

## CLINICAL REVIEW

### Managing wheeze in preschool children

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

#### What is wheeze?

Wheeze is a term that is often used imprecisely, as has been shown in studies with a video questionnaire and direct quantification of wheeze.<sup>5-8</sup> Indeed, some European languages do not even have a word for wheeze. Our definition is high pitched whistling sounds usually in expiration and associated with increased work of breathing, but which can also sometimes be heard in inspiration. In research studies, wheeze can be quantified directly by using surface microphones, which is the

ideal. With this technique, it was shown that physicians auscultating the chest accurately identify wheeze<sup>8</sup>; parents and nurses were much less reliable.

#### How common is wheeze in preschool children?

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

#### What is the best clinical approach to the preschool wheezer?

Once it is established that the child has actual wheeze, history and a careful physical examination should be used to place the child in one of four categories (table 1). History and physical examination are used to categorise the child and to decide whether further investigation is needed. In general, there are three reasons for a referral: if diagnosis is in doubt, if treatment is not working, and if any party (general practitioner, parent) is unhappy with progress. A report of two cross sectional, community based observational studies found that isolated dry cough in a community setting, without wheeze or breathlessness,

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Video on bmj.com (see also <http://bmj.com/video>)



Paediatric respiratory nurses show how to administer inhalers to a young child

### Summary points

Preschool wheeze should be divided into "episodic viral" and "multiple trigger" according to the history, and these categories, which can change over time, should be used to guide treatment

No treatment has been shown to prevent progression of preschool wheeze to school age asthma, so treatment is driven solely by current symptoms

In all but the most severe cases, episodic symptoms should be treated with episodic treatment

If trials of prophylactic treatment are contemplated, they should be discontinued at the end of a strictly defined time period because many respiratory symptoms remit spontaneously in preschool children

Prednisolone is not indicated in preschool children with attacks of wheeze who are well enough to remain at home and in many such children, especially those with episodic viral wheeze, who are admitted to hospital

### Sources and selection criteria

We performed a PubMed search using the terms ("asthma" or "wheeze") and preschool, with the filters "clinical trial", "published in the last 5 years", "humans", "English" activated, with the subject age range "infant" (0-23 months) and "preschool" (2-5 years). Additionally, we separately searched the Cochrane database and Clinical Evidence, as well as our personal archives of references, extending beyond the previous five years, and also checked the reference lists in all manuscripts.

We selected only those manuscripts that either related to practical phenotyping of preschool wheezers or contributed to the evidence base for treatment. We eliminated all manuscripts that also included children of school age and above unless we could differentiate data from pre-schoolers aged 5 and under from data from older children because the pathophysiology of wheeze and the treatment algorithms are different in these two age spans. We also eliminated small trials and case series if the findings had been subsumed into a meta-analysis or Cochrane review.

is most unlikely to be caused by any form of asthma.<sup>9</sup> Most preschool wheezers do not require any additional tests.

Confusion arises from the different uses of the term "bronchiolitis." In the United Kingdom, this is an illness characterised by respiratory distress and showers of fine crackles in a child aged under 1 year; though wheeze can be present as well, it is the crackles that define the illness. It should be emphasised that any rigid definitions based on age are likely, to some extent, to be artificial. In the United States and elsewhere, "bronchiolitis" is used synonymously with wheezing illness. We have not discussed the approach to bronchiolitis as defined in the UK; interested readers are referred elsewhere.<sup>10-12</sup>

## Should preschool wheezers be subdivided (phenotyped)?

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

- Epidemiological: patterns such as transient early (wheeze only in the first three years of life) and persistent (wheeze throughout the first six years of life).<sup>9 13</sup> These studies have led to many insights into the evolution of symptoms and lung function, but the categories can be determined only retrospectively and give no guide to treatment, so are not useful for the clinician
- Atopic versus non-atopic: early aeroallergen sensitisation is certainly predictive of ongoing symptoms and loss of lung function at school age,<sup>14</sup> but does not predict the response to treatment with inhaled corticosteroids<sup>15</sup>
- Symptom pattern: the European Respiratory Society Task Force<sup>1</sup> suggested that preschool wheezers should be placed into one of two pragmatic categories. This is our favoured categorisation for planning treatment:
  - Episodic viral wheeze (EVW): the child wheezes only with usually clinically diagnosed viral upper respiratory infections and is otherwise totally symptom free
  - Multiple trigger wheeze (MTW): the child wheezes with clinically diagnosed upper respiratory infections but also with other triggers, such as exercise and smoke and allergen exposure.

This last classification is used to guide treatment (see below). It has been criticised because children might change between categories over time,<sup>2</sup> but in that event pharmacological treatment should also change. This is analogous to the situation in school age children with asthma; treatment is not left fixed over time but is increased or decreased depending on symptom pattern and severity. Unfortunately, few studies adopt this classification; most randomised controlled trials and genetic and epidemiological studies combine children with both symptom patterns.

## Is it asthma?

This question is commonly asked by parents who want to know whether their child will continue to have symptoms and require drug treatment into school age and beyond. The answer, however, depends on what definition of asthma is being used by the questioner. If a purely symptomatic definition is used (symptoms of wheeze and breathlessness fluctuating over time and with treatment), then the answer is affirmative. If, however, the definition includes evidence of airway eosinophilic inflammation, the answer is more difficult as few if any have the ability to measure this in preschool children. What most parents actually want to know is whether their child will go on with symptoms and the need for treatment into school age and beyond. The evidence from cross sectional physiological work and studies of endobronchial biopsies in children with severe preschool wheeze is that multiple trigger wheeze is associated with more airflow obstruction than episodic viral wheeze, and the airway pathology (eosinophilic inflammation and remodelling) is similar to childhood and adult asthma.<sup>16</sup> By contrast, episodic viral wheeze is not associated with evidence of eosinophilic inflammation, so the use of inhaled corticosteroids in this group is questionable.

## Does preschool wheeze lead to asthma?

Several clinical predictive indices for future risk of asthma have been developed based on combinations of the presence of atopic manifestations, indirect evidence of airway inflammation, such as peripheral blood eosinophil count, and severity of preschool wheeze.<sup>17-19</sup> They all have a high negative predictive value and a poor positive predictive value (typically positive predictive values 44-54, negative 81-88<sup>17-19</sup>). Children who have episodic

viral wheeze only have no increased risk of atopy or respiratory symptoms in the long term once they reach the age of 14.<sup>20</sup>

## Can we prevent preschool wheeze progressing to school age asthma?

The clear cut evidence from good randomised controlled trials is that early use of inhaled corticosteroids, whether continuously or intermittently with viral colds, does not affect progression of disease.<sup>21-23</sup> A trial of oral cetirizine in high risk children seemed to show benefit in preventing symptoms in subgroups sensitised to particular aeroallergens,<sup>24</sup> but a subsequent trial with L-cetirizine did not replicate these findings (J Warner, personal communication, 2013). This means that we have no disease modifying drug treatments, and treatment should solely be focused on current symptoms.

## What are the broad treatment strategies for children with preschool wheeze?

Before any drugs are prescribed for either episodic viral wheeze or multiple trigger wheeze, it is essential to ensure that the home environment is optimal, particularly that the child is not exposed to tobacco smoke; parental smoking “not in front of the children” does not protect them from harm.<sup>25</sup> A birth cohort study found that air pollution can increase vulnerability to preschool wheeze,<sup>26</sup> but to date we have no specific advice based on individual exposure profiles. Drugs might reasonably be targeted at prevention of future complications such as airway remodelling and persistent airflow obstruction, and, additionally, to treat present symptoms. In practice, we have no drug strategies to reduce future risk of asthma; neither early use of continuous<sup>21</sup> nor intermittent<sup>23</sup> inhaled corticosteroids reduces the risk of progression to school age asthma. If inhaled drugs are prescribed, repeated education of the parents in the correct use of spacers is essential. If inhaled drugs in particular do not seem to be working, check that they are being properly administered rather than escalate treatment. The use of a skilled respiratory nurse to help carers give inhaled drugs to children is invaluable.

## How to treat episodic viral wheeze?

Intermittent symptoms should be treated with intermittent therapy (and in practice this is likely to be what parents do anyway). Failure to instigate regular inhaled treatment will not prejudice future respiratory health. It is important to consider whether the child needs treatment at all. The use of inhaled therapy to treat mild respiratory noises with minimal respiratory distress might be more problematic than the disease. If treatment is required, then initial treatment should be with an intermittent bronchodilator (either short acting  $\beta_2$  agonist or anticholinergic). If treatment needs to be escalated beyond intermittent  $\beta_2$  agonist or anticholinergic because of failure to control symptoms, the next options are intermittent leucotriene receptor antagonist (montelukast), intermittent inhaled corticosteroids, or both. There have been important recent randomised controlled trials of intermittent therapy.

The PREEMPT study examined intermittent montelukast compared with placebo in 220 children aged 2-14.<sup>27</sup> Treatment was initiated at the onset of symptoms of a respiratory tract infection and continued for a minimum of a week or until symptoms had disappeared for 48 hours. The montelukast group had fewer unscheduled consultations for asthma (odds ratio 0.65, 95% confidence interval 0.47 to 0.89) and fewer days away from school or childcare and less time off work for parents

(37% and 33%, respectively;  $P < 0.001$  for both). In a predefined subgroup analysis, the benefits were greater in children aged 2-5 (about 80% of the study group). These findings were not confirmed in a much larger three way comparison of intermittent montelukast, continuous montelukast, and placebo (nearly 600 children in each group).<sup>28</sup> A three way comparison between standard treatment, intermittent montelukast, and intermittent nebulised budesonide (the only aerosolised steroid permitted by the FDA in preschool children) in 238 children aged 12-59 months showed minor and equivalent benefits for the two active treatments compared with standard treatment.<sup>29</sup> Benefits were greater in the subgroup with a modified asthma predictive index. Taken together, these studies suggest that a trial of montelukast in preschool children with troublesome viral induced wheeze is worth attempting. We recommend starting treatment at the first sign of a viral cold and discontinuing it when the child is clearly better, rather than for a fixed period of days.

The Cochrane review identified use of intermittent inhaled corticosteroids as a partially effective strategy for episodic wheeze in preschool children.<sup>30</sup> A proof of concept study in 129 children aged 1-6 years showed that the pre-emptive use of 750  $\mu\text{g}$  twice a day (compared with the maximum licensed dose of 200  $\mu\text{g}$  twice daily in children aged 4 and above; not licensed in any dose below age 4) of fluticasone dipropionate for up to 10 days, starting at the first sign of a viral upper respiratory tract infection, led to a reduction in dose of rescue prednisolone (8% of upper respiratory tract infections in the fluticasone group v 18% in the placebo group; odds ratio 0.49, 95% confidence interval 0.30 to 0.83).<sup>31</sup> This huge dose, however, was unsurprisingly associated with side effects and cannot be recommended. Another study looked at regular twice daily nebulised budesonide 0.5 mg compared with intermittent nebulised budesonide 1 mg twice a day at the time of viral respiratory illnesses. This was a randomised double blind controlled trial in 278 children aged between 12 and 53 months who had a positive modified asthma predictive index.<sup>32</sup> There was no difference in any respiratory outcome, but in the absence of a placebo group it is not possible to state that either strategy was beneficial. What this study definitely shows is that regular nebulised budesonide does not prevent viral exacerbations of wheeze. Smaller older trials of inhaled beclometasone also failed to show a preventive effect.<sup>33</sup> There is currently no evidence to support the use of inhaled corticosteroids at licensed doses in children with episodic viral wheeze. As some studies suggest that intermittent inhaled corticosteroids might be a useful approach in children with viral induced wheeze at higher than licensed doses, further studies are required to clarify the dose and duration that might be beneficial in this setting. In practice, however, it would be unwise to go above a fluticasone dose of 150  $\mu\text{g}$  twice a day, given the number and duration of viral colds in normal preschool children and the risk of side effects including growth suppression and adrenal failure with higher doses. There are currently no studies that have combined intermittent inhaled corticosteroids with intermittent montelukast to treat episodic viral wheeze.

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

There is no evidence to support the use of regular inhaled corticosteroids in preschool children who do not wheeze between viral colds. In those children with really severe episodic wheeze who require repeated admission to hospital or have prolonged disruptive symptoms managed at home, however, a trial of

prophylactic inhaled corticosteroids can be given. In some cases it might become apparent that in fact there were interval symptoms that were underappreciated. In any event, the clinical trials of inhaled corticosteroids in episodic viral wheeze were carried out in relatively mildly affected children, so the evidence in severely affected children is less robust. Treatment should be reviewed and discontinued if there is no benefit; there is no evidence to suggest the optimal duration of the therapeutic trial, but six to eight weeks would seem a reasonable time period. If the viral wheezing improves on treatment, regular attempts should still be made to reduce the dose. It should be noted that, in a small study, even really severe episodic viral wheeze was not associated with eosinophilic airway inflammation<sup>4</sup> and that inhaled corticosteroids (fluticasone 100 µg twice a day) led to growth suppression in the PEAK trial,<sup>21</sup> so trials of inhaled corticosteroids in this context should be deployed only exceptionally. If there is a suspicion that the child might in fact have symptoms between colds, which are underappreciated by the carers, a trial of inhaled steroids can reveal that the child was previously much more symptomatic than was thought.

Whatever the context of therapeutic trials in preschool children, they should be for a fixed time period (such as six to eight weeks, see above) and discontinued at the end of the agreed period to see if symptoms recur or in fact have resolved and treatment has become unnecessary (see the three stage trial proposal below).

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

Recent evidence has questioned the role of prednisolone in acute episodes of episodic viral preschool wheeze. In a home based study, 217 preschool children who had at least one admission to hospital were randomised to a parent initiated course of prednisolone or placebo at the next wheezing episode. No benefit was observed in the treatment group.<sup>34</sup> A hospital study that randomised 687 preschool children admitted with wheeze to prednisolone or placebo in addition to bronchodilator therapy found there was no benefit in the prednisolone group.<sup>35</sup>

The implication of these two studies, involving more than 900 children, is that any preschool child with viral induced wheeze who is well enough to stay in the community should not be prescribed oral prednisolone, and many children admitted to hospital also should not be prescribed oral prednisolone.<sup>36</sup> These studies, however, were undertaken in children with relatively mild symptoms and most were discharged from hospital in less than 24 hours, so what these studies do not tell us is whether prednisolone is indicated in really severe preschool viral wheeze. In the absence of evidence, it is likely that prednisolone will continue to be prescribed in this small subgroup of children in hospital.

### How should I treat multiple trigger wheeze?

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

inflammation<sup>37</sup> and therefore more reluctance to use inhaled corticosteroids.

There is a dearth of evidence, but the box shows a pragmatic three stage trial of treatment, which is recommended in our practice.

The aim of this three step approach is to prevent children being falsely labelled and inappropriately treated because someone has started a drug when the child was about to get better spontaneously. Long acting  $\beta_2$  agonists are not licensed for use in preschool children.

### Are there any other new treatments around?

In a small double blind trial, a total of 41 children aged 1-6 years were randomised to nebulised hypertonic (7%) or normal (0.9%) saline, in each case combined with salbutamol twice 20 minutes apart in the emergency department and then, if the child was admitted to hospital, four times a day thereafter.<sup>38</sup> Admission rates and lengths of stay were significantly reduced in the hypertonic saline group, but there was no significant change in severity score, possibly because of the small size of the study. Further work in larger numbers of children is needed to define the role of hypertonic saline in acute preschool wheeze. Given the possibility of bronchoconstriction being induced by hypertonic saline, this treatment should be given only in a hospital setting.

Palivizumab has been used to prevent infection with respiratory syncytial virus in high risk infants—for example, survivors of extreme prematurity. The cost and inconvenience of monthly injections means this has never been, and is still not, a treatment strategy for all babies. A recent double blind study, however, randomised 429 infants born at 33-35 weeks' gestation to palivizumab or placebo.<sup>39</sup> Palivizumab reduced the number of days with wheeze in the first year of life by 61% and the proportion of infants with recurrent wheeze from 21% to 10%. The more interesting question, which this trial could answer, is the vexed one as to whether early respiratory syncytial virus infection causes asthma or is merely a sign that the child was previously predisposed to asthma, provided the infants are followed up to school age. The current position is that this is work in progress, rather than an indication for a change in public policy.

### What about treatment plans?

Treatment plans outlining self management actions to be taken depending on the severity of symptoms and peak flow measurements are widely recommended in school age children. In a randomised controlled trial in which 200 children age 18 months to 5 years who had an unscheduled hospital visit or admission with wheezing were allocated either to standard care or to receive a package consisting of a booklet, a written guided self management plan, and two structured educational sessions, there were no differences in any outcomes.<sup>40</sup> Despite this, many will use educational sessions and plans, but there is no evidence of efficacy.

### What is the role of nebulised therapy?

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

### Pragmatic regimen for trial of treatment

- Step 1: Trial of inhaled corticosteroids or montelukast in standard dose for a defined period, usually four to eight weeks
- Step 2: Stop treatment; either there has been no improvement, in which case further escalation is not valuable, or symptoms have disappeared; in the latter case, it is not possible to know if this was spontaneous or as a result of treatment. If there is no benefit and the symptoms are troublesome, referral for consideration of further investigation is recommended
- Step 3: Restart treatment only if symptoms recur; then reduce treatment to the lowest level that controls symptoms

### Questions for future research and ongoing studies

- Is nebulised hypertonic saline an effective strategy to contemplate in children with acute preschool wheeze needing admission to hospital?
- What is the minimum effective dose of inhaled corticosteroids for intermittent use in preschool children with episodic viral wheeze?
- Would fine particle inhaled corticosteroids, which might be expected to deposit in the peripheral airways, offer additional benefit?
- Is intermittent high dose inhaled corticosteroid safe and beneficial in children with acute preschool wheeze who need admitting to hospital?
- How can we predict which children with preschool wheeze will go on to develop asthma, and how can we prevent this?
- Does prevention of respiratory syncytial virus infection with palivizumab lead to a reduction in prevalence of school age asthma?
- Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate-5-lipoxygenase (ALOX5) promoter genotype (<http://clinicaltrials.gov/show/NCT01142505>). This is a randomised controlled trial of intermittent therapy with montelukast started at the first sign of a viral cold or wheeze by parents. Both phenotypes of wheeze were recruited and analysis is due January 2014

### Tips for non-specialists

- Wheeze is a term used by lay people as a description of a multiplicity of upper and lower airway noises; be sure what exactly the family means by wheeze
- Isolated dry cough in a community setting is rarely if ever due to asthma
- Nebulisers should not be used in preschool wheeze; inhaled drugs delivered by metered dose inhaler and spacer are at least as efficacious
- If inhaled drugs in particular do not seem to be working, check that they are being properly administered (or better yet, get a respiratory nurse to do this) rather than escalating treatment
- Although several predictive indices for future asthma risk have been proposed, negative predictive value is excellent but positive predictive value is poor

### Additional educational resources

#### Resources for healthcare professionals

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

World Allergy Organisation—summary of different management recommendations, including GINA, available free at [www.worldallergy.org/professional/allergic\\_diseases\\_center/treatment\\_of\\_asthma\\_in\\_children/](http://www.worldallergy.org/professional/allergic_diseases_center/treatment_of_asthma_in_children/)

#### Resources for patients

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

NHS Choices—Asthma in Children (free): [www.nhs.uk/conditions/Asthma-in-children/Pages/Introduction.aspx](http://www.nhs.uk/conditions/Asthma-in-children/Pages/Introduction.aspx)

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## Table

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

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