

# The problem of preschool wheeze: new developments, new questions

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Preschool wheeze is a common and often difficult to treat symptom. It may rarely be the first presentation of a severe underlying condition. Preschool wheeze is clearly a syndrome, not a single entity, and thus ripe for phenotyping. A number of approaches to phenotyping have been adopted. Epidemiology, based on the temporal patterns of symptoms, has taught us a lot about the medium and long-term implications of early life events, but is not useful for treatment planning. Atopic status is also not useful. Instead, symptom pattern (episodic (viral) and multiple trigger) should be used to decide on treatment. Reduced lung function at birth is associated with a number of maternal factors, including smoking (both by direct and epigenetic mechanisms), atopic status, and pregnancy complications; these children tend to have transient wheeze. Children whose symptoms persist into mid-childhood are born with normal lung function, but have evidence of airflow obstruction at 4–6 years of age. Early atopic sensitization is important in this group. Treatment of pre-school wheeze should be based on relief of present symptoms; there is no known therapy which prevents progression from episodic to multiple trigger symptoms and asthma. Episodic (viral) wheeze is a neutrophilic disease and should be treated with intermittent therapy. Options include inhaled anticholinergics or short-acting  $\beta$ -2 agonists, oral leukotriene receptor antagonists and short-course, high-dose inhaled corticosteroids. Prophylactic inhaled corticosteroids are not useful. Neither prophylactic nor inhaled corticosteroids are effective in preventing progression from an episodic viral to a multiple-trigger pattern. Multiple-trigger wheeze may merit a three-step trial (trial period, stop if apparent response, restart only if symptoms return) of prophylactic inhaled corticosteroids or leukotriene receptor antagonists. Recent data have shown that prednisolone should not be a routine treatment for acute exacerbations of episodic (viral) wheeze, but should only be used for really severe exacerbations, defined as being more severe than a routine admission and likely needing high dependency care. This is especially true in the setting of multiple trigger wheeze.

**Key words:** asthma, inhaled corticosteroid, leukotriene, neutrophil, prednisolone

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## INTRODUCTION

Paediatricians have been quick to point out to adult physicians that children are not small adults, but we have been very slow to understand that pre-schoolers are more than just small school-age children, and that pre-school wheeze has implications which are very different to school age asthma. These implications are in particular important for treatment and prognosis. The purpose of this review is to discuss the approach to pre-school wheeze, in particular in the light of new evidence in terms of excellent randomised controlled trials of treatment.

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## PRESCHOOL WHEEZE: THE CLINICAL APPROACH

The most obvious question, frequently neglected, is whether the noise being described by the family is truly wheeze (1–4), defined as polyphonic whistling noises in expiration, and sometimes also in inspiration. Parents are notoriously for using the word ‘wheeze’ to describe noises such as rattling and upper airway nasal noises (2). Even some nurses may be confused and use ‘wheeze’ inappropriately (2). The use of a video-questionnaire may be helpful (3, 4).

The second issue is to place the child into one of the five, and only five, groups of pre-school wheezers. This is done by a focused history and physical examination. This is covered in detail in a previous manuscript (5). The five groups of patients

are summarised in Table 1. The hardest diagnosis of all is 'normal child'. A large community based study documented that the median number of viral colds per year was five in childhood, but more than 10% of children have 10 or more colds per year (6, 7). A viral cold is usually a trivial illness, but although the mean duration of symptoms is around 8 days, the normal range extends beyond two weeks (7). Symptoms are nasal congestion, rhinorrhea, cough, sore throat, and fever. Thus a normal child may have symptoms of the common cold for nearly six months in the year. The frequency with which common symptoms such as noise from nasal congestion are misinterpreted as 'wheeze' may lead to an incorrect diagnosis of asthma. Not unexpectedly, early life attendance in child day care facilities increases the risks of viral colds (8). The frequency and duration of colds may come as a surprise to first time parents in particular, and misconceptions about the need for treatment are common (9). The investigation of a child with suspected severe illness is discussed elsewhere (5). In general, the younger the child, the more carefully an alternative diagnosis should be considered. Especially in young children, gastro-esophageal reflux is common. Reflux may be caused by respiratory disease, may itself be the primary cause of respiratory symptoms, or be a coincident fellow traveller. Furthermore, even if reflux does not cause wheeze, it may be misdiagnosed as 'asthma' because of the upper airway noises produced. A therapeutic trial of anti-reflux medications may be helpful and is a reasonable step before further investigation.

The rest of this manuscript deals with the problem of preschool wheeze, assuming that other diagnostic considerations have been eliminated.

Table 1. The five categories of pre-school coughing and wheezing syndromes

Category	Illustrative examples
Normal child	'Nursery school syndrome' Pertussis Post-bronchiolitic syndrome
Severe illness	Cystic fibrosis Bronchiectasis TB
An asthma syndrome	Episodic (viral) wheeze Multiple trigger wheeze
Co-morbidities mimicking or exacerbating an asthma syndrome	Rhinosinusitis Gastro-oesophageal reflux
Over-anxiety, overestimation of syndromes	Genuine anxiety (first child) Hidden gain (‘Can I have a letter for the housing, Dr?’)

Table 2. Wheezing phenotypes in the Tucson study

	Number (%)	Lung function shortly after birth	Wheeze age 3	Lung function age 6	Wheeze age 6
Normals	425 (51)	Normal	-	Normal	-
Transient wheeze	164 (20)	Obstructed	+	Some catch-up, still obstructed	-
Persistent wheeze	113 (14)	Normal	+	Obstructed	+
Late-onset wheeze	124 (15)	Normal	-	Normal	+

### Phenotyping pre-school wheeze – how do we tackle it?

**Why phenotype?** For clinical purposes, a phenotype may be considered as a cluster of either clinical or pathological features which tend to be associated, and which are useful in some way, such as in managing the child or understanding the mechanisms of disease (10). The emphasis has to be on utility, not just subdividing patients for the sake of it. Phenotypes may be divided into subjective (in which the clinician inspects the data and attempts to discern phenotypes) or objective (in which sophisticated mathematical techniques are used to determine phenotypes objectively). Both critically depend on accurate descriptions and the right information about the patients being gathered. Although objective mathematical techniques such as cluster analysis, or principal component analysis, are a great improvement on subjective techniques, no mathematical analysis can protect the investigator from the consequences of entering the wrong data.

**Epidemiological phenotypes.** The first attempts at phenotyping pre-school wheeze were epidemiological. The Tucson study (11) identified four phenotypes, the features of which are summarised in Table 2. Of note is that those who only wheezed in the first three years of life had abnormal lung function at birth, which focuses investigation on antenatal issues affecting lung health, whereas those who had persistent wheeze had normal lung at birth but developed airflow obstruction by age six, identifying the first six years of life as a crucial time frame for intervention. Similar findings were reported by the Manchester birth cohort study (12). However, it should be noted that for reasons that have not been resolved, the Perth cohort reported contradictory findings on smaller numbers of babies (13); they found that the group wheezing between one and three years of life ( $n = 17$ , transient wheeze, in the Tucson nomenclature; and note that Tucson followed up more than 100 transient wheezers into mid-childhood) had *normal* lung function at birth (using a tidal breathing, indirect measure of airway obstruction, or, in a subgroup,  $V_{max}FRC$ ), but  $FEF_{25-75}$  (which is probably the nearest equivalent in spirometry to  $V_{max}FRC$ ) was reduced at age 11. The persistent wheezers ( $n = 12$ ) had abnormal lung function shortly after birth, and it remained persistently lower than the never wheeze group. By contrast, and in this case similar to the Tucson findings, the group that only wheezed after age three had no impairment of lung function. Given the much bigger numbers in the Tucson study, most investigators favour the Tucson results as most likely to be accurate.

This approach has been studied in a more sophisticated way in the ALSPAC study. The Tucson phenotypes are

self-fulfilling, because the children were only studied at three time points in the first six years of life. The ALSPAC group has recently extended this work using sophisticated mathematical techniques (latent class analysis, LCA) to redefine phenotypes (14). LCA (15–17) is a statistical method developed in the social sciences, which is used to identify distinct subsets (classes) underlying the observed heterogeneity in a population. Such classes are not directly observable and must be determined from the actual data. The principle of latent class analysis is that the phenotypes are not forced on the data but derived from it by mathematical techniques. The ALSPAC group used data on more than 6,000 children analyzed from birth to seven years at seven time points (14). Their six phenotypes were never / infrequent wheeze, transient early wheeze, prolonged early wheeze, intermediate onset wheeze, late onset wheeze, and persistent wheeze. Wheeze of onset after 18 months was most strongly associated with atopy and bronchial responsiveness at age 7–9 years. Note that each of these epidemiological phenotypes may contain different symptom patterns and thus are not homogeneous (below).

Epidemiological phenotypes have taught us a lot about what happens to wheezing children in the medium and long term. They have been very useful in genetic studies; for example, ORMDL3 is particularly associated with early onset childhood asthma phenotypes defined epidemiologically (19, 20). However, epidemiological phenotypes, brilliant though they are for helping us to understand asthma, are clinically useless. We are not able prospectively to predict which children will go on to develop what we recognize as asthma in school-age children; in any case, we are powerless to intervene (below). A number of predictive indices have been described (20–22); they all have in common that their negative predictive value is good, but their positive predictive value is little better than flipping a coin. A different approach is needed to guide clinical management.

**Atopic wheeze?** Another proposed method of phenotyping is the presence or absence of atopy (23) manifested by either or both of atopic diseases such as dermatitis, or positive skin prick tests. This is theoretically dubious; many preschool children who go on to become atopic do not manifest before age three (24). Atopy may well not be a dichotomous ‘all-or-none’ phenomenon (25); atopy is a continuum, and more highly atopic children may be more at risk of atopic disease. Furthermore, just because a child has atopic dermatitis does not mean that it can be assumed that the same process is going on in the airway. A meta-analysis has shown that the presence or absence of atopy does not predict the response to inhaled corticosteroids (26). In older children with multiple trigger wheeze, airway histology is similarly independent of the presence or absence of atopy (27), confirming the findings in adult studies (28).

**Clinical phenotypes.** The European Respiratory Task Force on preschool wheeze has espoused a different approach to guide treatment (29). Wheeze was described on the basis of temporal patterns at the time of presentation. *Episodic (vi-*

*ral) wheeze* is defined as wheeze in discrete episodes, with the child being well in between episodes. This pattern is not unique to the preschool age group (30, 31) but appears to be most common in this age-group (32–34). Some young children who wheeze with viral infections also wheeze in response to other triggers such as exercise, allergen exposure and cold air (*multiple trigger wheeze*). It has sometimes been assumed that episodic (viral) wheeze and transient wheeze are terms describing the same condition, and also that multiple trigger wheeze and persistent wheeze are synonymous (transient and persistent as defined above by the Tucson study, but this is not the case. Episodic (viral) wheeze may persist into mid-childhood, whereas multiple trigger wheeze may abate before school age. These phenotypes may vary with time and treatment; for example, episodic (viral) wheeze may evolve into a multi-trigger phenotype, or treatment with inhaled corticosteroids may lead to multiple trigger wheeze reverting to an episodic (viral) pattern. The advantage of this classification is that (a) it can be determined at the time of presentation, and (b) it provides a practical framework for treatment (below). Furthermore, recent data have shown that multiple trigger wheezers have more severe airflow obstruction, more disturbance of gas mixing, and a higher exhaled nitric oxide than episodic (viral) wheezers (35), thus adding a physiological and inflammatory readout to the clinical phenotype.

#### Pathophysiology of pre-school wheeze – what is the relevance?

**Introduction.** Epidemiological evidence has shown that transient wheezers (who may have an episodic (viral) or multiple trigger phenotype, but are probably more likely to have the former) are born with airflow obstruction, whereas those with persistent wheeze (which again may be episodic (viral) or multiple trigger phenotype, more likely the latter) have normal lung function soon after birth, but lose lung function by age 4–6 years (11, 36, 37). Thus, attention focuses on the antenatal period for the transient wheezers and the immediate postnatal years for the persistent wheezers, the likely future asthmatics in mid-childhood.

**Adverse antenatal effects on airway development.** The single most important preventable factor ensuring normal airway development is maternal smoking. It has long been known that babies born to mothers who smoke have airway obstruction soon after birth (11, 36, 37). Studies in monkeys have shown that nicotine exposure (in this case, subcutaneous infusion but not placebo) lead to structural changes in the lungs, including increased Types 1 and 111 collagen (38). Another important mechanism relates to alveolar tethering. The attachment of alveoli by ‘tethering points’ to the airway is a mechanism of ensuring airway stability; as the child breathes in, this network of tether points ensures that the airway lumen is increased by interdependence. Autopsy studies have shown that the infants of mothers who smoke in pregnancy have an increased distance between alveolar attachment points, which could be the mechanism of the apparent altered

airway wall compliance (39) in some wheezy infants (40). It should be noted that neither of these structural changes are likely amenable to inhaled corticosteroid therapy.

There are important gene–environment interactions with respect to smoking. Smoke detoxification is in part by the family of glutathione S-transferases; in a large German study, the effects of maternal smoking on spirometry in mid-childhood were only seen in children with the null polymorphisms of the M and T alleles; similar findings were reported from California (41, 42).

Recent findings suggest a more extended role for maternal smoking. Epigenetics is the study of heritable changes in gene expression which occur without alteration in the DNA sequence, a way that the environment can alter gene expression (43). In the case of smoking, this may be modulated by changes in histone deacetylase (HDAC) activity (44). A recent three-generation study showed that grandmaternal smoking, in addition to increasing the risk of asthma in the next generation (the daughter), also increased risk in the second generation (grandchildren) even if the daughter did not smoke; the risk was even greater if both preceding generations smoked (45). Recently, epigenetic changes in DNA methylation were documented in children exposed to maternal cigarette smoke *in utero* (46). The hypothesis which awaits further confirmation is that smoking in pregnancy leads to heritable, epigenetic changes.

Smoking has effects on more than just lung structure. There are data showing that maternal smoking leads to lower cord blood IL-4 and IFN- $\gamma$  (47), and also increased cord mononuclear cell proliferation to house dust mite (48). Other cord blood studies showed that maternal smoking was associated with increased IL-13, and reduced IFN- $\gamma$  mRNA responses by stimulated cord blood cells (49). More recent work has also shown that maternal smoking has effects on fetal immune responses as well as airway anatomy. The Perth group (15) has investigated the effects of maternal smoking on fetal Toll-like receptors (TLRs) and their signalling. Smoking during pregnancy was associated with reduced TLR2 mediated IL-6, IL-10 and TNF- $\alpha$  production. TLR 3 and 4 mediated signalling of TNF- $\alpha$ , but not IL-6, IL-10 and IL-12 were reduced in the infants of mothers who smoked. In terms of TLR9 responses, there were attenuated IL-6 and increased IFN- $\gamma$  responses in the infants of smoking mothers. There is a substantial body of work linking these antenatal effects with the response to viral infections postnatally (50, 51). In summary, maternal smoking has profound effects on the immune responses of the newborn.

There are other antenatal effects which may be important. Maternal atopy has also been associated with impaired lung function in the newborn, although the precise mechanisms are not clear (9, 10). Maternal hypertension or pre-eclampsia are associated with an increased risk of transient early wheezing, persistent wheezing and late-onset wheezing. Use of antibiotics for urinary tract infections was associated with transient early wheezing, and antibiotic administration at de-

livery was associated with both transient early wheezing and persistent wheezing (52). Children who had a mother with diabetes were more likely to have persistent wheezing (52). Amniocentesis or chorionic villus sampling was associated with the subsequent development of wheezing (52). Birth order also affects cord blood immune function. Repeated pregnancies (or even miscarriages) lead to reduced cord mononuclear cell proliferative responses (the opposite effects compared with smoking). This could be a mechanism to account for the observations of the 'hygiene hypothesis' that atopy is less common if there are older siblings in the family (53). There is also increasing evidence that air pollution may act antenatally to compromise foetal development (54–56).

A new kid on the block is bacterial infection. The COP-SAC group showed that neonates with hypopharyngeal colonization with *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*, or with a combination of these organisms, had an increased risk of recurrent wheeze and asthma early in life (57). It was suggested that this may relate to a subtle defect of mucosal immunity (58), and this is plausible, but infection might equally be the primary initiating event. In this context, it is worth pointing out that the lower airway may not be as sterile as we were taught. We have recently used molecular microbiological techniques to demonstrate several thousand bacterial genomes, with differences between asthmatic and normal airways (59). The significance of these findings awaits further work.

If there is a link between antenatal events and postnatal lung function, one would predict that there would be genes common and important to both. *ADAM33* is important in branching morphogenesis of the fetal lung (60), but polymorphisms in this gene are also associated with lung function at three to five years of life (61). *ADAM33* polymorphisms are also important in accelerated decline in lung function with aging, thus acting as a link with COPD (62). Interestingly, recent work suggests that childhood factors are at least as important as smoking in the pathogenesis of COPD (63).

**Adverse postnatal effects on airway development.** The epidemiological evidence also confirms the significance of the early years. In the German MAS study (64), atopy did not affect the prevalence of wheezing in the first five years of life. However, babies who were sensitized to aeroallergens continued to wheeze in the next eight years of life, whereas wheeze prevalence declined in the non-sensitized. Furthermore, persistence of wheeze was associated with the loss of lung function and development of bronchial responsiveness. Immigration studies have also highlighted the importance of the early years. Women living in South India have a low prevalence of asthma, whereas second generation immigrants to Leicester, England have a much higher prevalence, the same as white, Leicester-born people. Women who moved to Leicester from South India after four years of age retained the low (South Indian) asthma prevalence, whereas women born in Leicester or who moved there in the first four years of life, had the high,

indigenous Leicester prevalence of asthma (65). (The study was performed only in women because the availability of antenatal records allowed movements to be tracked through time accurately). Thus, there are some unknown environmental triggers which are pivotal in determining asthma risk. If only we could determine what they are, because they offer the chance of halving the prevalence of asthma! The protective effects of early unpasteurised milk consumption against future atopic disease also highlights the importance of the early years (66).

*What have we learned from pathological data?* Pathological studies have been relevant in determining early structural changes, as well as giving a guide to treatment. Two cross-sectional studies have suggested that there is a window of around 18 months between symptom onset and the development of the airway wall changes consistent with asthma. In the first study, infants with a median age of 12 months were investigated for severe respiratory symptoms, using infant lung function, bronchodilator reversibility and rigid bronchoscopy. Despite the severity of symptoms, there was no evidence of airway inflammation or reticular basement membrane thickening, even in infants with documented atopy and bronchodilator reversibility (67). In a second cross-sectional study in infants (median age 30 months) referred with severe wheezing episodes, with wheeze being confirmed either by a physician or using a video-questionnaire, bronchoscopy and endobronchial biopsy were performed. This showed that in the confirmed wheezers, there was evidence of eosinophilic inflammation and reticular basement membrane thickening compared with a control group (babies with stridor and other upper airway issues) (68). Reticular basement membrane thickening was less marked than in previously studied children with severe asthma (69). It must be stressed that both studies were performed in very severely affected children in whom bronchoscopy could be justified on clinical grounds (70) and in whom the procedure frequently allowed other diagnoses to be made.

Other studies have confirmed that eosinophilic inflammation is not prominent in episodic (viral) wheeze. Bronchoalveolar lavage showed neutrophilic cytology in infant wheezers to the same degree of severity as infants with cystic fibrosis, unlike the eosinophilic lavage seen in asthmatics (71). A study employing blind bronchoalveolar lavage in children anaesthetised for routine paediatric surgery demonstrated that only those with atopic asthma and not those with episodic (viral) wheeze had an eosinophilic lavage, irrespective of the age of the child (72). Peripheral blood studies during a bout of episodic viral wheeze have shown evidence of neutrophil, but not eosinophilic activation (73, 74).

To summarise, epidemiological, physiological and pathological studies have demonstrated the crucial importance of the early years, but also that episodic (viral) wheeze is not an eosinophilic condition. This means that treatment strategies aimed at reducing airway eosinophils are unlikely to be helpful.

### Implications for treatment

Treatment for pre-school wheeze might be aimed at treating current symptoms or preventing the progression from episodic (viral) wheeze to a multiple trigger phenotype (a disease-modifying effect).

*Can we modify the course of the disease?* Three recent studies have addressed the question of whether inhaled corticosteroids are disease-modifying (75–77). In the first (PEAK study) (75), 285 children aged two or three years with a modified positive asthma predictive index (i. e., at high risk for developing asthma in childhood, based on a scoring system (22)) were randomly allotted treatment with fluticasone propionate (88 µg twice daily) or placebo for two years, followed by a one-year period of observation without study medication. The primary outcome was the proportion of episode-free days during the observation year. During the observation year, there were no differences in the proportion of episode-free days, the number of exacerbations, or lung function. During the treatment period, fluticasone treatment was associated with a greater proportion of episode-free days ( $P = 0.006$ ), a lower exacerbation rate ( $P < 0.001$ ) and less use of controller medication ( $P < 0.001$ ). In the fluticasone group, the mean increase in height was 1.1 cm less at 24 months ( $P < 0.001$ ), but by the end of the trial, the height increase was 0.7 cm less ( $P = 0.008$ ). Thus, during treatment, fluticasone reduced symptoms and exacerbations to a modest extent, but slowed growth, albeit temporarily and not progressively. The minor systemic effects at least confirmed that the children were being given a reasonable amount of the prescribed medication. The second study (76) was a randomised, double-blind, placebo-controlled study of the same dose of inhaled fluticasone propionate in young children who were followed prospectively and randomised after either one prolonged (>1 month) or two medically confirmed but briefer wheezy episodes. The dose of the study drug was reduced every 3 months to the minimum needed. If the symptoms were not under control by 3 months, open-label fluticasone propionate 100 µg twice daily was added to the treatment. Children were followed up to 5 years of age at which point their carers were given questionnaires, and the children's lung function and airway reactivity were measured. 173 (85 treatment, 88 placebo) of 200 randomised children completed the follow-up at age five years. There was no treatment effect at age five for the proportion of children with current wheeze, physician-diagnosed asthma or the use of asthma medication; lung function; or airway reactivity. There were no differences in the results after adjustment for open-label fluticasone propionate, nor between the two groups in the time before the open-label drug was added nor in the proportion needing the open-label drug. This confirms earlier work using nebulised budesonide (78, 79). In a study (COPSAC) testing an alternative strategy, namely the use of intermittent inhaled steroids, 411 one-month-old infants were randomly assigned to treatment with two-week courses of inhaled budesonide (400 µg per day,  $n = 294$ ) or placebo, initiated after a three-day epi-

sode of wheezing, in a randomized, double-blind, prospective study lasting three years (77). The primary outcome was the number of symptom-free days; key secondary outcomes were the time to discontinuation due to persistent wheezing and safety, as evaluated by height and bone mineral density at the end of the study. There was no effect of treatment on symptom-free days nor on the proportion of those who went on to persistent wheezing. This latter finding was unaffected by the presence or absence of atopic dermatitis. There were no safety issues. In summary, neither continuous nor intermittent inhaled steroids modified the course of asthma, even in infants who were in a high risk group for disease progression. Although there is some evidence in adults and older children that early use of inhaled corticosteroids *may* be beneficial in terms of long-term lung function (80, 81), this evidence does not exist in children, and, even in adults patients, physicians are moving away from dogmatically insisting on continuous and regular inhaled corticosteroids in mild asthmatics (82). It could be argued that higher doses might have been more beneficial, but in the PEAK study (75) there were systemic side-effects of fluticasone.

If inhaled corticosteroids are not disease-modifying, are there other possible approaches? The ETAC trial enrolled children with atopic dermatitis (as a group at high risk of developing wheeze) and randomised them to cetirizine or placebo for 18 months (83). There was no difference in wheeze prevalence for the group as a whole at the three-year follow-up. A planned subgroup analysis suggested that there was a benefit for those who at enrolment were sensitised to house dust mite, grass pollen or both (but therefore presumably detrimental to those who were not sensitised). However, a follow-up study using laevo-cetirizine failed to show any benefit (Warner JO, personal communication).

The only therapy that modifies the course of atopic disease is immunotherapy. A randomised controlled trial of grass pollen injection immunotherapy in adults established that it was (a) safe, (b) effective in preventing symptoms, and (c) after three to four years of treatment had modified the disease such that further immunotherapy was not needed (84). Injection immunotherapy in a small baby with severe wheeze is not an attractive option, but perhaps in the future, sublingual immunotherapy might prove to be beneficial. However, it is not yet ready for prime time (85), in part due to the poor standardisation of extracts, and should only be being performed as a disease-modifying therapy in the context of a randomised controlled trial.

***Symptomatic treatment of episodic (viral) wheeze.*** A normal child may be symptomatic from a viral cold for nearly six months in the year (above), and therefore safety is a factor when considering even intermittent therapy for pre-school wheeze, in particular high dose inhaled steroids (below).

The first question in episodic (viral) wheeze is whether treatment is indicated at all. If the infant is making noises, but is otherwise well, feeding and playing, perhaps no treatment at all is the right option, particularly since inhaled therapy

may not be easy to administer at this age. If symptoms mandate treatment, the first choice is either or both of inhaled intermittent short-acting  $\beta$ -2 agonist and anticholinergics, through a mask and spacer. Most children over the age of three years can and should dispense with the mask. There is no way I know of predicting which child will respond to which medication (if indeed they respond to any medication!) without performing an empirical trial.

The next treatment option for really severe symptoms is the intermittent use of oral leukotriene receptor antagonists. The use of montelukast as continuous therapy for pre-school wheeze has been well described. However, given that increased cysteinyl leukotriene release is only seen at the time of viral infections (86, 87), and also that mothers are probably reluctant to medicate well toddlers, the use of intermittent therapy would seem logical. The PREEMPT study randomised more than 200 children with episodic (viral wheeze) to either oral montelukast or placebo just at the time of viral colds (88). There was no difference in the number of episodes, but there was a one third reduction in the number of days missed by carers from work because their child was sick.

The next approach is to use intermittent, high dose inhaled corticosteroids. A Cochrane review suggested that this may be a beneficial approach (89), and a big proof of concept study has recently confirmed this. The intervention was a very high dose (1.5 mg/day) of fluticasone dipropionate, and this reduced the numbers of children prescribed oral corticosteroids (90). The treated group showed evidence of growth suppression, and there was no adequate assessment of adrenal function, so this regime cannot be recommended at the present time. However, it does suggest that studies to find the minimum dose required for benefit are indicated, with very careful attention to safety monitoring.

Intermittent oral montelukast was compared with intermittent nebulised budesonide in an excellent CARE network trial (91). Nebulised budesonide was used (an unusual choice to UK paediatricians) because this is the only inhalational form of steroid licensed in this age group in the USA. There were benefits in terms of amelioration of the severity of episodes in both groups compared to the use of  $\beta$ -2 agonist alone, with the most benefit being seen in those with a positive asthma-predictive index. On balance, I recommend intermittent montelukast prior to a trial of intermittent inhaled steroids because of a likely better safety profile. I have occasionally used both in combination, but there are no trials of this approach in the literature.

The use of prednisolone in acute episodes of viral wheeze has come under the microscope recently. Oral corticosteroids are the bedrock of the management of acute asthma in older children and adults, but the evidence in pre-school children is far less compelling. A large study stratified pre-school children with acute wheeze by levels of serum ECP and EPX (92). They were then randomised to have a parent-initiated course of treatment to be given at the onset of the next episode of (presumptively viral) wheeze, either placebo (n = 108) or

20 mg prednisolone ( $n = 109$ ) for five days. Only 120 (78%) of 153 children had a further episode of viral wheeze; 51 received prednisolone and 69 placebo. There was no clear benefit of treatment, irrespective of stratification by previous eosinophil activation.

It could be argued that these children were too mildly affected to see any benefit. The next study extended the findings to children brought up to hospital with an acute exacerbation of episodic (viral) wheeze (93). Hospitalised children (1–5 years) with clinical viral-triggered wheeze and no evidence of multi-trigger wheeze, who remained symptomatic after one nebulised dose of salbutamol, were recruited. Children were randomly assigned to receive either oral prednisolone for 5 days or placebo (20 mg 2–5 years and 10 mg 1–2 years). The joint primary outcomes were the time to “fit for discharge” from hospital and the time to “actual discharge”. Secondary outcomes included a validated respiratory symptom score and the time to the complete resolution of symptoms. 1180 children were assessed for eligibility and 699 were randomised. There was no difference between the placebo and oral steroid groups for the time “fit for discharge” (median 12 v 10 h,  $p = 0.17$ ) or duration to actual discharge (median 13 v 11 h,  $p = 0.22$ ). There were no differences between placebo and prednisolone for any secondary outcome variables.

In both these studies, together involving several hundred children, viral studies were not carried out, and the diagnosis of episodic (viral) wheeze was made clinically, as is almost invariably the case. In a much smaller study, oral prednisolone (2 mg/kg/day in three divided doses for 3 days) was compared with placebo in hospitalized wheezing children in whom a positive virological diagnosis was made. 661 patients were hospitalized, 293 randomized, and 58/661 (i. e. less than 10%) were finally analysed and contributed to the conclusions (94). The mean age was 2.6 (SD 1.3) years. The time to discharge was the same irrespective of treatment in all patients (prednisolone vs. placebo, median 18 vs. 24 h,  $p = 0.11$ ). However, prednisolone decreased the time until ready for discharge in children with picornavirus infection (respectively, 12 vs. 24 h,  $p = 0.0022$ ) and, more specifically, in children with enterovirus infection (6 vs. 35 h,  $p = 0.0007$ ). Prednisolone decreased the duration of cough and dyspnoea in rhinovirus-affected children ( $p = 0.033$  for both). These subgroup analyses were based on small numbers (rhinoviruses, 7 given prednisolone vs. 13 given placebo; enteroviruses, 9 given prednisolone vs. 12 placebo), and can at best be considered preliminary, underpowered and hypothesis-generating. Thus, it is possible that there may be effects of oral prednisolone with specific viruses, but this hypothesis needs further testing in a much larger population.

The role of prednisolone was summarized in an editorial (95). It is quite clear that this medication has been over-used in preschool children with episodic (viral) wheeze. If a child is deemed well enough not to need admission to hospital, then prednisolone should not be given. Unless the child is admitted to hospital, and is sufficiently unwell that transfer

to an intensive care or high dependency unit seems likely, then prednisolone should not be given in hospital, either. Although atopy did not make any difference to prednisolone response, there are those who would be more inclined to treat with prednisolone if the child was severely atopic. Practice needs to change.

**Symptomatic treatment of multiple trigger wheeze.** A trial of prophylactic medication (usually inhaled corticosteroids, sometimes daily montelukast) may be indicated in a pre-school child who is using inhaled short-acting  $\beta$ -2 agonist many days a week with benefit. There is no evidence to support the use of prophylactic inhaled corticosteroids in children with episodic (viral) wheeze. Although prophylactic inhaled corticosteroids reduce exacerbation rates in older children, this has never been shown in pre-school wheeze.

Since the natural history of many respiratory symptoms in childhood is for improvement, a three-stage protocol is recommended to ensure that children are not falsely given a label of asthma. My (non-evidence-based) practice is to commence inhaled budesonide in a relatively high dose (400 mcg twice daily via an age-appropriate spacer) for a period of two months. If symptoms have not improved at the end of that time, then the child does not have a steroid-sensitive asthma phenotype, and the treatment is stopped. The point about using this dose of budesonide is that a failed trial at this level means that going higher is not worth while. If, on the other hand, the child has improved, the treatment is also stopped, because at this stage one cannot be confident whether improvement was due to medication or spontaneous. Only if symptoms recur on stopping inhaled steroids and resolve on their reintroduction, would I continue treatment, titrating to the lowest dose needed to control symptoms. Furthermore, I would regularly repeat attempts to wean the dose.

## SUMMARY, THE FUTURE, AND CONCLUSIONS

The paediatrician managing the pre-school child with wheeze needs to remember that this is different from asthma in school-age children, and therefore there need to be some differences in approach. The pathology is completely different: school-age asthma is typically an eosinophilic disease, whereas pre-school children may have a degree of fixed air-flow obstruction and neutrophilic cytology. As at all ages, it is important to ensure that the family are describing true wheeze and not other, much less specific noises, and that a specific diagnosis is not being missed. The most useful way to phenotype pre-school wheeze is on the history as ‘episodic (viral)’ or ‘multiple trigger’, because this helps in planning treatment. There are no disease-modifying therapies, so symptoms should be treated on present merits. Episodic symptoms are treated with intermittent therapies, escalating through short acting inhaled  $\beta$ -2 agonists and anticholinergics, through intermittent leukotriene receptor antagonists,

to high-dose intermittent inhaled corticosteroids. Finally, prednisolone has been over-used for episodic (viral) wheeze and should be considered only in the most serious cases.

So what of the future? I suggest we need answers to the following questions:

1. How best can we predict which wheezing pre-school children will subsequently become asthmatic? Would grading atopy (above) be better? Or, are there other and better biomarkers? These would need to be good enough to be useful in individuals, not just groups.

2. How can we intervene in high risk individuals? Many with episodic viral wheeze will progress to multiple trigger wheeze. Clearly, inhaled corticosteroids are not the answer. Could macrolides, with their multiple immunomodulatory actions, be the answer (96–98)? I suspect we first need focused studies in animal models, and, in this context, a novel neonatal mouse model which relies solely on inhaled house dust mite challenge shows promise (99).

3. How can we reduce the population risk? Is allergen exclusion or high dose exposure the answer? Given the variable relationship between allergen levels and risk of sensitization (100), will the answer be allergen-specific?

4. Finally, how do we prevent or treat viral exacerbations of wheeze? This is an important area in which the therapeutic armamentarium is very bare. If we do decide to use inhaled corticosteroids as acute treatment, what is the minimum safe and effective dose?

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## IKIMOKYKLINIO AMŽIAUS VAIKŲ DUSULIO PROBLEMA: NAUJI KLAUSIMAI

### Santrauka

Ikimokyklinio amžiaus vaikų dusulys yra dažnas ir sunkiai gydomas simptomas. Retai jis gali būti pirmas sunkios ligos požymis. Ikimokyklinio amžiaus vaikų dusulys neabejotinai yra sindromas, o ne atskira liga, kurią galima fenotipuoti. Vyrauja keletas požiūrių dėl fenotipo nustatymo. Pasireiškiantys simptomai ar epidemiologija padeda spręsti apie vidutinės trukmės ir ilgalaikį veiksmų poveikį ankstyvojoje vaikystėje. Apsisprendimą dėl gydymo turėtų lemti epizodinis virusinis ar daugybinis simptomas. Nuo gimimo nepakankama plaučių funkcija yra susijusi su motinos rūkymu (tiesioginiai ir epigenetiniai mechanizmai), nėštumo komplikacijomis, atopine būkle. Tokiems vaikams dažniau pasireiškia tranzitorinis dusulys. Vaikai, kuriems simptomai atsiranda iki vaikystės vidurio, yra gimę su normalia plaučių funkcija, tačiau 4–6 gyvenimo metais jiems pasireiškia oro tėkmės obstrukcija. Šiems vaikams yra svarbi ankstyva atopinė sensitizacija. Ikimokyklinio amžiaus vaikų dusulio gydymas turi palengvinti esamus simptomus. Dar nežinoma, kaip užkirsti kelią epizodiniams simptomams progresuoti iki daugybinių ir astmos. Epizodinis (virusinis) dusulys yra neutrofilinė liga, kurią būtina gydyti nedelsiant. Galima rinktis inhaliacinius anticholinergikus ar trumpai veikiančius  $\beta$ -2 agonistus, oralinius leukotrenų receptorių antagonistus ir trumpą kursą didelėmis dozėmis inhaliuojamų kortikosteroidų. Profilaktiškai inhaliuoti kortikosteroidus nenaudinga. Nei profilaktiškai vartojami, nei inhaliuojami kortikosteroidai nėra efektyvūs užkertant kelią epizodiniams simptomams progresuoti iki daugybinių. Esant daugybinių simptomų dusuliui galima taikyti trijų etapų bandomąjį gydymą (bandomasis laikotarpis nutraukiamas, jei simptomai atsinaujina) profilaktiškai inhaliuojamais kortikosteroidais ar leukotrenų receptorių antagonistais. Pastaraisiais duomenimis, prednizolonu neturėtų būti gydomas epizodinis (virusinis) dusulio paūmėjimas, tačiau jį reikia skirti esant tikrai ryškiam paūmėjimui, t. y. sunkesniai nei įprasta. Tai ypač tinka kalbant apie daugybinių simptomų dusulį.

**Raktažodžiai:** astma, inhaliaciniai kortikosteroidai, leukotrenai, neutrofilai, prednizolonas