suggest that 5.8% of the population have ‘active asthma’ (defined as a diagnosis of asthma and a prescription for asthma treatment in the previous 12 months).2

Despite the focus in international guidelines on assessing and achieving good disease control in international...
surveys have consistently shown unacceptable morbidity associated with low expectations on the part of patients. It has been estimated that up to three-quarters of the 80,000 admissions for asthma in the UK in 2004 might have been prevented with improved long-term care. A key strategy for reducing the burden of asthma is a shift in emphasis from acute management to long-term care and supported self-management, in order to reduce chronic morbidity and impairment of quality of life, as well as reducing exacerbations, admissions and mortality. Proactive care, with structured reviews provided by clinicians with training in asthma care, improves outcomes.

After describing the policy and theoretical framework linking regular reviews and guided self-management, this discussion paper sets out the evidence base supporting the recommended content of good asthma reviews in primary care. It then discusses the role of ‘pay-for-performance’ – exemplified by the UK Quality and Outcomes Framework – as a driver for improving treatment outcomes. An Opinion sheet providing practical guidance for clinicians is available from www.pcrs-uk.org.

Policy and theoretical framework

The framework for monitoring chronic disease described by Glasziou et al. emphasises the inter-relationship between professional review and patient self-management, using asthma as an exemplar condition (see Figure 1). Cochrane reviews provide support for this concept, concluding that improved outcomes are the result of training in asthma self-management coupled with regular review. This dual approach is summarised in the GINA asthma guideline as ‘guided self-management’, is explicitly recommended (Grade A) in the 2008 update of the BTS/SIGN asthma guideline, and is a core strategy of national programmes to improve asthma care in Finland and Australia.

Self care is a ‘key pillar’ of the policy approach to meeting the challenge of providing care for people with long-term conditions. The widely cited Long-Term Conditions pyramid of care (LTC pyramid) emphasises the importance of self-management to “ensure patients and carers have the skills and knowledge they need to understand how to best handle their condition, including how to deal with flare-ups, to adjust medicines, improve their life-styles and access health care services”. Routine reviews operate in the boundary between patient self-care and professional management, not only offering opportunities specifically to reinforce and refine self-management skills, but also more generally to build the trusted relationship valued by patients (see Figure 2).

Asthma reviews

Asthma reviews in primary care should incorporate three key steps:

1. Assessing control in order to target care appropriately
2. Responding to that assessment by identifying reasons for poor control and adjusting management strategy accordingly
3. Exploring patients’ ideas, concerns and expectations, and guiding self-management to facilitate on-going control

1. Assessing control

Asthma control reflects the degree to which symptoms are reduced, exacerbations are prevented and normal lung function is maintained by treatment, with current guidelines defining ‘control’ as no symptoms, no exacerbations and normal lung function (see Table 1). Occasional daytime symptoms (defined as less than twice a week) may be consistent with good control, but disturbed sleep due to asthma signals loss of control. Challenge tests for assessment

---

**Figure 1. The inter-relationship between professional and self-monitoring (adapted from Glaziu et al. to illustrate the management and self-management of asthma).**

**Figure 2. The long-term condition pyramid with the boundary between professional and self care (adapted from Degeling et al.).**
of bronchial hyper-responsiveness are unlikely to be practical measures of control in primary care settings, though estimation of exhaled nitric oxide as a measure of inflammation may have a place in clinical care in the future.30

In primary care, asthma control is normally assessed on the basis of symptoms, supplemented by examination of the clinical records. Frequent use of reliever inhalers implies poor control, and intermittent requests for preventer treatment signals the need to address patients’ perception of, and fears about, regular treatment.31 The occurrence of an acute exacerbation is evidence of poor control over a longer time-frame than the duration of current symptoms.31 A primary care clinician with access to patient records can easily check the number of courses of oral steroid required over the previous year. A ‘one-off’ peak expiratory flow (PEF) or spirometry reading taken in clinic is of limited value in assessing the control of a variable condition, though if the patient is well-controlled it can provide an up-to-date ‘best’ reading for use in action plans. Although few patients will maintain an accurate paper-based PEF diary on a daily basis,32,33 use of mobile technology may engage some patients with on-going PEF and symptom monitoring.34,35

Surveys have consistently shown unacceptably high levels of asthma morbidity.36 Trials demonstrate that by adopting a policy of ‘zero tolerance’ to symptoms, patients with asthma can achieve good control;36 however, it remains unclear to what extent good control as defined by guidelines can be achieved in real-life practice.37 Patients will wish to balance the benefits of stepping up therapy until control is achieved against perceptions of, and preferences for, long-term treatment, and the practicalities of short consultations may restrict the time available to address all the diverse factors which result in poor control.37

- **Measures of morbidity**

Patients’ perception of control may differ markedly from that based on objective assessment of symptoms,31,32 and clinicians over-estimate improvements in asthma control.6 This has given impetus to the development of morbidity scores, suitable for use in clinical practice, which can facilitate detection of poor control. A review of some asthma control tools is available on the web-site of the International Primary Care Respiratory Group.38,39 Common to all these tools is specific enquiry about the presence of symptoms, interference with activities and disturbance at night.

There are two short, well-validated questionnaires widely used in research which may be suitable for use in clinical practice.38,39 The Asthma Control Questionnaire40,41 uses five morbidity questions plus an optional measure of the forced expiratory volume in one second (FEV1), has been tested for use in clinical practice, and a score of more than 1.5 indicates poor control.42 The Asthma Control Test uses similar morbidity questions but also includes a rating of overall control, with a score of 20 or more indicating good control.43,44 Both are available in a number of languages and have been validated for self-administration.

However, validity of questionnaires is determined under carefully controlled conditions, since the mode, circumstances and place of administration may affect the responses.45 By contrast, conditions of administration in routine clinical practice are likely to be very variable, with some practices arranging completion prior to the asthma review at home or in the waiting room, whilst others administer them formally in the consultation. Some clinicians may explain or paraphrase the questions to assist with completion. There is, therefore, a need to establish the value of such scores for assessing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (All of the following)</th>
<th>Partly Controlled (Any measure present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (twice or less/week)</td>
<td>More than twice/week</td>
<td></td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td>Three or more features of partly controlled asthma present in any week</td>
</tr>
<tr>
<td>Nocturnal symptoms/awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for reliever/rescue treatment</td>
<td>None (twice or less/week)</td>
<td>More than twice/week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV1)†</td>
<td>Normal</td>
<td>&lt; 80% predicted or personal best(if known)</td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>None</td>
<td>One or more/year</td>
<td>One in any week</td>
</tr>
</tbody>
</table>

1. Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
2. By definition, an exacerbation in any week makes that an uncontrolled asthma week.
3. In adults and older children.

<table>
<thead>
<tr>
<th>Table 2. The Royal College of Physicians three questions46.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the last month</td>
</tr>
<tr>
<td>1. Have you had difficulty sleeping because of asthma symptoms (including cough)?</td>
</tr>
<tr>
<td>2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?</td>
</tr>
<tr>
<td>3. Has your asthma interfered with your usual activities (eg housework, work, school, etc)?</td>
</tr>
</tbody>
</table>
control in a range of normal clinical scenarios.

The ‘Royal College of Physicians (RCP) three questions’ represent a consensus UK view on a short symptom questionnaire, which correlates with the Asthma Control Questionnaire and is responsive to change. A refinement of the RCP three questions which scores the number of days in the previous week affected by symptoms has been suggested to improve discriminatory power. The questions (or very similar precursors of the ‘RCP three questions’) have been used successfully to target care, including use by postal questionnaire and during telephone reviews. Whilst occasional symptoms (e.g. on two or less days a week) may be acceptable, any nocturnal waking or activity limitation should be considered as less than well-controlled disease, and management should be adjusted accordingly.2,10

2. Response to assessment and adjustment of management

If control is good, a reminder of action to be taken if asthma deteriorates may be all that is necessary. However, if assessment of symptoms, taken in conjunction with the reported and recorded use of short-acting bronchodilators and any recent history of any acute attacks, suggests that control is not ideal, the reasons for this should be considered and addressed appropriately before increasing asthma therapy. A recent primary care review has considered the causes for poor control in detail. Here, we present a summary of the key implications for routine practice:

- **Reviewing the diagnosis**

  An increase in symptoms, or failure to respond to treatment, should lead to reconsideration of the diagnosis. An unrecognised diagnosis (for example chronic obstructive pulmonary disease (COPD) in a smoker, gastro-oesophageal reflux as a trigger for cough, obesity as a cause of breathlessness), or the development of a co-morbid condition, may be responsible for apparent poor control. A wide range of rare conditions in childhood may be initially misdiagnosed as asthma.13

- **Checking and correcting inhaler technique**

  Poor inhaler technique is a well documented problem which results in ineffective and wasteful use of therapy, and is an important cause of poor control. As few as a quarter of patients make no mistakes when using a pressurised metered-dose inhaler (pMDI), while just over a half can use dry powder inhalers, breath-actuated pMDI or pMDI with a spacer without errors. Provision of a spacer for use in an acute situation may improve effectiveness at a time when breathlessness makes usual pMDI technique more difficult.

  Meta-analysis of the effect of teaching inhaler technique shows significant improvement after an educational intervention with a ‘number needed to teach’ (to achieve an ‘ideal’ technique) of 2.6 patients. However, repeated training is required to maintain good technique. Those unable to master or maintain good technique with one device should be offered an alternative. This has been specifically highlighted in children, where inadequate technique – resulting either from poor training or from choosing a device poorly suited to the child – significantly reduces drug delivery to the lungs and results in poor asthma control.

  Practical training when a device is first prescribed, supported by review of inhaler technique at every asthma consultation (whether with a nurse, doctor, pharmacist or other healthcare professional) is good practice.

- **Assessing adherence**

  Adherence with regular preventative medication is known to be poor, and under-use should be considered when there is a failure to control asthma symptoms. Patients self-reporting and health care professional assessment both overestimate regular use of prophylactic medication. In primary care, repeat prescribing records provide an indication of adherence with prescribed asthma regimens.

  Simple, verbal and written instructions and information on asthma and its treatment for patients and carers may help to overcome unintentional non-adherence. Patients balance their perceived need for treatment against their concerns about taking a medication. Enquiry, based on a non-judgemental assumption of non-adherence, can facilitate an open discussion of the rationale and potential benefits of regular therapy versus the disadvantages of taking a drug with (perceived or real) side effects, thus enabling the patient to reach an informed decision about concordance with clinical advice on the use of inhaled steroids.

- **Asking about, and treating rhinitis**

  Rhinitis and asthma are common diseases which co-exist in 75-80% of patients and are associated with substantial cost to patients, employers and health care systems. The relationship between rhinitis and asthma is strongly supported by epidemiological, pathophysiological and clinical evidence. Patients with co-existent asthma and rhinitis incur greater prescription drug costs and experience more general practitioner (GP) visits and hospitalisations for asthma than those with asthma alone.

  Treatment of concomitant allergic rhinitis, particularly with intranasal steroids and/or leukotriene receptor antagonists, is associated with significant reductions in risk of emergency room treatment and hospitalisation for asthma. Rhinitis (including seasonal rhinitis) should therefore be sought as a co-morbidity in all patients with uncontrolled asthma and treated appropriately.

- **Assessing smoking status and offering cessation advice**

  Smoking adversely affects asthma control. This may signal a diagnosis of COPD, either as a co-morbidity or because the COPD has been incorrectly diagnosed as asthma. Smoking also reduces
the effectiveness of inhaled steroids.\textsuperscript{63,77,78} It is therefore important to enquire about smoking status and to offer cessation advice to patients with poorly controlled asthma. Persistent smokers may need relatively high doses of inhaled steroids.\textsuperscript{10}

- **Adjusting therapy according to evidence-based guidelines**

After consideration of diagnosis, compliance, inhaler technique, smoking status, triggers and rhinitis, the identification of poor control should result in a step-up of treatment in accordance with the evidence-based advice of international or national guidelines.\textsuperscript{8,10} Discussion of the advantages and disadvantages of treatment options, and acknowledgement of patient preferences – i.e. whether to accept symptoms, or whether to accept a change or an increase in treatment such as a higher dose of inhaled steroids, an additional therapy, a combination inhaler instead of separate inhalers, a long-acting bronchodilator or an oral leukotriene receptor antagonist – is good consulting practice and would seem likely to optimise future concordance.\textsuperscript{79}

Control should be maintained on the lowest possible dose and stepping down treatment is an important and frequently-overlooked step for patients who are consistently well controlled, especially in children who often ‘grow out’ of their asthma.\textsuperscript{3,10}

### 3. Exploring perceptions and supporting self-management

- **Guideline recommendations**

International guidelines emphasise that “Patient education is the key to success of every aspect of asthma management and prevention”,\textsuperscript{3} as many of the obstacles to achieving best control relate to misunderstanding of the condition, under-estimation of the potential benefits of regular treatment, and exaggerated fears about side effects of asthma treatment. The UK national guideline includes the Grade A recommendation that “Patients with asthma should be offered self-management education that should focus on individual needs, and be reinforced by a written action plan”.\textsuperscript{10}

The provision of self-management education, incorporating a written asthma action plan, can reduce hospitalisation,\textsuperscript{80} unscheduled consultations, time lost from work and nocturnal asthma, as well as improving self-efficacy and asthma-related quality of life.\textsuperscript{16,81} Similar benefits have been shown in school age children,\textsuperscript{20} though an innovative approach may be required for pre-school children.\textsuperscript{81}

Clear advice from a systematic review on the components of effective asthma action plans – i.e. written instructions, 2-3 action points triggered by symptoms or based on best peak flow, advice on increasing inhaled steroids and commencing oral steroids – is now available.\textsuperscript{96} Health professionals should tailor the self-management intervention to allow for patient preference (e.g. preferred degree of autonomy versus frequency of professional review; peak flow versus symptom monitoring) as well as the severity of asthma, risk of very severe attacks and the maintenance treatment plan.\textsuperscript{19}

- **Implementation in primary care**

The challenge for primary care is that of implementing these evidence-based recommendations. Studies have shown consistently that provision of self-management education is poorly implemented in practice.\textsuperscript{8,83,84} Some of the recognised barriers, such as time and resources, are practical issues which need to be addressed when planning routine care for people with asthma.\textsuperscript{85,86} Confusion about details of action plans (such as the relevance of increasing inhaled steroids) are a further barrier.\textsuperscript{87} Despite the growing body of evidence from primary care,\textsuperscript{88-92} there is scepticism about whether the evidence applies to the relatively low-risk mild patients in whom benefit is harder to demonstrate.\textsuperscript{84} More fundamentally, provision of asthma action plans is often perceived as an optional task delegated to a nurse educator.\textsuperscript{93} Recognition that self-care and professional care are inextricably linked as complementary aspects of the management of all people with long-term conditions – as illustrated in the framework for monitoring and self-monitoring (see Figure 2)\textsuperscript{17} – may be the conceptual key that will help unlock implementation.

A systematic review of the implementation of asthma action plans highlighted the importance of this inter-relationship between the facilitation of regular, structured review and the provision of self-management education.\textsuperscript{95} All three primary care studies in this review demonstrated increased ownership of asthma action plans,\textsuperscript{92,94,95} and showed a consistent trend to improved clinical outcomes, though the only significant benefits were a reduction in episodes of ‘speech limiting wheeze’,\textsuperscript{92} and night time waking.\textsuperscript{94} Similarly, within managed care programmes, nurse-led telephone-based reviews incorporating self-management education supported by written information can increase the use of inhaled steroids.\textsuperscript{96,97} This inter-relationship is encompassed in international guidelines as the concept of ‘guided self-management’.\textsuperscript{3}

### Ensuring access to professional advice

Patients value flexible access to professional advice in order to support self-care,\textsuperscript{25,98} but not all patients are willing to attend a pre-arranged appointment for a regular review.\textsuperscript{83,99} Repeat prescribing arrangements should aim to be sufficiently flexible to enable patients to order more inhalers promptly when needed, but should include checks to ensure that those patients requesting reliever inhalers frequently are reminded to arrange a review.

There is now evidence to inform the appropriate role of telephone asthma reviews.\textsuperscript{95,99,101,102} Telephone asthma reviews
increase the proportion of patients reviewed without loss of clinical effectiveness, though patients whose asthma is causing concern prefer a face-to-face review. Asking standard morbidity questions by telephone can identify those who should be invited for a face-to-face review whilst offering a convenient telephone option to those currently under good control. The provision of a telephone asthma review option within routine practice showed that opportunistic telephone calls could provide consultations to non-responders who would otherwise not have had a review. A suggested model of care incorporating this evidence is given in Table 3.

### Ensuring quality

#### Appropriate training

Asthma reviews should be undertaken by healthcare professionals with appropriate training to enable them not only to assess control but also to adjust treatment as necessary. In the UK, this is frequently an experienced practice nurse, though a survey published in 2007 highlighted that 20% of nurses did not have any specialist asthma training. Whilst guidelines (and clinical governance) might recommend that at least one member of the primary care team has specialist respiratory training, this raises concerns about the potential deskilling of other members of the team. Poorly defined inter-professional roles and inadequate communication between colleagues can act as barriers to the implementation of guideline recommendations, an issue of particular importance in the context of guided self-management. Although a specialist clinician may initiate education, it is incumbent on all members of the team to provide the on-going, consistent support for guided self-management. Multi-disciplinary education and support for professionals was a core component of the successful Finnish programme.

#### Audit and standards

A systematic review of 118 randomised controlled trials spanning a range of countries, professionals and disease areas concluded that audit and feedback can be moderately effective at improving professional practice. The process of asthma reviews, particularly when the consultations are recorded on computer templates, offers ready opportunities for repeated audit cycles. However, detailing and auditing all the possible functions of an asthma review, whilst potentially improving process, risks automating the consultation and making it less responsive to individual patient needs. The UK Quality and Outcomes Framework (QOF) – a ‘pay for performance’ scheme which was introduced as part of the UK General Medical Services Contract in 2004 and which rewards practices for achieving pre-determined standards of care for a range of long-term conditions – recognised this potential risk, and the approach adopted was to reward the ‘provision of an asthma review’ recorded as a single coded entry in the computerised clinical records. Concerns remain about the quality of the review represented by this ‘tick box’, though serial detailed audits in 60 representative practices showed significant progress in assessing control by the recording of specific symptoms, and checking inhaler technique as part of the review. Disappointingly, despite uniformly high achievement in the process measures for QOF, the proportion of well-controlled patients varies considerably between practices.

### Conclusion

Too many of the 300 million people around the world living with asthma are coping on a daily basis with a variable condition that significantly affects their quality of life, despite the existence of treatment which could substantially improve their symptoms. At the core of a routine review is the opportunity to identify patients with sub-optimal control and (for both patients and professionals) the need to adopt an approach of ‘zero tolerance’ to symptoms. Recognition of the inter-relationship of professional reviews and patient self-
management underpins the partnership as future management strategies are negotiated.

**Funding**

No direct funding. HP is supported by a Primary Care Research Career Award from the Chief Scientist’s Office, Scottish Government.

**Conflict of interest declarations**

None known.

**Acknowledgements**

This paper builds on work on asthma reviews, commissioned by the Primary Care Respiratory Society UK (PCRS-UK) formerly known as the General Practice Airways Group (GPAG), together with the British Thoracic Society, Education for Health and Asthma UK, in preparation for a joint submission to the UK QOF review panel. We thank Professor Chris Griffiths for his helpful comments on an earlier draft.

**Contributorship**

HP, BW, JL, IV, MF, and RR prepared the original QOF submission and all the authors contributed to the preparation of this discussion paper.

**References**

2. The Information Centre. Quality and Outcome Framework http://www.ic.nhs.uk/servicesnew/qof06/
4. Smith NM. The ‘Needs of people with asthma’ survey and initial presentation of the data. *Asthma J 2000;5:133-7.*
25. Long Term Conditions Team Primary Care, Improving care, improving lives. Department of Health. 2005
28. Olson L, Olson J, Olson P. Monitoring in asthma: a randomized clinical trial comparing peak flow with the Asthma Control TestTM. *Thorax 2006;61:663-70.* http://dx.doi.org/10.1136/thx.2005.055699
34. Reddel HK, Toelle BG, Marks GB, Ware SJ, Jenkins CR, Woolcock AJ. Analysis of adherence to peak flow monitoring when recording of data is electronic.
Routine asthma reviews


89. Mougdl H, Marshall T, Honeybourne D. Asthma education and quality of life in the community: a randomised controlled study to evaluate the impact on white European and Indian subcontinent ethnic groups from socioeconomically deprived areas in Birmingham, UK. *Thorax* 2000;55:177-83. http://dx.doi.org/10.1136/thorax.55.3.177


PRIMARY CARE RESPIRATORY JOURNAL
www.thepcrj.org
Managing wheeze in preschool children

Andrew Bush professor of paediatrics and head of section (paediatrics)¹, professor of paediatric respirology² consultant paediatric chest physician³, Jonathan Grigg professor of paediatric respiratory and environmental medicine⁴, Sejal Saglani reader in paediatric respiratory medicine⁵

¹Imperial College, London UK; ²National Heart and Lung Institute, Imperial College, London, UK; ³Respiratory Paediatrics, Royal Brompton Harefield NHS Foundation Trust, London, UK; ⁴Blizzard Institute, Barts and the London Hospital, London, UK; ⁵Leukocyte Biology, NHLI, Imperial College London, UK

Lower respiratory tract illnesses with wheeze are common, occurring in around a third of all preschool children (here defined as aged between 1 and 5 years). They are a major source of morbidity and healthcare costs, including time off work for carers, and are often difficult to treat. This review focuses on the two areas in which there have been recent developments. The first is the classification of these children by symptom pattern into “episodic viral” and “multiple trigger” wheezers.¹ These phenotypes can change within an individual over time,² but they are a useful guide to current treatment, and there are also physiological and pathological rationales for their use.³ ⁴ The second area is the recent series of large randomised controlled trials of treatment, specifically related to the roles of intermittent montelukast and inhaled and oral corticosteroids. These trials have shown clearly that inhaled corticosteroids and prednisolone in particular have been misused and overused in the past, mandating a reappraisal of treatment algorithms.

What is wheeze?

Wheeze is a term that is often used imprecisely, as has been shown in studies with a video questionnaire and direct quantification of wheeze.⁵ ⁶ ⁷ Indeed, some European languages do not even have a word for wheeze. Our definition is high pitched whistling sounds usually in expiration and associated with increased work of breathing, but which can also sometimes be heard in inspiration. In research studies, wheeze can be quantified directly by using surface microphones, which is the ideal. With this technique, it was shown that physicians auscultating the chest accurately identify wheeze⁸; parents and nurses were much less reliable.

How common is wheeze in preschool children?

Preschool wheeze is common. In the Avon Longitudinal Study of Parents and Children (ALSPAC) study, a prospective longitudinal observational study, 26% of 6265 infants reported on had at least one episode of wheeze by the age of 18 months.⁹

What is the best clinical approach to the preschool wheezer?

Once it is established that the child has actual wheeze, history and a careful physical examination should be used to place the child in one of four categories (table⇓). History and physical examination are used to categorise the child and to decide whether further investigation is needed. In general, there are three reasons for a referral: if diagnosis is in doubt, if treatment is not working, and if any party (general practitioner, parent) is unhappy with progress. A report of two cross sectional, community based observational studies found that isolated dry cough in a community setting, without wheeze or breathlessness, is most unlikely to be caused by any form of asthma.⁹ Most preschool wheezers do not require any additional tests. Confusion arises from the different uses of the term “bronchiolitis.” In the United Kingdom, this is an illness characterised by respiratory distress and showers of fine crackles in a child aged under 1 year; though wheeze can be present as well, it is the crackles that define the illness. It should be emphasised that any rigid definitions based on age are likely, to some extent, to be artificial. In the United States and elsewhere, “bronchiolitis” is used synonymously with wheezing illness. We have not discussed the approach to bronchiolitis as defined in the UK; interested readers are referred elsewhere.¹⁰ ¹¹

Should preschool wheezers be subdivided (phenotyped)?

Several approaches have been used to categorise preschool wheezers. The first two are mentioned because they are of scientific importance and are widely quoted in the literature, but they are not useful in guiding treatment.
Is it asthma?

This question is commonly asked by parents who want to know whether their child will continue to have symptoms and require drug treatment into school age and beyond. The answer, however, depends on what definition of asthma is being used by the questioner. If a purely symptomatic definition is used (symptoms of wheeze and breathlessness fluctuating over time and with treatment), then the answer is affirmative. If, however, the definition includes evidence of airway eosinophilic inflammation, the answer is more difficult as few if any have the ability to measure this in preschool children. What most parents actually want to know is whether their child will go on with symptoms and the need for treatment into school age and beyond. The evidence from cross sectional physiological work and studies of endobronchial biopsies in children with severe preschool wheeze is that multiple trigger wheeze is associated with more airflow obstruction than episodic viral wheeze, and the airway pathology (eosinophilic inflammation and remodelling) is similar to childhood and adult asthma. By contrast, episodic viral wheeze is not associated with evidence of eosinophilic inflammation, so the use of inhaled corticosteroids in this group is questionable.

Does preschool wheeze lead to asthma?

Several clinical predictive indices for future risk of asthma have been developed based on combinations of the presence of atopic manifestations, indirect evidence of airway inflammation, such as peripheral blood eosinophil count, and severity of preschool wheeze. They all have a high negative predictive value and a poor positive predictive value (typically positive predictive values 44-54, negative 81-88). Children who have episodic viral wheeze only have no increased risk of atopy or respiratory symptoms in the long term once they reach the age of 14.

Can we prevent preschool wheeze progressing to school age asthma?

The clear cut evidence from good randomised controlled trials is that early use of inhaled corticosteroids, whether continuously or intermittently with viral colds, does not affect progression of disease. A trial of oral cetirizine in high risk children seemed to show benefit in preventing symptoms in subgroups sensitised to particular Aeroallergens, but a subsequent trial with L-cetirizine did not replicate these findings (J Warner, personal communication, 2013). This means that we have no disease modifying drug treatments, and treatment should solely be focused on current symptoms.
What are the broad treatment strategies for children with preschool wheeze?

Before any drugs are prescribed for either episodic viral wheeze or multiple trigger wheeze, it is essential to ensure that the home environment is optimal, particularly that the child is not exposed to tobacco smoke; parental smoking “not in front of the children” does not protect them from harm.23 A birth cohort study found that air pollution can increase vulnerability to preschool wheeze,24 but to date we have no specific advice based on individual exposure profiles. Drugs might reasonably be targeted at prevention of future complications such as airway remodelling and persistent airflow obstruction, and, additionally, to treat present symptoms. In practice, we have no drug strategies to reduce future risk of asthma; neither early use of continuous21, 22 nor intermittent25 inhaled corticosteroids reduces the risk of progression to school age asthma. If inhaled drugs are prescribed, repeated education of the parents in the correct use of spacers is essential. If inhaled drugs in particular do not seem to be working, check that they are being properly administered rather than escalate treatment. The use of a skilled respiratory nurse to help carers give inhaled drugs to children is invaluable.

How to treat episodic viral wheeze?

Intermittent symptoms should be treated with intermittent therapy (and in practice this is likely to be what parents do anyway). Failure to instigate regular inhaled treatment will not prejudice future respiratory health. It is important to consider whether the child needs treatment at all. The use of inhaled therapy to treat mild respiratory noises with minimal respiratory distress might be more problematic than the disease. If treatment is required, then initial treatment should be with an intermittent bronchodilator (either short acting β₂ agonist or anticholinergic). If treatment needs to be escalated beyond intermittent β₂ agonist or anticholinergic because of failure to control symptoms, the next options are intermittent leucotriene receptor antagonist (montelukast), intermittent inhaled corticosteroids, or both.

There have been important recent randomised controlled trials of intermittent therapy.

The PREEMPT study examined intermittent montelukast compared with placebo in 220 children aged 2-14.27 Treatment was initiated at the onset of symptoms of a respiratory tract infection and continued for a minimum of a week or until symptoms had disappeared for 48 hours. The montelukast group had fewer unscheduled consultations for asthma (odds ratio 0.65, 95% confidence interval 0.47 to 0.89) and fewer days away from school or childcare and less time off work for parents (37% and 33%, respectively; P<0.001 for both). In a predefined subgroup analysis, the benefits were greater in children aged 2-5 (about 80% of the study group). These findings were not confirmed in a much larger three way comparison of intermittent montelukast, continuous montelukast, and placebo (nearly 600 children in each group).28 A three way comparison between standard treatment, intermittent montelukast, and intermittent nebulised budesonide (the only aerosolised steroid permitted by the FDA in preschool children) in 238 children aged 12-59 months showed minor and equivalent benefits for the two active treatments compared with standard treatment.28 Benefits were greater in the subgroup with a modified asthma predictive index.

Taken together, these studies suggest that a trial of montelukast in preschool children with troublesome viral induced wheeze is worth attempting. We recommend starting treatment at the first sign of a viral cold and discontinuing it when the child is clearly better, rather than for a fixed period of days.

The Cochrane review identified use of intermittent inhaled corticosteroids as a partially effective strategy for episodic wheeze in preschool children.29 A proof of concept study in 129 children aged 1-6 years showed that the pre-emptive use of 750 µg twice a day (compared with the maximum licensed dose of 200 µg twice daily in children aged 4 and above; not licensed in any dose below age 4) of fluticasone dipropionate for up to 10 days, starting at the first sign of a viral upper respiratory tract infection, led to a reduction in dose of rescue prednisolone (8% of upper respiratory tract infections in the fluticasone group v 18% in the placebo group; odds ratio 0.49, 95% confidence interval 0.30 to 0.83).29 This huge dose, however, was unsurprisingly associated with side effects and cannot be recommended. Another study looked at regular twice daily nebulised budesonide 0.5 mg compared with intermittent nebulised budesonide 1 mg twice a day at the time of viral respiratory illnesses. This was a randomised double blind controlled trial in 278 children aged between 12 and 53 months who had a positive modified asthma predictive index.30 There was no difference in any respiratory outcome, but in the absence of a placebo group it is not possible to state that either strategy was beneficial. What this study definitely shows is that regular nebulised budesonide does not prevent viral exacerbations of wheeze. Smaller older trials of inhaled beclometasone also failed to show a preventive effect.31 There is currently no evidence to support the use of inhaled corticosteroids at licensed doses in children with viral episodic wheeze. As some studies suggest that intermittent inhaled corticosteroids might be a useful approach in children with viral induced wheeze at higher than licensed doses, further studies are required to clarify the dose and duration that might be beneficial in this setting. In practice, however, it would be unwise to go above a fluticasone dose of 150 µg twice a day, given the number and duration of viral colds in normal preschool children and the risk of side effects including growth suppression and adrenal failure with higher doses. There are currently no studies that have combined intermittent inhaled corticosteroids with intermittent montelukast to treat episodic viral wheeze.

Is there any role for prophylactic continuous inhaled corticosteroids in episodic viral wheeze?

There is no evidence to support the use of regular inhaled corticosteroids in preschool children who do not wheeze between viral colds. In those children with really severe episodic wheeze who require repeated admission to hospital or have prolonged disruptive symptoms managed at home, however, a trial of prophylactic inhaled corticosteroids can be given. In some cases it might become apparent that in fact there were interval symptoms that were underappreciated. In any event, the clinical trials of inhaled corticosteroids in episodic viral wheeze were carried out in relatively mildly affected children, so the evidence in severely affected children is less robust. Treatment should be reviewed and discontinued if there is no benefit; there is no evidence to suggest the optimal duration of the therapeutic trial, but six to eight weeks would seem a reasonable time period. If the viral wheezing improves on treatment, regular attempts should still be made to reduce the dose. It should be noted that, in a small study, even really severe episodic viral wheeze was not associated with eosinophilic airway inflammation⁴ and that inhaled corticosteroids (fluticasone 100 µg twice a day) led to growth suppression in the PEAK trial,32 so trials of inhaled corticosteroids in this context should be deployed only exceptionally. If there is a suspicion that the child might in fact
have symptoms between colds, which are underappreciated by the carers, a trial of inhaled steroids can reveal that the child was previously much more symptomatic than was thought. Whatever the context of therapeutic trials in preschool children, they should be for a fixed time period (such as six to eight weeks, see above) and discontinued at the end of the agreed period to see if symptoms recur or in fact have resolved and treatment has become unnecessary (see the three stage trial proposal below).

Is there a role for oral prednisolone in primary care for preschool wheeze?

Recent evidence has questioned the role of prednisolone in acute exacerbations of episodic viral preschool wheeze. In a home based study, 217 preschool children who had at least one admission to hospital were randomised to a parent initiated course of prednisolone or placebo at the next wheezing episode. No benefit was observed in the treatment group. A hospital study that randomised 687 preschool children admitted with wheeze to prednisolone or placebo in addition to bronchodilator therapy found there was no benefit in the prednisolone group. The implication of these two studies, involving more than 900 children, is that any preschool child with viral induced wheeze who is well enough to stay in the community should not be prescribed oral prednisolone, and many children admitted to hospital also should not be prescribed oral prednisolone. These studies, however, were undertaken in children with relatively mild symptoms and most were discharged from hospital in less than 24 hours, so what these studies do not tell us is whether prednisolone is indicated in really severe preschool viral wheeze. In the absence of evidence, it is likely that prednisolone will continue to be prescribed in this small subgroup of children in hospital.

How should I treat multiple trigger wheeze?

Preschool children who have wheeze or cough responsive to bronchodilator treatment and breathlessness on most days even when they do not have a viral cold should be considered for a trial of preventive drug treatment, either inhaled corticosteroids or a leucotriene receptor antagonist (montelukast). As airway inflammation cannot routinely be measured in this age group, and many children will become asymptomatic before school age, it would be incorrect to assume the pathophysiology of the disease is the same as school age asthma. Furthermore, the younger the child, the less likely there is to be any eosinophilic inflammation and therefore more reluctance to use inhaled corticosteroids.

There is a dearth of evidence, but the box shows a pragmatic three stage trial of treatment, which is recommended in our practice. The aim of this three step approach is to prevent children being falsely labelled and inappropriately treated because someone has started a drug when the child was about to get better spontaneously. Long acting β₂ agonists are not licensed for use in preschool children.

Are there any other new treatments around?

In a small double blind trial, a total of 41 children aged 1-6 years were randomised to nebulised hypertonic (7%) or normal (0.9%) saline, in each case combined with salbutamol twice 20 minutes apart in the emergency department and then, if the child was admitted to hospital, four times a day thereafter. Admission rates and lengths of stay were significantly reduced in the hypertonic saline group, but there was no significant change in severity score, possibly because of the small size of the study. Further work in larger numbers of children is needed to define the role of hypertonic saline in acute preschool wheeze. Given the possibility of bronchoconstriction being induced by hypertonic saline, this treatment should be given only in a hospital setting.

Palivizumab has been used to prevent infection with respiratory syncytial virus in high risk infants—for example, survivors of extreme prematurity. The cost and inconvenience of monthly injections means this has never been, and is still not, a treatment strategy for all babies. A recent double blind study, however, randomised 429 infants born at 33-35 weeks’ gestation to palivizumab or placebo. Palivizumab reduced the number of days with wheeze in the first year of life by 61% and the proportion of infants with recurrent wheeze from 21% to 10%. The more interesting question, which this trial could answer, is the vexed one as to whether early respiratory syncytial virus infection causes asthma or is merely a sign that the child was previously predisposed to asthma, provided the infants are followed up to school age. The current position is that this is work in progress, rather than an indication for a change in public policy.

What about treatment plans?

Treatment plans outlining self management actions to be taken depending on the severity of symptoms and peak flow measurements are widely recommended in school age children. In a randomised controlled trial in which 200 children age 18 months to 5 years who had an unscheduled hospital visit or admission with wheezing were allocated either to standard care or to receive a package consisting of a booklet, a written guided self management plan, and two structured educational sessions, there were no differences in any outcomes. Despite this, many will use educational sessions and plans, but there is no evidence of efficacy.

What is the role of nebulised therapy?

There is no role for nebulised therapy to deliver bronchodilator apart from in children too sick to use inhalers. For all other purposes, the evidence is clear that metered dose inhalers and spacers are at least as good as nebulisers.

Contributors: AB wrote the initial draft of the manuscript and is guarantor. The manuscript was reviewed and edited by SS and JG; all authors agreed the final version.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: AB was supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London. Provenance and peer review: Not commissioned; externally peer reviewed.

Pragmatic regimen for trial of treatment

Step 1: Trial of inhaled corticosteroids or montelukast in standard dose for a defined period, usually four to eight weeks

Step 2: Stop treatment; either there has been no improvement, in which case further escalation is not indicated, or symptoms have disappeared; in the latter case, it is not possible to know if this was spontaneous or as a result of treatment. If there is no benefit and the symptoms are troublesome, referral for consideration of further investigation is recommended

Step 3: Restart treatment only if symptoms recur; then reduce treatment to the lowest level that controls symptoms

Questions for future research and ongoing studies

Is nebulised hypertonic saline an effective strategy to contemplate in children with acute preschool wheeze needing admission to hospital?

What is the minimum effective dose of inhaled corticosteroids for intermittent use in preschool children with episodic viral wheeze?

Would fine particle inhaled corticosteroids, which might be expected to deposit in the peripheral airways, offer additional benefit?

Is intermittent high dose inhaled corticosteroid safe and beneficial in children with acute preschool wheeze who need admitting to hospital?

How can we predict which children with preschool wheeze will go on to develop asthma, and how can we prevent this?

Does prevention of respiratory syncytial virus infection with palivizumab lead to a reduction in prevalence of school age asthma?

Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate-5-lipoxygenase (ALOX5) promoter genotype (http://clinicaltrials.gov/show/NCT01142505). This is a randomised controlled trial of intermittent therapy with montelukast started at the first sign of a viral cold or wheeze by parents. Both phenotypes of wheeze were recruited and analysis is due January 2014

Tips for non-specialists

• Wheeze is a term used by lay people as a description of a multiplicity of upper and lower airway noises; be sure what exactly the family means by wheeze

• Isolated dry cough in a community setting is rarely if ever due to asthma

• Nebulisers should not be used in preschool wheeze; inhaled drugs delivered by metered dose inhaler and spacer are at least as efficacious

• If inhaled drugs in particular do not seem to be working, check that they are being properly administered (or better yet, get a respiratory nurse to do this) rather than escalating treatment

• Although several predictive indices for future asthma risk have been proposed, negative predictive value is excellent but positive predictive value is poor

Additional educational resources

Resources for healthcare professionals

The European Respiratory Society e-learning resources has the following link for “paediatric asthma” (needs registration): www.ers-education.org/publications/european-respiratory-monograph/archive/paediatric-asthma.aspx

World Allergy Organisation—summary of different management recommendations, including GINA, available free at www.worldallergy.org/publications/european-respiratory-monograph/archive/paediatric-asthma.aspx

The European Respiratory Society e-learning resources has the following link for “paediatric asthma” (needs registration): www.ers-education.org/publications/european-respiratory-monograph/archive/paediatric-asthma.aspx

Resources for patients

Asthma UK webpage (free): www.asthma.org.uk/advice-children-and-asthma


Table 1 | Four groups of childhood wheezing disorders, based on personal practice

<table>
<thead>
<tr>
<th>Wheeze category</th>
<th>Suggestive features</th>
<th>Suggested actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal child—commonest and also the hardest diagnosis</td>
<td>Child well and thriving, with no other features on history or examination to raise concerns</td>
<td>Reassurance</td>
</tr>
<tr>
<td>to make (includes those with postviral cough, pertussis, and parents who are overanxious about minor symptoms or do not appreciate the number of viral infections a normal preschooler will acquire)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious condition (such as immunodeficiency)—rare but essential to diagnose or refer</td>
<td>Suspect if history of symptoms from first day of life, chronic wet cough, sudden onset of symptoms, continuous unremitting symptoms, systemic illness; physical examination shows digital clubbing, unusually severe chest deformity, stridor, fixed wheeze, or asymmetric signs on auscultation, anything to suggest systemic disease</td>
<td>Refer for investigation (by telephone if sudden onset of signs suggesting endobronchial foreign body)</td>
</tr>
<tr>
<td>Minor conditions that might may exacerbate or mimic wheezing syndrome—for example, gastro-oesophageal reflux, chronic rhinitis</td>
<td>Otherwise well and thriving child with history of easy vomiting, arching away from breast, poor feeder (gastro-oesophageal reflux), or prominent upper airway disease, inflamed nose, adenotonsillar hypertrophy</td>
<td>Initial empirical trials of treatment; refer if no response and symptoms troublesome. Child with prominent snoring should be considered for referral for sleep study</td>
</tr>
<tr>
<td>True wheezing syndrome: episodic viral wheeze (EVW); multiple trigger wheeze (MTW)</td>
<td>An otherwise well and thriving child with wheeze only at time of viral cold, often but not invariably with no personal or family history of atopic disorders (EVW); wheeze with viral colds and also between colds with typical asthma triggers such as exertion and excitement, cold air, allergens (MTW). There is often but not invariably a personal or family history of atopic disorders</td>
<td>Treatment options discussed in text. Refer if child is not responding</td>
</tr>
</tbody>
</table>