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ERS TASK FORCE

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

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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 β_2-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

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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 1, 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 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

TABLE 1 Definitions used in the present report

Term	Definition
Temporal pattern of wheeze	
Episodic (viral) wheeze	Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes
Multiple-trigger wheeze	Wheezing that shows discrete exacerbations, but also symptoms between episodes
Duration of wheeze	
Transient wheeze	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
Persistent wheeze	Symptoms that are found (retrospectively) to have continued until the age of $\geq$6 yrs; persistent wheeze may be episodic or multiple-trigger wheeze
Late-onset wheeze	Symptoms that start after the age of 3 yrs; late-onset wheeze may be episodic or multiple-trigger wheeze

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 (F_{ENO}) 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]. F_{ENO} in infants are affected by environmental exposures

and genetic predisposition to atopy [75]. Reference values for F_{eNO} are only available for children aged $\geq$4 yrs [76]. For uncooperative children aged <4 yrs, measurement of F_{eNO} has not been standardised and there is no evidence supporting the usefulness of measuring or monitoring F_{eNO} 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 hyperresponsiveness 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 β_2-agonists

Inhaled rapidly acting β_2-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 β_2-agonist. Thus, infants possess functional β_2-receptors from birth, and stimulation of these receptors can produce the same effects as in older children, although paradoxical responses to inhaled β_2-agonists have been reported in infants [50, 101]. Oral administration of β_2-agonist is also effective but is limited by systemic side-effects [102]. Intravenous infusion of β_2-agonists has only shown an advantage over hourly inhaled treatment in very severe acute wheeze in young children [103].

After inhalation, β_2-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 β_2-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 β_2-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 $\mu g \cdot day^{-1}$ 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 $\mu g \cdot day^{-1}$ beclometasone equivalent (or 200 $\mu g \cdot day^{-1}$ 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 $\mu g \cdot day^{-1}$), 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 $\mu g \cdot day^{-1}$ 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 $\mu g \cdot day^{-1}$ 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 $\mu g \cdot day^{-1}$ 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 $\geq$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 $\mu g \cdot day^{-1}$ 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 $\mu g \cdot day^{-1}$ 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 $mg \cdot day^{-1}$ fluticasone for $\leqslant$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 cysteinyl 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 β_2-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 β_2-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 β_2-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 $\mu g \cdot day^{-1}$ 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.

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