

EVOLVING CONCEPTS IN THE MANAGEMENT OF THE PRESCHOOL WHEEZER

Andrew Halkas, FCPaed(SA), MMed, FCCP
Johannesburg

Robin Green, PhD, FRCP

Department of Paediatrics, University of Pretoria, South Africa

ABSTRACT

Dividing preschool wheezing infants into episodic wheezers or multitrigger wheezers, or into groups used in longitudinal cohorts may only be clinically useful if temporal factors such as severity and frequency, and clinical parameters such as age of onset, pattern and severity, atopy and eczema are taken into account. There is little evidence to suggest that phenotypes described are related to pathobiological processes. The challenge is to identify phenotypes associated with a pathobiological process and longitudinal outcome and response to a specific therapy. In clinical practice therapy should be decided by identifying the preschool infant as an episodic viral wheezer or a multitrigger wheezer and by determining the association with the child's asthma predictive index (API), age of onset of wheeze and degree of atopic sensitisation. The wheezy preschool child with a positive API and evidence of multiple atopic sensitisation is more likely to respond to therapy.

There is strong epidemiological evidence that approximately two-thirds of all children who wheeze because of viral infections in early life (and are not atopic) have a temporary condition that tends to disappear during early school years. All respiratory viruses may be implicated in the wheezing episodes, the commonest being respiratory syncytial virus (RSV) and human rhinovirus, and with a lower frequency, adenovirus and parainfluenza virus. Infants and preschool children have on average 6-8 'colds' per year but the illness tends to be limited to the upper respiratory tract alone in a considerable proportion, without causing symptomatic involvement of the lower respiratory tract. The variety of factors determining the different outcomes are only partially known, but complex interactions between the intrinsic pathogenicity of the virus and host factors, including the socio-economic conditions of the family, are central to define the type of manifestations and the severity of the process. Not only the presence of atopy but multiple early IgE sensitisation is the strongest determinant of persistent wheeze, and this might be thought of as asthma.

Different longitudinal patterns of wheezing in the preschool child have been identified by a number of cohort studies. These studies have suggested that transient wheeze early in childhood is a result of viral infection in a child with small airways and is associated with decreased lung function at birth, maternal smoking during pregnancy, male gender, the presence of older siblings, attendance at day care and the absence of atopy.¹

From the ALSPAC cohort² it is apparent that wheezing after 18 months (not 3 years) is associated with the development of asthma and atopy. Wheezing in the first few months of life is only associated with asthma

(bronchial hyperresponsiveness and atopy) if wheeze persists to an age of 8-9 years.

The Manchester birth cohort³ has highlighted the fact that multiple early IgE sensitisation is strongly related to asthma in later childhood, more than the presence of atopy *per se*.

In the Tucson study¹ persistent and late-onset wheeze had the strongest association with atopy. This is different from the ALSPAC study² where intermediate-onset wheeze (wheeze most prevalent >18 months) was most strongly associated with atopy and airway responsiveness.

The clinical risk index (asthma predictive index (API)⁴) devised from the Tucson data suggests that a child with a positive index has a 50% chance of developing asthma; however, 80% of children with a negative index will never develop asthma. Predicting outcome of wheeze in individual patients to a useful degree of reliability in the clinical setting is challenging.

Episodic viral wheeze (EVW) is defined as wheeze in discrete episodes, with the child being well between episodes, and multiple trigger wheeze (MTW) is defined as wheezing that shows discrete exacerbations, but also symptoms in between episodes.⁵ This classification proposed by the European Respiratory Society (ERS) task team is perhaps an oversimplification as the classification does not allow for different severity and frequency, or age of onset, and it does not take atopic sensitisation into account.

Infants with MTW tend to be atopic and have positive markers of atopy as demonstrated by skin-prick testing or radioallergosorbent testing (RAST). These infants have elevated exhaled nitric oxide levels⁶ and abnormal lung function as measured by lung clearance index (LCI), spirometry and resistance measurements.⁷

Children with MTW have increased inflammation, airway remodelling is present and they resemble asthmatics pathologically. Preschool children with MTW have abnormal lung function while those with EVW do not, irrespective of atopic and current wheeze status.⁷

Episodic wheezers have normal lung function and nitric oxide levels, tend not to be atopic and have a negative API. Pathologically they resemble non-wheezy controls; they have no remodelling, no increase in inflammation⁸ and no elevation of exhaled nitric oxide.

AN APPROACH TO THE WHEEZY INFANT (Fig. 1)

The infant should be classified as having MTW or EVW, bearing in mind that there can be overlap between the two phenotypes.

A thorough history with emphasis on whether there is a history of parental asthma, eczema and the pattern of wheeze, i.e. is there wheeze at discrete periods associated with viral infection, and are there symptoms between episodes?

Determine the child's API and ascertain whether there are markers of atopy by doing a skin-prick test or ImmunoCAP. Note should be taken of the degree of sensitisation as it is a marker of persistent wheezing. Most settings will not have sophisticated equipment to measure nitric oxide, airway resistance or LCI; a modified

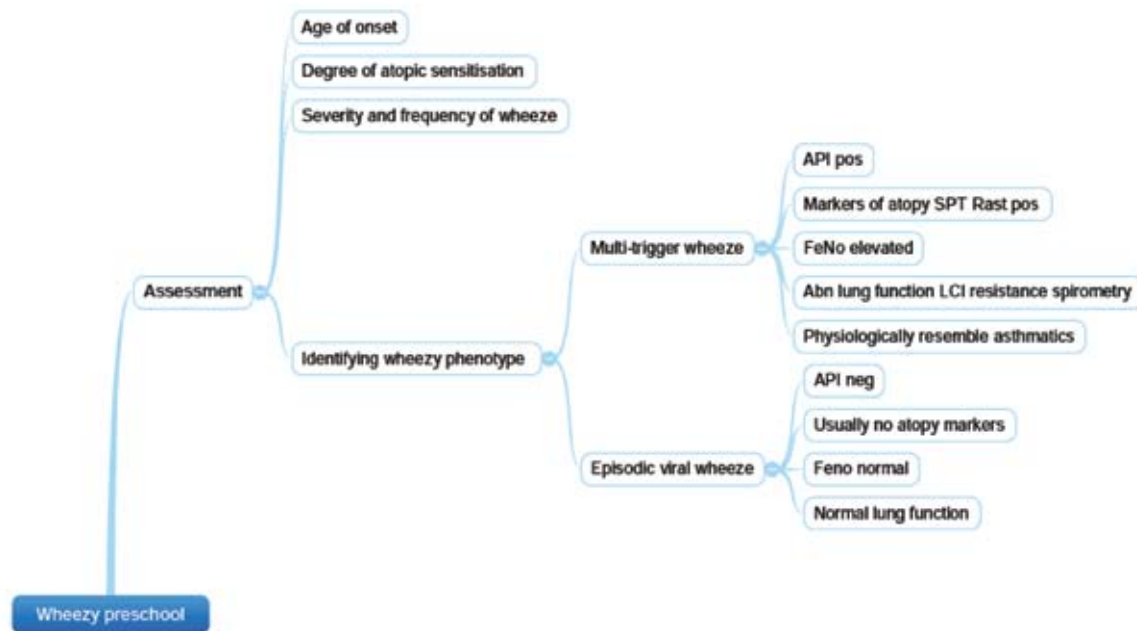


Fig. 1. Approach to the preschool wheezer (API – asthma predictive index, FeNO – inhaled nitric oxide).

bronchodilator test is of value in these settings to determine reversibility.

Treatment of the preschool wheezer

The treatment of the preschool wheezer presents many challenges. Oral steroids are often used but there is no clear evidence that they are effective in the preschool wheezer. Oral steroids have no effect on symptom scores, duration of hospitalisation and readmission in children with EVW.⁹ In children with a positive API, despite oral steroids having been extensively used in practice, there is no evidence to suggest that there is any benefit.

Figures 2 and 3 summarise management of MTW and EVW respectively

In preschool wheezers with a positive API there is evidence to suggest that inhaled corticosteroids decrease symptoms and exacerbations; however hospitalisations are not decreased.¹⁰ The efficacy of maintenance inhaled corticosteroids to improve symptoms and prevent exacerbations in patients of all ages with MTW is well established.

Pre-emptive use of high-dose inhaled corticosteroids in children with EVW will lead to a decrease in symptom-free days, and a reduction in the use of rescue oral steroids. However this management strategy cannot be recommended because of negative effects on growth.¹¹ Regular-dose inhaled corticosteroids have no effect on symptom-free days, exacerbations, health care visits or hospital admissions in EVW.¹²

Regular leukotriene receptor antagonist (LTRA) use in episodic viral wheezers has an effect on the exacerbation rate but has no effect on symptom-free days, health care visits, rescue steroid use and hospital admissions.¹³ Episodic use of LTRA has a favourable effect on symptom scores in both episodic viral wheezers and episodic viral wheezers with positive API.

Comparison of intermittent use of high-dose inhaled corticosteroid versus montelukast showed that both modalities of treatment reduce symptom scores; when compared to other outcomes there was no reduction in event-free days, health care utilisation, oral corticosteroid use or hospitalisation.¹⁴

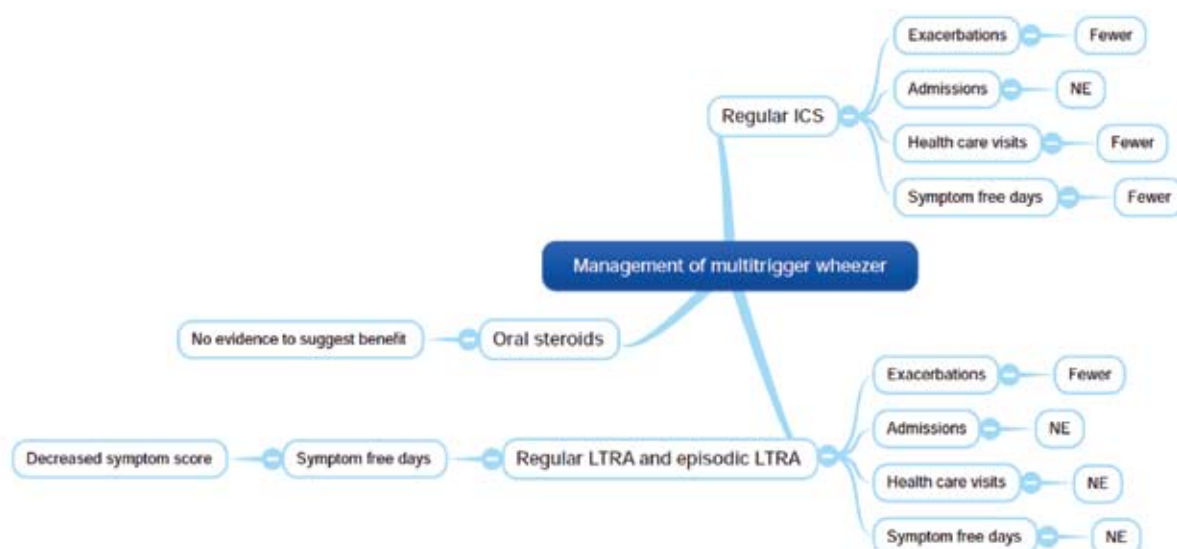


Fig. 2. Management of multitrigger wheeze (LTRA – leukotriene receptor antagonist, ICS – inhaled corticosteroid, NE – no effect).



Fig. 3. Management of episodic viral wheeze (LTRA – leukotriene receptor antagonist, ICS – inhaled corticosteroid).

CONCLUSION

Wheezy infants who have a positive API or are atopic are more likely to respond to treatment than episodic viral wheezers. Oral steroids are not effective in preschool wheezers and should be avoided. Current wheezy phenotypes need to be refined so as to reflect an association with the underlying pathobiological process and response to treatment.

Declaration of conflict of interest

Prof Robin Green has received honoraria from Abbott, Aspen/GSK, AstraZeneca, MSD, Pfizer and Sanofi Aventis.

REFERENCES

- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332: 133-138.
- Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; 63: 974-980.
- Simpson A, Tan VY, Winn J, Svensen M, Bishop CM, Heckerman DE, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010; 181(11): 1200-1206.
- Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; 162(4 Pt 1): 1403-1406.
- Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheez-

ing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; 32:1096-1110.

- Moeller A, Diefenbacher C, Lehmann A, Rochat M, Brooks-Wildhaber J, Hall GL, Wildhaber JH. Exhaled nitric oxide distinguishes between subgroups of preschool children with respiratory symptoms. *J Allergy Clin Immunol* 2008; 121(3): 705-709.
- Sonnappa S, Bastardo CM, Wade A, Saglani S, McKenzie SA, Bush A, Aurora P. Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol* 2010; 126(3): 519-526.
- MacLennan C, Hutchinson P, Holdsworth S, Bardin PG, Freezer NJ. Airway inflammation in asymptomatic children with episodic wheeze. *Pediatr Pulmonol* 2006; 41(6): 577-583.
- Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, Grigg J. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009; 360(4): 329-338.
- Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354(19): 1985-1997.
- Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009; 360: 339-353.
- Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995; 72: 317-320.
- Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171: 315-322.
- Bacharier LB, Phillips BR, Zeiger RS, Szeffler SJ, Martinez FD, Lemanske RF Jr, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127-1135.