A review of the use of inhaled corticosteroids in pre-school wheezing

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Ruth is currently a fifth-year student at Lancaster Medical School. This SSM report was presented at the end of her fourth year. The management of wheezy pre-school children is a challenge for both primary- and secondary-care health professionals, and the impact to the NHS of pre-school wheezing in the current financial climate cannot be underestimated. The main message is that the whole clinical picture of each individual case should be taken into account when managing these children and their families. An appreciation from both healthcare professionals and carers that pre-school wheezing is a clinical entity separate from asthma is crucial. It is difficult to accurately predict the future path that a child's wheezing will take, although Ruth does allude to some of the risk factors that make asthma more likely. There is a lot of work still to be done in terms of education and research, in order to optimise the care and management of these children to the highest and most effective standards.

INTRODUCTION

Wheezing in pre-school children is a condition commonly encountered by both general practitioners (GPs) and paediatricians. Often it can be managed at home, but some children require more intensive management and may require admission. The prevalence of the condition was highlighted on the first day of RA's clinical placement in early July 2012 when the ward round consisted of 12 patients, ten of whom were admitted with wheezing; the majority of these were pre-school age. It is known that many children 'grow-out' of these wheezing episodes and there is debate as to whether or not wheezy pre-school children should be given preventative medication, and if so whether the management should be similar to that of asthma in older children and adults where inhaled corticosteroids (ICS) are the first step. Due to the prevalence of the problem, as well as the potential side-effects of ICS in young children, it is important that this issue is addressed and the results interpreted. This review aims to assess the current literature base regarding the preventative use of ICS in pre-school children troubled by wheeze, and come to a conclusion on their advantages, disadvantages and when they should be instigated. Until recently there was very little evidence surrounding this issue and pre-school wheezing was treated in a similar manner to asthma in older children.

DEFINITION

Wheeze is a musical high-pitched expiratory sound resulting from intrathoracic airway narrowing or obstruction.^(1,2) Bronchial obstruction can have many causes, including mucus plugging, oedema and bronchoconstriction.⁽²⁾ The noise arises from the smaller bronchi of the bronchial tree; it occurs during expiration, as this is when the airways are most constricted and therefore are producing higher pressure.⁽³⁾ Parents often

incorrectly describe upper airway sounds as wheeze and, therefore, ideally the wheeze should be heard by a health professional before it is diagnosed.^(2,4,5)

Asthma is chronic reversible airway obstruction caused by bronchial spasm due to hyper-reactivity. It causes characteristic intermittent signs and symptoms including cough, wheeze and shortness of breath.⁽⁶⁾ These symptoms typically follow a diurnal pattern.

Pre-school wheeze can be divided into transient or persistent, but this classification is mainly used in epidemiological studies due to the retrospective nature of the diagnosis.⁽¹⁾ A more useful classification for general use is episodic viral wheeze (EVW) and multiple trigger wheeze (MTW). With EVW, the child wheezes intermittently (with a viral infection) but is symptom free in between exacerbations. In MTW, the child suffers from wheeze outside of distinct events. These classifications are not fixed as children may change from one group to another;⁽⁷⁾ a recent study showed that when diagnosed on a one-off parental history, a third of EVW resolved, a third remained as EVW and a third changed to MTW – just over half of those with MTW remained in that category, just under a third had changed to EVW and the remainder had ceased to wheeze.⁽⁸⁾ This highlights that it is important not to label a child straight away, but also suggests that parental reporting could be inaccurate and unreliable.

EPIDEMIOLOGY

It is reported that one in three under-threes wheeze, and this rises to one in two by six years.^(1,5,9,10) It has been suggested that this figure is increasing.⁽⁵⁾ By the age of six, two in three children

have stopped wheezing.⁽¹⁰⁾ It is important to remember that 80% of asthma has begun by the age of six,⁽¹¹⁾ before dismissing wheezing in pre-school children. It is difficult to predict in which young children with wheezing it will be transient and in which it will persist.⁽⁹⁾ It is, therefore, difficult to diagnose 'asthma' in young children due to the natural history of pre-school wheeze outlined above.⁽¹⁾ There are indicators: a more severe first attack and greater initial persistence indicates a higher risk of developing wheezing later in childhood.^(1,5,12) The presence of atopy (eczema and allergic rhinitis) can also indicate a propensity to develop atopic asthma.⁽¹³⁾ An attempt to assess likelihood can be carried out using the asthma predictive index, which lists major risk factors – parental history of asthma or personal history of atopic dermatitis – and minor risk factors – allergic rhinitis, eosinophilia (defined as eosinophils making up more than 4% of the white blood cell count) and MTW.⁽¹⁴⁾ To give high risk there must be at least one major or two minor risk factors.^(14,15)

TRIGGERS

The most common trigger for wheezing in all young children is viral infection;^(4,9,16) indeed as the name suggests, it is the only trigger in EVW. Other common triggers in MTW are similar to triggers for asthma exacerbations and include: exercise; emotions; pollutants; aero-allergens (although these are more important in older children); cold or damp air; and bacterial infection.^(1,3,4,5,7,10) Arguably, one of the most important avoidable factors is tobacco smoke exposure. There is evidence that smoke exposure in utero causes a reduction in the responsiveness of the young child's airways, making them more prone to wheezing as well as potentially decreasing their responsiveness to ICS.⁽¹⁶⁾ Avoidance of smoke exposure is very important for prevention of recurrent wheezing and parents should be advised that merely smoking outside does not negate the risk.^(1,2,5)

RISK FACTORS AND PATHOLOGY

A recent article suggests the following risk factors for wheeze: maternal atopy; maternal hypertension or pre-eclampsia during pregnancy; and a more clean childhood environment (the hygiene hypothesis).⁽⁷⁾ Increased maternal BMI early in pregnancy has been proposed as a risk factor for childhood asthma.⁽¹⁷⁾ It has been reported that rhinovirus-induced wheezing early in life can cause decreased lung function up to the age of eight years.⁽¹⁷⁾ Risk of wheeze and asthma is decreased by breast-feeding; it has been suggested that this protection lasts for up to eight years.^(16,18)

Generally, pre-school children presenting with wheezing do not need further investigation. The main investigation of peak-flow rate or spirometry in older children is clearly a very difficult exercise in pre-school children and therefore does not advance future decision making. Even in older children with high probability of asthma it is recommended to start treatment and assess response.^(6,18)

Wheeze is produced by narrowing of the airways. Young children are, therefore, at an increased risk of wheezing as their airways are smaller; a problem that is enhanced by the fact that 'airway resistance is inversely proportional to the fourth power of the airway radius' (Poiseuille's law), meaning that a small change in the radius leads to an significant change in airway resistance.⁽⁵⁾

It is unknown if there is shared pathology between atopic asthma, MTW and EVW.^(4,9) Histology or bronchial lavage in asthma demonstrates eosinophilic inflammation which can occur in MTW, but in EVW the leucocytes are more likely to be neutrophils.^(7,11) Exposure to smoke in utero or passive smoking also causes non-eosinophilic inflammation.⁽¹³⁾ The site of damage is thought to be the reticular basement membrane, which may be thickened.^(4,7,11)

MANAGEMENT

The aims of treatment are similar for asthma and pre-school wheeze: to prevent exacerbations; to decrease the need for salbutamol by lessening symptoms; and to allow the child to live as normal a life as possible.^(6,13) It is important to try and achieve this with minimal medications and, therefore, fewer side-effects.⁽⁹⁾

Step 1

- SABA as required (regularly during exacerbation)

Step 2

- Regular low dose ICS or LTRA

Step 3

- Add on LABA

Step 4

- Increase ICS

*Figure 1 Summary of stepwise asthma management.
(Adapted from ⁽³⁾ and ⁽¹⁸⁾)*

The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines advocate a stepwise management for asthma in children.⁽¹⁹⁾ They recognise that younger children require different management to older asthmatic children and, therefore, have issued separate guidelines for under fives. Figure 1 summarises these recommendations: the first step is the use of a short-acting β_2 agonist (SABA) such as salbutamol. However, if this is not controlling the symptoms and the patient is requiring frequent use of salbutamol the recommendation is to add an ICS, or if ICS cannot be used a, leukotriene-receptor antagonist (LTRA). If the symptoms persist the next step is the addition of a long-acting β_2 agonist (LABA); these are particularly beneficial in exercise-induced wheeze.⁽²⁾ However, the British National Formulary for Children (BNFC) only licences LABA for children above the age of five.⁽¹⁹⁾ If these measures do not control the wheeze, then they recommend referral to a respiratory paediatrician who can increase the ICS or try other measures. The most frequently forgotten part of management is stepping down,⁽⁹⁾ which should be done through regular review.⁽¹⁸⁾

There has been a review which highlighted the potential use for anti-histamines such as cetirizine and ketotifen.⁽⁴⁾

In terms of non-pharmacological therapy, parental education is important,^(1,2,5) as well as giving the parents an action plan.^(2,17) Although avoidance of triggers is generally advised where they are known, this is not always possible, particularly with EVW. It has been shown that although children may be allergic to dustmites, attempting to decrease levels of dustmites in the home is not effective at decreasing the symptoms of wheeze, and as these measures are burdensome on the family they are not recommended.⁽⁵⁾

Acute attacks are treated with regular salbutamol; if it is required more than four hourly, it is advised that the child be admitted to hospital for more intensive management. If the child requires oxygen (saturation of less than 92%), practice usually dictates that salbutamol is given by nebuliser. However, it has been suggested that spacers are actually more effective than nebulisers in pre-school children.⁽⁵⁾ Children less than one year old often do not respond well to salbutamol, but there have been suggestions that they are more likely to respond to ipratropium bromide.⁽²⁾ A fundamental element in the treatment of an acute attack in asthma is systemic steroids (either oral prednisolone or intravenous hydrocortisone). However, the role that oral prednisolone has to play in pre-school wheeze is debated and there is varied support;⁽⁴⁾ it has been suggested that they may prevent the need for hospitalisation in moderate or severe attacks and that they may allow an earlier discharge, more so in MTW than EVW.^(4,5) Prednisolone is agreed to be beneficial only when instigated by professionals and not by the parents.⁽⁵⁾ In acute EVW regular salbutamol may be all that is needed.⁽²⁾

Inhaled corticosteroids

ICS are the foundation of asthma management,^(9,20) and have been since their advent in the 1970s.⁽⁹⁾ As can be seen in the guidelines outlined above, ICS are still the second line of management and the first prophylactic treatment recommended in young children with wheeze. Their use in pre-school children who wheeze remains more controversial. This controversy has arisen due to the potential side-effects of ICS outlined later and questions over their efficacy given that the underlying pathology in pre-school wheezing may be different to that of asthma in older children and adults.⁽²¹⁾

ICS act to decrease inflammation within the airways, thereby increasing the airway diameter and decreasing symptoms. Their mechanism of action is via activation of intracellular cytoplasmic glucocorticoid receptors which leads to a reversal of inflammation. This is in contrast to other anti-inflammatory treatment options, such as LTRAs which block certain inflammatory pathways.^(4,22)

Until recently, there have been few studies looking at ICS in pre-school children, and pre-schoolers have been treated similarly to older children. Evidence about the use of ICS in EVW had been particularly scanty. Given the natural history of pre-school wheeze to resolve in a significant number of children, there have been questions raised about when preventative treatment should be started.

There has been more scrutiny recently about the use of ICS in pre-school children, with several important trials adding to the current evidence base: the PEAK trial; the PAC trial and the IFWIN trial.

The PEAK trial, which had two years of treatment with fluticasone propionate (FP) followed by an observation year in children with a positive predictive index for asthma, showed that ICS have no disease modifying effect so they should not be used in high-risk children with the hope of preventing the development of asthma. However, it did conclude that during the two treatment years, children receiving FP had fewer episodes of wheezing, more asymptomatic days and decreased use of supplementary SABA.⁽¹⁵⁾ These findings were supported by the IFWIN trial, which showed treatment with FP improves symptoms and leads to fewer unscheduled trips to the GP.⁽²³⁾ The IFWIN trial also showed there was no difference in lung function between those treated with FP and those with

placebo at five years.⁽²³⁾ A meta-analysis concluded that the number needed to treat with ICS to prevent a wheezing episode or asthma exacerbation is seven.⁽¹¹⁾

It has been shown that in EVW, treatment with low- or moderate-dose ICS does not impact the number or severity of episodes of wheezing. The PAC trial looked at whether intermittent high-dose ICS could prevent development of MTW or asthma, but as with the PEAK trial there was no impact on the natural history of the disease. The PAC trial concluded that intermittent high-dose ICS do not affect the symptom duration.⁽²⁴⁾

Other literature supports the conclusions of the above trials that the use of ICS does not prevent development of asthma.^(7,9,11,12) A recent Cochrane review into the use of ICS in EVW concluded that continuous use of low to intermittent ICS is not effective at preventing wheezing episodes, but, in contrast to the conclusions of the PAC trial, intermittent high-dose may be effective at reducing the severity of mild EVW.⁽¹⁰⁾ ICS appear to be more beneficial in the management of MTW,⁽⁷⁾ with the PEAK trial demonstrating that continuous treatment decreases the symptoms.⁽¹⁵⁾ A meta-analysis concluded that ICS were better than placebos at preventing recurrent wheeze and that ICS were useful in pre-school children with persistent wheeze, potentially leading to a 40% reduction in exacerbations.⁽¹¹⁾ When ICS are started, it has been recommended that if there is improvement in symptoms there should be a trial of stopping them after three months to see whether it is ICS that are reducing the symptoms or if the natural history of the wheeze was to improve.^(1,5,11)

However, as with all treatment there are side-effects which can occur as a result of systemic absorption of the corticosteroid, both via the lung and the gastrointestinal tract. The most common side-effect of ICS in pre-school children appears to be decreased linear growth as a result of suppression of the hypothalamic-pituitary axis.^(1,4,7,15) This suppression of growth was shown to be maximal during the first year of treatment during the PEAK trial, with comparable growth between the FP and placebo group during the second year of treatment. The FP treatment group grew faster than the placebo group in the observation year, but still had reduced linear height at the end of the trial.⁽¹⁵⁾ There is a dose-response: the higher the ICS, the greater the suppression of growth.⁽⁵⁾ It has been reported that the decrease in growth observed with ICS is comparable to the decrease in growth that occurs in untreated asthmatics, and that the child's final height will be equivalent to if they had not been treated.⁽⁹⁾ It is important to monitor a child's height.^(1,2,21)

There have been concerns that systemic absorption of steroids could lead to adrenal suppression. One study measured the cortisol urinary excretion rate and demonstrated that there is some evidence of suppression, but there appeared to be no effect on the child or symptoms attributable to the suppression during the trial period, leading to questions about the clinical effect and, therefore, its relevance.⁽²¹⁾ Other side-effects of ICS appear to be rarer in children than adults, but potentially include glaucoma, skin changes, oral candida and hoarseness.^(1,9,23) The decreased incidence of the latter two could be due to delivery via a spacer, leading to decreased deposition in the oral cavity.

One paper has extrapolated studies on rats to children, suggesting that the use of ICS in early life (up to five years) could adversely affect alveolar development.⁽⁴⁾ The IFWIN trial also questioned at the end whether there may be adverse effects on lung development in 'very young children'.⁽²³⁾

Parents are often averse to giving their children medication if it is not essential. Pre-school children are often not enthusiastic about taking inhalers as they invariably need to take them via a spacer, and when they are younger a facemask as recommended by the National Institute for Health and Clinical Excellence (NICE).⁽²⁵⁾ Spacers are needed as pre-school children are unable to coordinate their breathing. This is also true for some older children and adults. They also increase the amount of drug that is delivered to the lung.⁽²⁶⁾ There are a variety of different spacer devices that are available; each device has its own advantages and disadvantages.⁽²⁷⁾ There is evidence that large-volume spacers are more effective than smaller spacers, such as aerochambers, although the difference varies depending on the drug being given.^(28,29) However, there may be reduced concordance due to the bulkiness of the large-volume spacers and the benefits of increased delivery should be weighed against the likelihood of compliance. Non-concordance should always be kept in mind, particularly if the child's symptoms are not improving. The technique should also be checked: one actuation followed immediately by several normal breaths (count to ten) before another actuation is given.^(26,29) This should always be demonstrated, especially on introduction of any inhaled therapy. Local audits have shown that demonstration of how to administer an inhaler via a spacer device is often **not** carried out by health professionals.

CONCLUSION

Recent trials looking at wheezing, and at the use of ICS in pre-school children who wheeze, have added to our understanding of the different types of pre-school wheezing and potential management options. However, there are still many questions to be answered; this report has achieved its aims but highlights areas for future research. It is already known that ICS act to decrease inflammation in asthma and have a highly beneficial effect. Trials have shown that the use of longterm ICS does not impact on the number or severity of attacks of EVW. Short-term high dose ICS started at the beginning of an exacerbation may decrease the severity of the attacks. In MTW there is a place for prolonged treatment with ICS to decrease the number and severity of attacks as well as increase the number of symptom-free days. When deciding when to start ICS the impact the wheezing is having on the child and their activities and the potential side-effects of ICS must be carefully weighed. The most common of these side-effects is a decrease in linear growth, particularly initially. Inhalers should be given via a spacer; ideally a large-volume spacer; but if this is likely to adversely affect concordance concessions should be made. Non-pharmacological management, including parental smoking cessation and trigger avoidance, should not be forgotten.

Areas that still need further research include a study to give better understanding of when to start preventative treatment. More detailed guidelines on management of pre-school wheezing rather than asthma from the BTS/SIGN may enhance care. This could be made easier if there was a large-scale study to determine which pre-school children are most likely to continue to wheeze into later childhood and adulthood; this work could build on the asthma positive predictive index.

REFERENCES

1. Brand P, Baraldi E, Bisgaard H, *et al.* Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32:1096-110
2. Peckham C. Wheezy toddlers. *MBMJ* 2004;4(9):215-7
3. Newell S, Darling J. Lecture notes on paediatrics, 8th ed. Blackwell Scientific: 2008
4. Kaditis AG, Winnie G, Syrogiannopoulos GA. Anti-inflammatory pharmacotherapy for wheezing in preschool children. *Pediatr Pulmonol* 2007;42:407-20
5. Bhatt JM, Smyth AR. The management of pre-school wheeze. *Paediatr Respir Rev* 2011;12:70-7
6. Hogg A, Simon C. Asthma in children. *InnovAiT* 2011;4:160-70
7. Bush A. The problem of preschool wheeze: new developments, new questions. *Acta Medica Lituanica* 2012;17:40-50
8. Schultz ADS, Savenije OEM, Sly PD, Le Souef PN, Brand PLP. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatrica* 2009;99:56-60
9. van Aalderen W, Sprinkelman A. Inhaled corticosteroids in childhood asthma: the story continues. *Eur J Pediatr* 2011;170:709-18
10. McKean MC, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database of Systematic Reviews* 2000
11. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009;123:519-25
12. Lenny W. Asthma in children. *Medicine* 2012;40:238-41
13. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: origin, effect, and prevention. *J Allergy Clin Immunol* 2011;128:1165-74
14. Castro-Rodriguez J, Holberg C, Wright A, Martinez F. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6
15. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97
16. Szeffler SJ. Advances in pediatric asthma in 2010: Addressing the major issues. *J Allergy Clin Immunol* 2010;127:102-15
17. Szeffler SJ. Advances in pediatric asthma in 2011: Moving forward. *J Allergy Clin Immunol* 2011;129:60-8
18. BTS/SIGN. British guideline on the management of asthma: quick reference guide. 2011. Available at: <http://www.sign.ac.uk/pdf/qrg101.pdf> (accessed 3 July 2012)
19. BMA, RPSoGB, RCPCH, Neonatal and Paediatric Pharmacists Group. British National Formulary for Children 2012-2013. 8th ed. London: BMJ Group; 2012
20. Ukena D, Biberger C, Steijnmans V, *et al.* Ciclesonide is more effective than budesonide in the treatment of persistent asthma. *Pulm Pharmacol Ther* 2007;20:562-70
21. Carlsen KCL, Stick S, Kamin W, Cirule I, Hughes S, Wixon C. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. *Respir Med* 2005;99:1393-402
22. McKay G, Reid J, Walters M. Lecture notes on clinical pharmacology and therapeutics. 8th ed. Wiley-Blackwell: 2010
23. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. Secondary prevention of asthma by the use of inhaled fluticasone propionate in wheezy infants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006;368:754-62
24. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354:1998-2005
25. NICE. Guidance on the use of inhaler systems (devices) in children under the age of 5 with chronic asthma. 2000. Available at: <http://www.nice.org.uk/nicemedia/live/11400/32073/32073.pdf>
26. Borton C. Which device in asthma? Patient UK. Available at: 2010 <http://www.patient.co.uk/doctor/Which-Device-in-Asthma.htm> (accessed 17th July 2012)
27. Berg E, Madsen J, Bisgaard H. In vitro performance of three combinations of spacers and pressurized metered dose inhalers for treatment in children. *Eur Respir J* 1998;12:472-6
28. Barry PW, O'Callaghan C. Inhalational drug delivery from seven different spacer devices. *Thorax* 1996;51:835-40
29. O'Callaghan C, Barry P. Spacer devices in the treatment of asthma. *Br Med J* 1997;314