Curr Pediatr Res 2013; 17 (2): 71-77 ISSN 0971-9032
http://www.pediatricresearch.info

Evaluation of asthma risk index application in treating early childhood asthma.

Marita Paassilta[1]*, Hanna Kerminen[2], Matti Korppi[2,3]

[1]Allergy Centre, Tampere University Hospital, Tampere, Finland
[2] Pediatric Research Centre, Tampere University and Tampere University Hospitalm Finland
[3]Department of Pediatrics, Tampere University Hospital, Tampere, Finland

Abstract

Finnish current care guidelines recommend that the treatment of asthma in young children should be based on the number of wheezing episodes and on the assessment of asthma risk profile consisting of two major and three minor criteria, constructed on the basis of the international asthma predictive index. The aim of the present study was to assess whether the current guidelines and risk profile determination are applied in the treatment of asthma in children aged less than three years. In all, 179 children aged 1-35 months were admitted for wheezing during four winter-months from 1st Nov, 2006 to 28th Feb. 2007. The data on treatment decisions, and major and minor asthma risk factors were retrospectively collected from patient records. Recorded data sufficient for the retrospective determination of the asthma risk profile were found for 112/179(63 %) children. Data on minor criteria were missing in almost all cases. Most of the children with data not available were first-time wheezers. Twenty-one children (19%) were on maintenance medication at admission. The decision whether or not to start maintenance medication was in line with the current care guidelines in 76/91(84 %) children. In conclusion, the treatment of asthma in young children mostly took place according to the national current care guidelines, though the application of the asthma risk profile was insufficient. The minor criteria of the asthma risk profile are not sufficiently sensible for clinical practice, and therefore need to be up-to-dated.

Keywords: Asthma, risk index, child, infant, wheezing

Accepted April 17 2013

Introduction

Early childhood wheezing is a heterogeneous condition. Current knowledge about the wheezing phenotypes and outcomes mainly comes from the Tucson birth cohort, now followed until 22 years of age [1-4]. Some other birth cohort studies have generated important additional information, such as the Isle of Wight Study (IoWS) [5] from the UK, the Multicenter Allergy Study (MAS) [6] from Germany, and the Prevention and Incidence of Asthma and Mite Allergy study (PIAMA) [7] from the Netherlands. In short: about 60% of early wheezers suffer from transient wheezing, which ceases before the age of three years; about 20% suffer from non-atopic persistent wheezing, which continues beyond the age of 3-6 years; and about 20% suffer from atopic persistent wheezing, which at school age continues as chronic asthma.

The Tucson study group has constructed an asthma predictive index (API) [8], which consists of 2 major and 3 minor risk factors for chronic school age asthma, and is

relevant in young wheezing children treated in primary health care. The major risk factors are asthma in parents and atopic dermatitis in the child. The minor risk factors are wheezing apart from respiratory infection, blood eosinophilia and allergic rhinitis. When a more precise algorithm was needed for an intervention study, the API was modified (mAPI) [9] by deleting wheezing apart from respiratory infection, and by adding sensitization to inhaled allergens as a major and sensitization to food allergens as a minor risk factor. Though the API was originally aimed for identifying subgroups of preschool wheezers who are at greatest risk for asthma, the index has been later recommended for decision making when to start maintenance therapy for young wheezing children [10, 11].

In Finland, the evidence-based current care guidelines for asthma treatment were up-dated in 2006, and according to these guidelines [12], the decision to start maintenance medication for asthma in young children should be based on the assessment of an individual asthma risk profile, constructed on the basis of the mAPI [9].

The aim of the present study was to evaluate, by collecting data retrospectively from hospital records, the modes of asthma treatment in 1-35-month-old wheezing children in the emergency room and emergency ward of a children`s hospital. A special attention was paid on whether or not the decision about the start of inhaled corticosteroids was based on the asthma risk profile determination.

Materials and Methods

In all, 179 children aged 1 to 36 months were treated as either outpatients in the emergency room (ER) or inpatients in the emergency ward (EW) in the Department of Pediatrics, Tampere University Hospital (Finland), from 1st Nov, 2006 to 28th Feb, 2007. Tampere University Hospital is the only hospital providing inpatient care for a population of about 90 000 children aged <16 years. The number of <36 months old children was 16 480 in the area during the study. The patients were screened from the electronic files of the hospital by using the ICD-10 codes J21* (obstructive bronchitis), J45* (asthma) and R06* (obstructive breathing). One of the authors (HK) charted the hospital records, and only children with wheezing confirmed by a doctor on duty in the ER or EW were included. Data were collected retrospectively from hospital records, including the records of pediatric ER, pediatric outpatient clinic, pediatric EW and all other pediatric wards treating acute patients; the markings made by the nurses were also checked.

The collected data consisting of the risk factors for asthma were registered in line with the Finnish current care guidelines (the up-dated 2006 version) including asthma in parents, and atopic dermatitis, food allergy, seasonal (allergic) rhinitis, wheezing apart from infection and blood eosinophilia (>4%) in the child (Table 1).

In addition, the use of inhaled corticosteroids (ICS) and the numbers of wheezing episodes in children treated as outpatients or inpatients during the preceding 12 months before the study period were charted. Data on parental smoking, maternal smoking during pregnancy separately, were collected if available.

The patients were not contacted, and all analyses were based on existing data extracted from the patient records. According to regional Ethics Review Committee's instructions, the chief physician of the University Hospital gave the permission to the study.

Results

Eighty % of the patients were <24 months old, and 62% were boys (Table 2). Thirteen % of the patients used ICSs, and a third of those not on ICSs had been treated for wheezing in the ER or EW of the children`s hospital during the preceding year.

Hospital record annotations on parental asthma were found in 58% of cases (parental asthma present in 17%; in 30% of those with data available), but on parental smoking in only 40% of cases (parental smoking present in 17%; in 42% of those with data available). An annotation on atopic dermatitis in the child was found in >90% of cases (present in 16%). Food allergy (11%) and allergic rhinitis (5%) were evidently registered only if present. Wheezing apart from infection was registered in 2% of children, and blood eosinophilia had not been measured in any child (Table 2).

Current wheezing was the first one in 55/68 (81%) of the <12 months old, in 31/76 (41%) of the 12-23 months old and in 20/35 (57%) of the 24-35 months old children. Only two (3%) of the <12 months old children used ICSs; the respective figures were 16 (21%) and 6 (17%) in the two other age groups, respectively.

Sufficient data for an assessment of the asthma risk profile were found from the hospital records of 112(63%) patients (Table 3). The asthma risk profile was positive in 47-48% of the children in the three age groups, and in 52% of those who already used ICSs.

The agreement between asthma treatment modes and the current care guidelines was evaluated by using two measures, prescribing of ICSs and organizing of control visits (Table 4). ICS therapy was started for 14/91 (15%) children, in agreement with the guidelines in 11 cases and in disagreement in 3 cases only. ICSs were not started for 12 children with an indication to start according to the guidelines. Thus, the decision to start or not to start ICSs was in line with the guidelines in 76/91 (84%) of the cases.

The assessment of the risk profile does not influence the treatment in those children who have not wheezed previously. There were 13 children with previous wheezing, in whom risk profile was not possible to be assessed. If we propose that the treatment of these 13 children was not in line with the current care guidelines (worst scenario analysis), the solution whether or not to start ICSs was wrong in 28 (16%) of the all 179 cases.

Thus, the result of the “intention-to-treat” analysis with a worst scenario model was the same as the result of the primary “per protocol” analysis; the decision was in line with guidelines in 84% of the cases.

In the 2012 updating of the current care guidelines for asthma, sensitization to inhaled allergens confirmed by positive skin prick tests or by presence allergen specific IgE was included as a major criterion, and sensitization to basic food allergens, respectively, as a minor criterion, also in non-symptomatic cases.

Table 1. *Asthma risk profile for young wheezing children (Finnish current care guidelines for asthma, from year 2006)*

Major criteria

Doctor-diagnosed asthma in the mother or farther
Doctor-diagnosed atopic dermatitis or food allergy in the child

Minor criteria
Seasonal, presumably allergic rhinitis
Wheezing apart from infection
Blood eosinophilia (>4%)

The presence of one major or two minor criteria means significant asthma risk in a child with two or more wheezing episodes during the preceding 12 months.

Table 2. *Basic data and asthma risk factors in 179 study children*

	N	%
	68	38.0
Age 0-11 months		
Age 12-23 months	76	42.5
Age 24-35 months	35	19.6
Males	111	62.0
Females	68	38.0
Previous wheezing[1]	49/155	27.4
Use of inhaled corticosteroids	24/179	13.4
Atopic dermatitis in the child	28/169	15.6
Food allergy in the child	20/38	11.2
Allergic rhinitis in the child	8/15	4.5
Parental smoking[2]	30/72	16.8

Table 3. *Asthma risk profile in relation to wheezing history in those 112 children with sufficient data available*

Wheezing history[1]	**Risk profile +**	**Risk profile –**
	(N=54)	(N=58)
One episodes (N=55)	26	29
Two episodes (N=20)	7	13
Three or more episodes (N=16)	10	6
Inhaled corticosteroids in use (N=21)		10

[1] *Number of episodes during 12 months, current episode included*
For risk profile positivity and negativity, see Table 1
There were no statistically significant differences between the asthma risk profile + vs. – groups

Table 4. *Follow-up treatment in relation to asthma risk profiles and wheezing histories, in those 91 children who did not use inhaled corticosteroids*

Criteria	Inhaled corticosteroids were started		Control visits were organized	
Risk profile +	***Yes***	***No***	***Yes***	***No***
One wheezing episode	0	26	1	25
Two wheezing episodes[1]	2[1]	5[1]	1	6
Three or more wheezing episodes[1]	6[1]	4[1]	4	6
Risk profile –	***Yes***	***No***	***Yes***	***No***
One wheezing episode	0	29	0	29
Two wheezing episodes	3	10	2	11
Three or more wheezing episodes[1]	3[1]	4[1]	4	6

[1]*ICSs are indicated according to the Finnish current care guidelines*

Table 5. *Asthma predictive indices, constructed for children with wheezing at less than 3-4 years of age*

Index	Major risk factors	Minor risk factors
Asthma predictive index from the Tucson birth cohort, USA (API) [3,8] Positive: One major or two minor present	Doctor-diagnosed parental asthma Doctor-diagnosed atopic dermatitis in the child	Wheezing apart from respiratory infection Blood eosinophilia (>4%) Doctor-diagnosed allergic rhinitis
Modified asthma predictive index from the Tucson birth cohort, USA (mAPI) [9] Positive: One major or two minor present	Doctor-diagnosed parental asthma Doctor-diagnosed atopic dermatitis in the child Atopic sensitization to aeroallergens	Wheezing apart from respiratory infection Blood eosinophilia (>4%) Atopic sensitization to food allergens (milk, egg, peanuts)
Asthma predictive index for hospitalized children constructed from the Finnish and Swedish post-bronchiolitis cohorts (hAPI) [17] Positive: One major or two minor present	Doctor-diagnosed parental asthma Doctor-diagnosed atopic dermatitis and/or food allergy in the child Parental, especially maternal smoking	Atopic sensitization to aeroallergens Wheezing due to respiratory infection not caused by respiratory syncytial virus (RSV) Blood eosinophilia (>450/mm^3) or lack of eosinopenic response during viral infection
Asthma predictive index from the Isle of Wight birth cohort, the UK (IoWS) [5] Positive: 4/4 criteria	Family history of asthma Recurrent chest infections during the second year of life Atopic sensitization at four years of age (skin prick tests) Absence of recurrent nasal symptoms in the first year of life	Not classified into major and minor criteria
Asthma predictive index from the birth cohort of the Multicenter Allergy Study (MAS), Germany [26] (re-analyzed to be comparable with the IoWS birth cohort) Positive: 3/4 criteria	Family history of asthma Recurrent chest infections during the second year of life Atopic sensitization at three years of age (allergen-specific IgE) Absence of recurrent nasal symptoms in the first year of life	Not classified into major and minor criteria

This artcle may be cited as:

Paassilta M, Kerminen H, Korppi M. Evaluation of asthma risk index application in treating early childhood asthma. Curr Pediatr Res 2013; 17 (2): 71-77.

Discussion

There are two main results in the present pragmatic study on starting asthma controller therapy for young wheezing children. First, the decision whether or not to start therapy with ICSs was in accordance with the Finnish evidence-based current care guidelines in >80% of the cases. The result was similar also in the supplementary worst scenario sensitivity analysis. Second, the risk profiles were appropriately registered for only 60% of the patients. Thus, the beneficial result of the study was based on the fact that the wheezing episode was the first one in 60% of the patients, thus with no need to consider ICS therapy. In addition to ICSs, the clinical benefits of leukotriene modifiers have been shown in viral-induced asthma exacerbations of children aged >2 years with a history of intermittent asthma [10]. The use of montelukast was, however, rather rare (6.1%) in this study population. The retrospective design of the study lessens the reliability of many individual observations. However, the retrospective approach, opposite to a prospective approach, had no confounding effect to the way how the doctors did decisions in their clinical practice. Thus, retrospective designs often are the only possible ways to study the health care practices.

Currently available predictive indices for asthma development among children with wheezing in early childhood are summarized in Table 5. The API was the first index, originally constructed by the Tucson study group on the basis of a prospective, long-term follow-up of a birth cohort, and consisted of clinical, usually parent-reported observations with no objective confirmation [8]. Loose index (wheezing at <36 months of age and one major or two minor criteria) means a moderate asthma risk, and stringent index (repeated wheezing at <36 months of age and one major or two minor criteria) means a high asthma risk [8]. The mAPI included a new risk factor, that is sensitization to allergens documented by skin prick tests or allergen-specific IgE measurements [9]. Sensitization to inhaled allergens was included as a major and to basic food allergens as a minor risk factor. The validity of mAPI has not been, at least this far, confirmed with a longitudinal study. The API was originally aimed for identifying subgroups of preschool wheezers who are at risk for asthma [13], and the mAPI was constructed for intervention studies [14]. Later, the API has been started to be used in deciding whether or not to introduce maintenance medication with ICSs for young wheezing children, as recommended in the global strategy for asthma management and prevention in 2008 by Global Initiative for Asthma (GINA) [10]. The American Expert Panel Report up-dated in 2007 included sensitization to both aeroallergens and food allergens as risk factors of persistent asthma, but not earlier than after the age of 5 years [11].

The Finnish evidence-based current care guidelines [12] for asthma have since 2006 recommended that maintenance medication with ICSs for asthma in children aged <3 years of age should be based on the number of wheezing episodes during the preceding 12 months and on the determination of asthma risk profile constructed on the basis of the mAPI with minor modifications [12]. Unlike the mAPI, non-symptomatic sensitization to inhaled allergens was not included as a major criterion. The recent Swedish post-bronchiolitis studies have revealed the important role of parental, especially maternal smoking, in asthma development [15,16]. Parental smoking was not included in the Finnish current care guidelines, but was included in the API for hospitalized children (hAPI) [17], and therefore with no doubt influences the decision whether or not to start maintenance medication for young children with severe wheezing. In the present study, retrospective information about parental smoking was available in less than half of the cases, but when available, half of the children were regularly exposed to tobacco smoke. Evidently, ICSs should be started more easily if the child is exposed to passive smoking, but also can later be stopped more easily if the child grows out of asthmatic symptoms.

In the Finnish long-term, post-bronchiolitis studies, asthma in parents and symptomatic food allergy, sensitization to aeroallergens (but only to wheat and egg white among food allergens) and wheezing induced by other than respiratory syncytial viruses (rhinoviruses in particular) have been independent risk factors for asthma at school and teen age and even in young adulthood [17-21]. In the present study, information about parental asthma was available in two-thirds and information about food allergy in one-fifth of the children, but the history of allergic rhinitis, sensitization to inhalant or food allergens and wheezing-associated viruses were documented only in occasional cases. Blood eosinophils were measured in no case, though eosinophilia (>4%) belongs to the risk factors of the Finnish current care guidelines [13], and both eosinophilia and the lack of eosinopenic response during viral infection are entered in the hAPI [17]. The mAPI and hAPI are substantially based on laboratory confirmation of atopy [9,17]. The strength of the original API is that the index is simple, including 2 clinical major criteria, 2 clinical minor criteria and only 1 laboratory-based minor criterion [8,13].

In the present study, the role of the minor asthma risk factors of the Finnish current care guidelines was really low. In addition, the minor risk factors may be difficult to interpret. Allergic rhinitis and wheezing with no infection are rare in young children, and the allergic origin of both rhinitis and wheezing is difficult to confirm, or *vice versa*, the involvement of viruses is difficult to rule out. For example, subclinical rhinovirus and bocavirus infections are common [22,23], and may induce wheezing in suscep-

tible individuals. Blood eosinophilia is a useful risk factor if studied when the child is healthy. If studied during viral infection, the lack of an eosinopenic response, which means a value within normal limits, may be pathologic [24]. Low eosinophil count <2% if found repeatedly when healthy, speaks strongly against any asthma risk [25].

Matricardi *et al.* [26] presented an interesting comparison on the persistence of wheezing at 10–13 years of age between two birth cohorts: the IoWS birth cohort from the UK and the MAS birth cohort from Germany. When the results of the MAS cohort were re-evaluated by harmonizing the data with the IoWS data, family history of asthma, absence of recurrent rhinitis at <1 year, recurrent chest infections at <2 years of age and atopic sensitization at <3-4 years of age were independent risk factors for wheezing at 10 years, with some differences between early-life wheezers and non-wheezers, but with only minor differences between the two cohorts [26]. When 3/4 of these risk factors were present, the index was highly specific but non-sensitive in predicting persistent wheezing at >10 years of age: sensitivity 0.53, specificity 0.85 and positive likelihood ratio (LR+) 6.4. The LR+ values of the API were 7.3 for asthma at 6-8 years of age and 5.0 for asthma at 11-13 years of age, and the respective LR+ value of the IoWS algorithm was 7.9 [13]. In the PIAMA birth cohort study, the diagnostic parameters are dependent on the used cut-off limits of the scores, and therefore poorly comparable with other studies [13].

On the basis of the long-term Finnish and Swedish post-bronchiolitis studies [18-24], the asthma risk indices for young children seem to need further modification. New risk factors should include parental, especially maternal tobacco smoking [15,16], and wheezing induced by rhinoviruses [17,19,23]. The results of the present study suggest that current minor criteria, such as allergic rhinitis (rare at age <3 years), wheezing apart from infection (requiring viral assays) and blood eosinophilia could even be omitted. The children with repeated wheezing should be invited to control visits, and at these visits, eosinophils can be studied at time when the children are not infected, and skin prick tests can be done to reveal sensitization to inhaled allergens. In addition, one algorithm does not fit to all cases in predicting persistence of wheezing or emergence of asthma [26], and separate algorithms are needed for early-life wheezers needing and not needing treatment in hospital. To be used in clinical practice, the algorithms should be simple and sensible.

References

1. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's respiratory study: 1980 to present. J Allergy Clin Immunol 2003; 111: 661-675.
2. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med 2005; 172: 1253-1258.
3. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet 2007; 370: 758-764.
4. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. Proc Am Thorac Soc 2009; 6: 272-277.
5. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. Eur Respir J 2003; 22: 767-771.
6. Matricardi PM, Illi S, Grüber C, Keil T, Nickel R, Wahn U, et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. Eur Respir J 2008; 32: 585-592.
7. Caudri D, Wijga A, A Schipper CM, Hoekstra M, Postma DS, Koppelman GH, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. J Allergy Clin Immunol. 2009; 124: 903-910 e1-7.
8. Castro-Rodríguez 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: 1403-1406.
9. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 2004; 114: 1282-1287.
10. Global strategy for asthma management and prevention 2008 (update). Globar Initiave for asthma (GINA) <http://www.ginasthma.org/>.
11. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma - Summary Report 2007. <http://www.nhlbi.nih.gov/guidelines/asthma/index.htm>
12. Finnish Current Care Guidelines. Asthma. www.-kaypahoito.fi. Updated: 28.03.2006. Summary: Diagnosis and treatment of asthma. Duodecim. 2006; 122: 1107-1108 (Finnish).
13. Castro-Rodriguez JA. The Asthma Predictive Index: a very useful tool for predicting asthma in young children. J Allergy Clin Immunol. 2010; 126: 212-216.
14. 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: 1985-1997
15. Goksör E, Amark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood – what happens then? Acta Paediatr 2006; 95: 471-478.
16. Goksör E, Amark M, Alm B, Gustafsson PM, Wennergren G. The impact of pre- and post-natal smoke exposure on future asthma and bronchial hyperresponsiveness. Acta Paediatr. 2007; 96: 1030-1035.

17. Piippo-Savolainen E, Korppi M. Wheezy babies – wheezy adults? Review on long-term outcome until adulthood after early childhood wheezing. Acta Paediatr 2008; 97: 5-11.
18. Kotaniemi-Syrjänen A, Reijonen TM, Romppanen J, Korhonen K, Savolainen K, Korppi M. Allergen-specific immunoglobulin E antibodies in wheezing infants: the risk for asthma in later childhood. Pediatrics. 2003; 111: e255-261.
19. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy--the first sign of childhood asthma? J Allergy Clin Immunol. 2003; 111: 66-71.
20. Piippo-Savolainen E, Korppi M, Korhonen K, Remes S. Adult asthma after non-respiratory syncytial virus bronchiolitis in infancy: subgroup analysis of the 20-year prospective follow-up study. Pediatr Int. 2007; 49: 190-195.
21. Hyvärinen MK, Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Korppi MO. Lung function and bronchial hyper-responsiveness 11 years after hospitalization for bronchiolitis. Acta Paediatr. 2007; 96: 1464-1469.
22. Jartti T, Lee WM, Pappas T, Evans M, Lemanske RF Jr, Gern JE. Serial viral infections in infants with recurrent respiratory illnesses. Eur Respir J. 2008; 32: 314-320.
23. Jartti T, Korppi M. Rhinovirus-induced bronchiolitis and asthma development. Pediatr Allergy Immunol. 2011; 22: 350-355.
24. Piippo-Savolainen E, Remes S, Korppi M. Does blood eosinophilia in wheezing infants predict later asthma? A prospective 18-20-year follow-up. Allergy Asthma Proc. 2007; 28: 163-169.
25. Karakoc F, Remes ST, Martinez FD, Wright AL. The association between persistent eosinophilia and asthma in childhood is independent of atopic status. Clin Exp Allergy. 2002; 32: 51-56.
26. Matricardi PM, Illi S, Keil T, Wagner P, Wahn U, Lau S. Predicting persistence of wheezing: one algorithm does not fit all. Eur Respir J 2010; 35: 701-703.

Correspondence to:

Marita Paassilta
Allergy Centre, Tampere University Hospital
PB 2000, FIN-33521 Tampere
Finland