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Asthma in preschool children: the next challenge

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Abstract

Purpose of review—To describe a prospective classification for preschool wheezers according to temporal symptom pattern, and summarise findings relating to the management of viral wheeze and the use of short term therapy for intermittent severe wheeze.

Recent findings—Phenotypes defined from cohort studies should only be applied retrospectively at school-age. A new classification that can be applied prospectively is discussed. The importance of early rhinovirus induced wheezing as a risk factor for asthma has become apparent. However, there is no benefit from short-course oral steroids for acute viral wheeze in the majority of cases. There is conflicting evidence for the role of intermittent montelukast or inhaled steroids in the treatment of acute, intermittent wheeze. A link between reduced vitamin D intake during pregnancy and increased preschool wheeze in offspring has emerged, suggesting a potential role for vitamin D supplementation in primary prevention.

Summary—Based on current evidence, a trial of bronchodilators is first line therapy for viral wheeze, and maintenance montelukast or inhaled steroids may be considered in preschool wheezers with persistent symptoms and risk factors for future asthma. No disease modifying therapies are available. New therapeutic options for preschool wheezing disorders are desperately needed.

Keywords

preschool wheeze; management; diagnosis; phenotypes

Introduction

The title of this review suggests asthma can be diagnosed in preschool children. This depends on the diagnostic criteria; if airway inflammation is a prerequisite (1) then it cannot, but if purely symptom based criteria are used (2), it can. The key question is what does the diagnostic label 'asthma' lead to? If asthma is considered a syndrome (3) and not a label leading to the inevitable prescription of inhaled steroids, then the use of the term in the preschool years may be appropriate. The European Respiratory Society have now set out guidelines for the definition, assessment and management of preschool wheezing disorders *(4). This group felt on balance that the term 'asthma' has become so inextricably entwined with airway inflammation that it is better not used in the preschool years.

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Unfortunately, the main findings state that the evidence on which to base any recommendations in this age-group is very limited. There are many reasons for this: objective end-points are scarce, and there are difficult ethical issues in researching very young children. We here consider recent evidence on the diagnosis and management of infants and preschool children with wheezing disorders, and ideas for future research.

Episodic wheeze and Multiple-trigger wheeze

The European Respiratory Society Task Force guidelines have proposed a new classification of preschool wheezing disorders according to the patient's temporal symptom pattern ^{*(4)}. This can be applied contemporaneously in the clinic and can be used to guide management. Episodic (viral) wheeze occurs at discrete time periods usually with symptoms of a viral cold, and with no wheeze between episodes. Multiple-trigger wheeze is characterised by wheezing present with and apart from acute viral episodes. It is important to distinguish this classification from that used in epidemiological studies which is based on duration of wheeze. Cohort studies have used the terms transient, persistent and late onset wheeze (5), each of these may be episodic or multiple-trigger in nature, but these epidemiological labels can only be assigned retrospectively once the child is 6 years old and the duration of wheeze is known. These preschool wheeze phenotypes are extremely useful epidemiologically, but useless clinically, and, for interventional studies the two clinical categories of episodic and multiple-trigger wheeze are preferable.

Episodic (viral) wheeze – interventions / management

Increasingly, episodic symptoms are being treated episodically. Treatment options include intermittent montelukast, high dose inhaled corticosteroids (6) and oral prednisolone. The role of oral steroids in episodic (viral) wheeze has been clarified. The lack of efficacy of a parent initiated course of prednisolone at symptom onset was reported in 2003 (7), and there is now evidence from a randomised, placebo-controlled trial of 699 children aged 1-5 years, that a short course of steroids given to infants and preschool children hospitalised for acute viral wheeze is also ineffective either in terms of time to discharge or impact on symptom duration or severity (8). This had previously been shown in a smaller trial that recruited only children that were hospitalised with rhinovirus or respiratory syncytial virus (RSV) induced wheezing. Prednisolone reduced symptom recurrence in the 2 months after admission in the rhinovirus subgroup; however, numbers are small (9). Interestingly, the rhinovirus infected children had more blood eosinophils and had a higher prevalence of atopy than RSV infected children. Subsequently a 1 year follow-up has shown that in the placebo group recurrent wheezing was present in more rhinovirus infected than RSV infected children ^{*(10)}. Furthermore, of the prednisolone treated group, less recurrent wheeze was seen in rhinovirus infected patients, but there was no change for the RSV infected patients (10). The authors suggest that although prednisolone appears ineffective in altering the course of the acute illness in viral wheeze, it may have an effect on symptom recurrence, specifically for rhinovirus induced wheeze. However, the initial trial was conducted to investigate the efficacy of prednisolone during the acute illness and the follow-up data was based on post-hoc analyses. The evidence showing the lack of efficacy of a short course of systemic steroids in episodic wheeze forces a re-think in our approach to the management of this

specific preschool wheeze phenotype. There is no data suggesting this phenotype is associated with eosinophilic inflammation or with increased atopic sensitisation, the two factors that might be associated with steroid responsiveness. A role for prednisolone in multiple-trigger wheeze with a severe viral exacerbation (11), or in a severe exacerbation of episodic wheeze which is likely to lead to the need for intensive care cannot be excluded. However, it is clear that prednisolone has been over-prescribed in the past to preschool children with episodic (viral) wheeze.

It may seem paradoxical that the inhaled route of administration of corticosteroids may succeed where the oral route failed. It is clear that continuous low dose inhaled corticosteroids do not prevent episodic wheeze. However, a Cochrane review suggested that intermittent high-dose inhaled corticosteroids at the time of acute viral wheezing may be beneficial (6). A subsequent study has investigated very high dose (1.5 mg/day) fluticasone at the time of viral wheeze (12) and shown benefit, albeit with concerns about safety (13). More work is needed on the optimal timing and dosage of intermittent inhaled corticosteroids for episodic wheeze.

RSV bronchiolitis

The role of montelukast in providing symptom relief in children hospitalised for RSV associated wheezing initially looked promising (14). However, subsequent data from a larger double-blind, placebo-controlled trial of 979 infants aged 3 to 24 months hospitalised for RSV bronchiolitis showed no benefit of continuous montelukast for 4 or 20 weeks over placebo *(15).

Multiple-trigger wheeze - newer therapeutic approaches to symptom control

The effect of a short course of parent-initiated montelukast at the onset of acute asthma symptoms, or at the onset of a viral upper respiratory tract infection in intermittent asthma has been assessed in a year long study in children age 2-14 years *(16).

Montelukast was continued for at least 7 days, or until 48 hours after symptoms had resolved. There was a significant reduction in the number of unscheduled health care resource utilisations and a reduction in symptoms by 14% in the montelukast group. This pragmatic approach of only administering a therapy during acute symptoms in preschool wheezers is very attractive, and has now been formally studied in a randomised placebo-controlled 1 year trial *(17). This compared the use of intermittent montelukast (4mg daily) or nebulised steroids (budesonide 1mg twice daily) to placebo in preschool children with moderate-to-severe intermittent wheeze. The therapy was initiated by parents at the onset of symptoms and continued for 7 days. 238 children aged 12-59 months were randomised and the primary end-point was episode free days. Unfortunately, there was no difference between the three groups in the number of episode free days, courses of prednisolone used, health care utilisation, quality of life or linear growth. There was some suggestion of benefit in those with a positive clinical asthma predictive index (18). Although this leaves us with no evidence for the intermittent use of either montelukast or high dose inhaled steroids in

children with intermittent wheeze, it is difficult to be sure whether the children recruited were episodic (viral) wheezers or had multiple-trigger wheeze. The inclusion criteria required at least 2 wheezing episodes in the context of a lower respiratory infection in the previous year, and previous urgent health care visits for wheezing or prednisolone prescription. Although it seems certain that subjects had relatively severe symptoms, the pattern of wheeze remains uncertain. Perhaps a clear distinction between episodic and multiple-trigger wheeze in such a trial would allow us to better understand the effects of these therapies. Also, it may be that the severity of wheeze was such that a 7 day course of treatment was insufficient, and the approach of Robertson et al of using a minimum duration of therapy until 48 hours after resolution of symptoms may have been more effective.

Therefore, in the category of multiple-trigger wheeze, all we are left with for acute symptomatic relief is the use of bronchodilators. However, there is evidence for the efficacy of maintenance, low dose inhaled steroids or montelukast in preschool children with multiple-trigger wheeze with clinical risk factors for the development of future asthma (19-21). What must be remembered in this context is there is no evidence to suggest the use of maintenance inhaled steroids in preschool children at high risk of developing asthma is disease modifying (22-24). What has not yet been investigated is the potential use of montelukast as a disease modifying agent in high risk preschool children.

Risk factors for asthma

Early sensitisation to perennial allergens is important in the development of future asthma (25;26). Recent data has also shown that high risk children in both the lowest and highest quintiles of exposure to dust mite in the first 5 years of life had a lower prevalence of both atopy and asthma compared to those with intermediate exposure levels, suggesting a biphasic effect of allergen exposure on the development of future asthma (27).

Importantly, it is now also apparent that the development of virus associated wheezing illnesses, specifically with rhinovirus, in early life also predict the development of asthma later ** (28). A high risk birth cohort study of 259 children followed to 6 years has shown a significantly increased risk of asthma at 6 years in those children that had wheezing associated with RSV, rhinovirus or both in first 3 years (28). However, the novel finding was that at age 3 years, rhinovirus associated wheezing illnesses were much more strongly associated with asthma at 6 years (odds ratio 25.6) than either aero-allergen sensitisation (odds ratio 3.4) or RSV associated wheezing. This suggests that early rhinovirus infection may play a key role in the development of asthma in children known to have risk factors for the disease, such as positive family history and early atopic sensitisation. Unfortunately, there are no data on lung function in this cohort so it is not possible to determine whether the viral illness is the initiating event that results in the early and sustained reduction in lung function seen in persistent wheezers and future asthmatics (5;29;30).

Phenotype specific therapy: a possible future approach?

Use of inflammatory and structural changes to define pathophysiological phenotype in high risk patients and targeting therapy to the individual preschool child may be the way forward in the treatment of preschool wheezing disorders. Using the known clinical risk factors for

future asthma (18), together with a strict classification of temporal symptom pattern (episodic or multiple-trigger), identification of appropriate symptom clusters (31;32) and assessments of pathology (33-35) and physiology, it may be possible to phenotype each preschool wheezer, and subsequently adopt an approach to therapy. The aim of the therapy needs also to be clear, be it acute symptom relief, long term symptom control or long term disease modification. The phenotype treated and therapy used may be determined by each of these factors in the future.

Symptoms and phenotype - preschool wheezing syndrome

Data published from 2 separate cohorts have shown that in children assessed at 3 and 5 years old, classification merely according to the presence or absence of wheeze is insufficient. Clusters of co-existing symptoms including wheeze and cough, and the relationship of symptoms to viral colds, atopy and family history need to be considered to accurately reflect underlying lung function and risk for future asthma (31;31;32).

Non-invasive assessments of phenotype - Lung function and exhaled nitric oxide

Techniques for the performance of lung function testing in children aged 2-5 years have recently been standardised (36), however, the paucity of appropriate reference values is still an issue (37).

Guidelines and standards for the assessment of exhaled nitric oxide levels in preschool children are available, and its usefulness in distinguishing preschool wheezers with a high and low clinical risk of developing asthma from preschool coughers has also been proposed (38). However, there is still no longitudinal evidence to show whether this tool can be used early, and prospectively, to distinguish persistent wheezers and likely future asthmatics from other wheeze phenotypes. If this were possible, then exhaled nitric oxide measurements could be used to guide phenotype specific therapy in preschool wheezers.

Early interventions for high risk preschool wheezers - Primary preventive strategies

It may be that the only way to alter the natural history of early onset asthma is to intervene before the onset of symptoms, either *in utero* or postnatally. In either situation, the intervention must be both easily applicable and safe. The two main approaches that have been investigated include maternal and/or fetal probiotic supplementation and vitamin D deficiency. It is important to differentiate the possible different impacts of the intervention specifically on wheeze, atopy and other allergic diseases; these are not necessarily the same thing.

Probiotics

The clinical data on probiotics is mainly on eczema rather than wheeze. Some trials have shown protection, whilst others have failed to show any effect (39). However, animal studies have shown a promising impact on allergic airways disease in the offspring of mothers given probiotics before conception, during pregnancy and lactation (40) (a primary preventive strategy) and when administered to mice with established allergic airways (41) (a

therapeutic strategy). The mechanism for the latter has been shown to be via non-antigen specific regulatory T cells (42). Important factors are the choice of probiotic (of which there are many, very differently formulated and therefore likely with different effects) the timing of administration and the risk level of the chosen population.

Maternal vitamin D levels

Associations between maternal vitamin D, E and zinc intakes during pregnancy and asthma in early childhood have been proposed. Some convincing data has now emerged of a possible link between maternal vitamin D intake during pregnancy and subsequent risk of wheeze. Maternal vitamin D intake was recorded from questionnaires at 32 weeks gestation from an unselected cohort of 2000 women recruited at 12 weeks gestation in Aberdeen. Subsequently wheezing symptoms, spirometry, bronchodilator response, atopic sensitization, and exhaled nitric oxide outcomes were assessed in children at 5 years old *(43). Comparing the highest and lowest quintiles for maternal vitamin D intake during pregnancy revealed lower risks for ever wheeze, wheeze in the previous year and persistent wheeze in children with mothers in the highest quintile. Very similar findings of the lowest quintile of maternal vitamin D intake during pregnancy resulting in more wheeze in children aged 3 years have been shown from a cohort in North America *(44). Vitamin D supplementation during pregnancy may therefore be a very real option towards achieving a primary preventive strategy for early onset wheeze. However, before this is formally undertaken, studies investigating the mechanism of action of vitamin D are needed, as any potential harmful effects of supplementation during pregnancy should be known.

Conclusion

Preschool wheezing disorders: The next challenge

The only therapies we have at present for preschool wheezing disorders include inhaled or oral steroids, cysteinyl leukotriene receptor antagonists or bronchodilators. However, the evidence points to poor efficacy of all of these both in episodic wheeze and when used intermittently for exacerbations of multiple-trigger wheeze. There is some evidence for their effect when used as maintenance therapies on symptom control and lung function in children at high risk of future asthma (20;22). Novel therapies are urgently required. Furthermore, since preschool persistent wheezers are born with normal lung function which is irreversibly and significantly reduced by school-age (5), and is likely associated with parallel changes in airway inflammation and remodelling (33;45), there is a desperate need to search for agents which when introduced early, to the correctly phenotyped preschool wheezer, will alter the natural history of the disease and minimise these pathophysiological abnormalities. Some promising data relating to primary preventive strategies, particularly with vitamin supplementation has recently emerged and needs to be explored further.

Acknowledgments

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