ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803–5253

REGULAR ARTICLE

The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze

A Schultz (andre.schultz@health.wa.gov.au)[1,2,3], SG Devadason[1,4], OEM Savenije[5], PD Sly[6], PN Le Souëf[1,3], PLP Brand[7,8]

1.School of Paediatric and Child Health, University of Western Australia, Perth, WA, Australia
2.Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital for Children, Perth, WA, Australia
3.Department of Respiratory Medicine, Princess Margaret Hospital for Children, Perth, WA, Australia
4.Division of Clinical Research, Princess Margaret Hospital for Children, Perth, WA, Australia
5.Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
6.Telethon Institute for Child Health Research and Centre for Child Health Research, University of Western Australia, Perth, WA, Australia
7.Princess Amalia Children's Clinic, Isala Klinieken, Zwolle, the Netherlands
8.UMCG Postgraduate School of Medicine, University Medical Centre, Groningen, the Netherlands

Keywords
Classification, Episodic wheeze, Multiple trigger wheeze, Preschool wheeze, Viral wheeze

Correspondence
A Schultz, Princess Margaret Hospital for Children, GPO Box D184, Perth, WA 6840, Australia.
Tel: +61-8-9340-8222 |
Fax: +61-8-9340-8092 |
Email: andre.schultz@health.wa.gov.au

Received
14 May 2009; revised 27 July 2009; accepted 20 August 2009.

DOI:10.1111/j.1651-2227.2009.01508.x

Abstract

Background: A recently proposed method for classifying preschool wheeze is to describe it as either episodic (viral) wheeze or multiple trigger wheeze. In research studies, phenotype is generally determined by retrospective questionnaire.

Aim: To determine whether recently proposed phenotypes of preschool wheeze are stable over time.

Methods: In all, 132 two to six-year-old children with doctor diagnosed asthma on maintenance inhaled corticosteroids were classified as having episodic (viral) wheeze or multiple trigger wheeze at a screening visit and then followed up at three-monthly intervals for a year. At each follow-up visit, standardized questionnaires were used to determine whether the subjects wheezed only with, or also in the absence of colds. Stability of the phenotypes was assessed at the end of the study.

Results: Phenotype as determined by retrospective parental report at the start of the study was not predictive of phenotype during the study year. Phenotypic classification remained the same in 45.9% of children and altered in 54.1% of children.

Conclusion: When children with preschool wheeze are classified into episodic (viral) wheeze or multiple trigger wheeze based on retrospective questionnaire, the classification is likely to change significantly within a 1-year period.

INTRODUCTION

Preschool recurrent wheeze is very common, with a cumulative prevalence of up to 40% during the first 6 years of life (1). Different phenotypes of recurrent wheezing have been recognized in this age group and various labels have come into widespread use (2–6). The European Respiratory Society Task Force on Preschool Wheeze has recently published a report (7) recommending that preschool children with wheezing disorders should be classified as episodic (viral) wheeze (EVW) and multiple trigger wheeze (MTW). These phenotypic categorizations are believed by some to be important determinants of response to treatment (6,8,9): patients with EVW are thought not to respond to maintenance inhaled corticosteroids (6,8,10,11), while those with MTW do respond to maintenance inhaled corticosteroids (2,4,6,8,12–19). Conversely, EVW seems to respond favourably to montelukast (20–22) or episodic high dose inhaled steroids (15,23,24). Methodological issues related to diagnostic labels have led to problems in interpreting studies and pooling of data (8). In particular, many studies of children with preschool wheezing do not report the wheezing phenotype using any published category at all, but simply refer to their patients as suffering from 'wheezing' or 'asthma'. Classification of preschool wheeze into EVW or MTW, to study either group, is usually based on parental responses at a single visit to questions regarding wheeze in the previous year (1,10). Little is known about the stability of wheezing phenotypes in preschool children over time.

AIM

To determine whether preschool wheeze phenotypes classified as Episodic Viral Wheeze or Multiple Trigger Wheeze are stable over time in preschool children.

HYPOTHESIS

Wheezing phenotypes EVW and MTW are not stable over a one-year period in 2–6 year old children with doctor diagnosed asthma who are receiving inhaled steroid treatment.

METHODS

This study was performed using data derived from a randomized clinical trial of two small-volume spacers

conducted in preschool asthmatics. This analysis focused on the stability of characteristics of wheeze over time in these children, while they were on maintenance treatment with inhaled corticosteroids.

Study participants

Preschool children (2–6 year old) in whom asthma had been diagnosed by a doctor in the community, and who had been on inhaled steroids for treatment of their asthma, were eligible for inclusion in the study. In Australia, preschool children with wheeze are usually labelled with 'asthma', and treated with inhaled corticosteroids when symptoms are recurrent and appear to respond to bronchodilators. Exclusion criteria were: known or suspected immunodeficiency, other chronic lung diseases (such as bronchopulmonary dysplasia or cystic fibrosis), known allergy to study medication and having taken systemic steroids in the 3 months prior to enrolment. Ethics approval was obtained from Princess Margaret Hospital for Children's Ethics Committee. Parents or guardians provided written informed consent.

Protocol

Subjects were seen at a screening visit, at a baseline visit and then followed up for a year. At the screening visit, candidates were checked for eligibility, and background information was obtained by standardized questionnaire about symptoms of wheeze and cough, personal and family history of atopy and asthma, smoking in the house and during pregnancy. All children were treated with inhaled fluticasone.

Initial (retrospective) classification

At the screening visit, parents were asked whether their child had wheezed in the absence of colds in the past year and if they had only wheezed during colds. Based on the response to these questions, subjects were classified as having either *episodic viral wheeze* (*EVW*, wheezing only during colds and not in the absence of colds), *multiple trigger wheeze* (*MTW*, wheeze in the absence of colds, irrespective of the presence or absence of wheeze with colds).

The screening visit was followed by a month long run-in period where the subject had to prove a certain degree of asthma stability before the actual study commenced. For practical purposes, 'stable asthma' was defined as not requiring oral steroids for the past 3 months. If the subject's asthma was unstable, the run-in period was extended and the medication dose adjusted appropriately.

After the run-in period, the subjects were seen for a baseline visit and followed up at three-monthly intervals for a year. At each visit, inhalation technique was checked and corrected if necessary. At each visit, the inhaled asthma preventer medication was reduced if a subject did not have regular asthma symptoms or recent asthma exacerbations and the parents agreed to it. Regular asthma symptoms was defined as having daytime asthma symptoms more than twice a week or night time awakenings more than twice a month. At each visit, if the subject's asthma was not controlled, the study medication was increased, if appropriate

Re-classification

At each follow-up visit, information was collected on whether the subjects had wheezed in the month preceding each visit. This information was collected by the study doctor using a standardized questionnaire. If the subjects did wheeze in the month preceding the visit, the subjects' parents were asked whether the wheeze was present during colds, or also apart from colds.

The variation in wheezing phenotype classification in individual patients throughout the study period was determined. Children were labelled *stable no wheeze* if they had never wheezed throughout the entire follow-up of 1 year. They were labelled *stable viral wheeze* if they wheezed only in the presence of colds in the months prior to one or more follow-up visits and no wheeze at the other visits, *stable MTW* if they wheezed during, but also apart from colds in the month prior to one or more visits and no wheeze at the others.

To investigate the effect of season on wheeze symptoms, we then re-organized the first four study visits by season. Parental answers to the question 'Did your child wheeze with or without colds in the month before this visit?' were analysed based on season.

At the final visit, skin prick allergy testing was performed for rye grass pollen, house dust mite, cat dander and egg white. A positive skin prick test was seen as a wheal size greater than the positive control.

Statistical analysis was performed with SPSS version 15.0. Comparison of phenotypes was based in Chi square statistics. Binary logistic regression was used to investigate the effect of co-variates, e.g. atopy on the retrospectively determined phenotype (EVW and MTW). Multinomial logistic regression was used to investigate the effect of co-variates on the prospectively determined phenotype (EVW, MTW and No Wheeze).

RESULTS

One hundred and thirty two preschool children with physician diagnosed asthma entered the study. Over the 1-year follow-up period, 21 subjects (16%) dropped out of the study: six subjects were lost to follow-up, four moved away from the study centre, five cited time constraints, four lost interest, one cited parental illness and one cited not liking the spacer allocated for the study. Of the 111 patients who completed the study, one was excluded from analysis after being found to have been randomized on its seventh birthday and one was excluded from analysis after being unable to answer necessary study questions. Therefore, 109 (83%) subjects were included in the analyses of phenotype classification and stability reported here. Clinical characteristics of these patients are given in Table 1.

At the screening visit, 38 patients (34.9%) were classified as EVW, 71 (65.1%) as MTW. The retrospectively

Table 1 Subject characteristics

	Phenotype determined retrospectively at screening visit		Phenotype determined prospectively			
	EVW	MTW	EVW	MTW	No Wheeze	All subjects
N (% within sub-group)	38 (34.9)	71 (65.1)	34 (31.2)	51 (46.8)	24 (22.0)	109 (100)
Median age in months (range)	53 (29–81)	52 (24–83)	48 (24–82)	47 (25–83)	55 (27–79)	51 (24–83)
Male n (% within sub-group)	23 (60.5)	43 (60.6)	21 (61.8)	30 (58.8)	15 (62.5)	66 (60.6)
Eczema diagnosed by doctor n (%)	19 (50.0)	43 (60.6)	21 (61.8)	27 (52.9)	14 (58.3)	62 (56.9)
1st degree relative with atopy[†] n (%)	29 (76.3)	65 (91.5)	29 (85.3)	44 (86.3)	21 (87.5)	94 (86.2)
Hayfever previously diagnosed n (%)	4 (10.5)	10 (14.1)	5 (14.7)	6 (11.8)	3 (12.5)	14 (12.8)
Skin prick test positive	12 (31.6)	16 (22.5)	7 (20.6)	14 (27.5)	7 (29.2)	28 (25.7)
Parent report of smoker living in home n (%)	7 (18.4)	14 (19.7)	3 (8.8)	14 (27.5)	4 (16.7)	21 (19.3)
Mother reports smoking during pregnancy n(%)	7 (18.4)	6 (8.5)	1 (2.9)	7 (13.7)	5 (20.8)	13 (11.9)
Daily dose of ICS at baseline in microgram median (range)	200 (0–500)	200 (0–500)	200 (50–400)	200 (0–500)	150 (0–500)	200 (0–500)
[‡]Dose of ICS at final visit median (range)	100 (0–250)	100 (0–500)	100 (0–500)	200 (0–500)	100 (0–250)	100 (0–500)
On concurrent salmeterol at baseline n (%)	13 (34.2)	29 (40.8)	11 (32.4)	23 (45.1)	8 (33.3)	42 (38.5)
On concurrent salmeterol by end of study n (%)	9 (23.7)	31 (43.7)	9 (26.5)	22 (43.1)	9 (37.5)	40 (36.7))

[†]Atopy defined as a history of asthma, eczema or hay fever.
[‡]38 children had inhaled steroids discontinued during the study period.

Table 2 Retrospective phenotype determined at start of study compared with phenotype determined prospectively

		Retrospective phenotype determined at start of study		
		EVW	MTW	Total
Phenotype determined prospectively	No wheeze	13 (34.2%)	11 (15.5%)	24 (22.0%)
	EVW	12 (31.6%)	22 (31.0%)	34 (31.2%)
	MTW	13 (34.2%)	38 (53.5%)	51 (46.8%)
	Total	38 (100%)	71 (100%)	109 (100%)

EVW = Episodic viral wheeze; MTW = Multiple trigger wheeze.
Numbers in brackets indicate percentage of phenotype at the start of the study.

determined phenotype at screening was independent of gender, presence of eczema, hay fever, smokers living in the home or family history of atopy ($p > 0.05$).

The change in phenotype classification during the study, i.e. by comparing the classification based on parental report at the screening, and that determined prospectively during the study, is presented in Table 2. Phenotypic classification remained the same in 50 (45.9%) children and altered in 59 (54.1%) children. A similar number of children who changed from EVW to MTW, changed from EVW to no wheeze. (Table 2). Eleven (15.5%) of subjects who where classified as MTW at screening were classified as 'no wheeze' by the end of the study.

Overall, prospectively determined, there were 24 (22.0%) non-wheezers, 34 (31.2%) viral wheezers, 51 (46.8%) MTW patients. The prospectively determined phenotype was independent of gender, atopy, smokers in the home and maternal smoking during pregnancy (all p values >0.05).

The age range of subjects classified into different groups were very similar throughout the study (median age for all classification groups ranged between 47 months and 55 months). 'All subjects in the study had been prescribed inhaled corticosteroids for at least a month before the screening visit'. The median dose of fluticasone was 200 mcg per day at the beginning of the study, while the median dose of fluticasone for subjects classified as 'no wheeze', 'episodic viral wheeze' and 'multiple trigger wheeze' by the end of the study was respectively 100 mcg, 100 mcg and 200 mcg.

DISCUSSION

This study demonstrates that in a group of preschool children with recurrent wheezing being treated with inhaled steroids, wheezing phenotype (EVW, MTW) as determined by a single assessment at the beginning of a 12 month observation period was not predictive of wheezing patterns in the following year. Based on data obtained from standardized parental reports each 3 months, patients classified as EVW at screening were equally likely to be re-classified as No wheeze, EVW or MTW by the end of the study.

As our results are based on subjects recruited on the basis of 'doctor diagnosed asthma', we cannot comment on outcomes for children who had not been given this diagnosis. The children in this study, therefore, are representative of the overall population of children with more severe recurrent wheezing and presence of risk factors for persistence of wheezing that may be prescribed maintenance treatment with inhaled corticosteroids in primary care or in a hospital-based environment. Change in classification was independent of age.

Based on the retrospective data gathered by parental report at the screening visit, a third of the subjects were initially classified as EVW and two thirds as MTW. Only one third of subjects who where classified as having EVW at the screening visit were still found to have EVW by the end of the study. One third was classified prospectively as MTW and another third fell into the 'no wheeze' category when

classified prospectively. Therefore, subjects who initially had EVW were equally likely to remain having EVW, to develop MTW or to stop wheezing.

Multiple reasons for a change in phenotype have been described. First, episodic (viral) wheezers, especially if atopic, frequently evolve with the passage of time into a multi-trigger pattern, or, if non-atopic, lose their symptoms altogether. In our study, change in phenotype appeared to be independent of atopy.

It could be argued that the decrease of interval symptoms was the result of inhaled corticosteroid treatment (8,25,26). Steroids certainly would have had a role in influencing wheezing symptoms (27), but the effect of inhaled steroids on preschool wheeze appears to be the modest (7), and unlikely to cause a change in phenotype as marked as the change seen in this study. A recent meta-analysis (27) concluded that seven children with preschool wheeze need to be treated with inhaled corticosteroids to prevent a single wheeze exacerbation. When considering MTW, as noted in the ERS Task Force report (7), 'Compared to placebo, children using 200 mcg/day fluticasone exhibit a mean of 5% fewer days with symptoms' (19). Therefore, MTW would unlikely have been be completely changed to EVW by the use of inhaled corticosteroids.

During the prospective part of the study, parents were only asked about their children's wheeze in the month prior to each study visit. Symptoms during the two-month periods after each study could therefore have been missed, resulting in the misclassification of a number of subjects. However, the 34.2% of subjects who were classified at the start of the study as EVW, and reclassified as MTW during the study, all had symptoms in the absence of colds reported during the study, and therefore were unlikely to have been misclassified due to the monitoring process.

These data illustrate that in preschool children with recurrent wheeze, the wheezing phenotype, as determined by the pattern and the trigger of wheezing from retrospective parental report, cannot be used to predict the wheezing phenotype in the year to come. Although factors such as atopy, family history of atopy and gender were not helpful in predicting whether the phenotype would be stable or variable, this study was not designed to study predictors of wheeze patterns.

The unreliability of clinical classification of preschool wheeze into different phenotypes has implications for both clinical practice and for research purposes. From a research perspective, classification of children with preschool wheeze based on a single parental report of wheezing phenotype bears little relation to phenotype in the year to come, and this may seriously undermine the applicability of study data to clinical practice. Our data, therefore, suggest that taking a once-off history from parents of preschool children with recurrent wheeze may be insufficient to provide a reliable classification of wheezing phenotype as EVW or MTW. Clinical decisions on treatment options that rely on studies where the EVW/MTW classification system was used may therefore be compromised.

In conclusion, this study demonstrates that when children with preschool wheeze are classified into EVW or MTW based on retrospective questionnaire, the classification is likely to change significantly within a one-year period. Preschool children whose parents report that they only wheezed during colds in the past year stand a significant chance of wheezing in the following year. Conversely, preschool children whose parents report that they wheezed in the absence of colds in the past year stand a significant chance of only wheezing during colds in the following year. Therefore, a system of classifying preschool wheeze into EVW or MTW based on parental questionnaires may not be accurate for researching these phenotypes prospectively.

CONFLICT OF INTEREST

The fluticasone used in this study was sponsored by GlaxoSmithKline.

Half of the small-volume spacer devices used to administer fluticasone to the study subjects were sponsored by Visiomed, Australia.

In 2003, Glaxo paid for André Schultz's flight ticket and registration fees to attend a national scientific conference.

Paul Brand has received funding for research and for consulting activities from Glaxo Smith Kline in 2006, 2007 and 2008.

ACKNOWLEDGEMENTS

André Schultz received a salary as a research fellow from the Telethon Institute for Child Health Research, Perth, Australia for one year of the study.

References

1. 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: 133–8.
2. Kuehni CE, Strippoli MP, Low N, Brooke AM, Silverman M. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy* 2007; 37: 1738–46.
3. De Baets F, Van Daele S, Franckx H, Vinaimont F. Inhaled steroids compared with disodium cromoglycate in preschool children with episodic viral wheeze. *Pediatr Pulmonol* 1998; 25: 361–6.
4. Chauliac ES, Silverman M, Zwahlen M, Strippoli MP, Brooke AM, Kuehni AC. The therapy of pre-school wheeze: appropriate and fair? *Pediatr Pulmonol* 2006; 41: 829–38.
5. Silverman M, Wang M, Hunter G, Taub N. Episodic viral wheeze in preschool children: effect of topical nasal corticosteroid prophylaxis. *Thorax* 2003; 58: 431–4.
6. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev* 2000; 2: CD001107.
7. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; 32: 1096–110.

8. Kaditis AG, Winnie G, Syrogiannopoulos GA. Anti-inflammatory pharmacotherapy for wheezing in preschool children. *Pediatr Pulmonol* 2007; 42: 407–20.
9. Saglani S, Payne DN, Zhu J, Wang Z, Nicholson AG, Bush A, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007; 176: 858–64.
10. Doull IJ, Lampe FC, Smith S, Schreiber J, Freezer NJ, Holgate ST. Effect of inhaled corticosteroids on episodes of wheezing associated with viral infection in school age children: randomised double blind placebo controlled trial. *BMJ* 1997; 315: 858–62.
11. 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: 317–20.
12. Doull IJ. Limitations of maintenance therapy for viral respiratory infection-induced asthma. *J Pediatr* 2003; 142 Suppl 2: S21–4; discussion S4-5.
13. Bisgaard H, Gillies J, Groenewald M, Maden C. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med* 1999; 160: 126–31.
14. Bisgaard H, Munck SL, Nielsen JP, Petersen W, Ohlsson SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet* 1990; 336: 649–51.
15. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child* 1993; 68: 85–7.
16. Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999; 103: 414–21.
17. Kemp JP, Skoner DP, Szefler SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999; 83: 231–9.
18. Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol* 1998; 102: 789–96.
19. de Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol* 1996; 98: 14–20.
20. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007; 62: 758–66.
21. 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: 315–22.
22. Fitzgerald DA, Mellis CM. Leukotriene receptor antagonists in virus-induced wheezing: evidence to date. *Treat Respir Med* 2006; 5: 407–17.
23. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990; 65: 407–10.
24. Svedmyr J, Nyberg E, Thunqvist P, Asbrink-Nilsson E, Hedlin G. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr* 1999; 88: 42–7.
25. Gold DR, Fuhlbrigge AL. Inhaled corticosteroids for young children with wheezing. *N Engl J Med* 2006; 354: 2058–60.
26. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354: 1985–97.
27. 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: e519–25.