

Understanding mild persistent asthma in children: The next frontier

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Limitations in asthma prevalence studies and difficulties in diagnosing pediatric asthma lead to uncertainty over the full extent of mild persistent asthma in children and adolescents. Although recent surveys have reported that the majority of pediatric patients with asthma in the United States and Europe have symptoms consistent with mild disease, these surveys have limitations in design. Thus, the true prevalence of mild asthma remains unknown. It is unclear whether children with mild persistent asthma progress to more severe asthma, but the risk of severe asthma exacerbations seems to be unrelated to the symptom severity. Clinical studies restricted to pediatric patients with mild asthma are limited, but available data do suggest substantial morbidity of mild persistent asthma in this population and support inhaled corticosteroid intervention. There is a need for further investigation into the true prevalence of mild persistent asthma in children and adolescents, and optimal treatment. (*J Allergy Clin Immunol* 2005;115:708-13.)

Key words: *Children, adolescents, persistent asthma, mild*

Recent surveys conducted in Europe and the United States underscore the burden of pediatric asthma in terms of activity limitations, missed school days, and the need for emergency care.¹⁻³ However, these surveys fail to provide specific data regarding the burden of asthma as it relates to the underlying disease severity. Although current survey results suggest that the majority of the pediatric asthma population has mild persistent or mild intermittent asthma symptoms, the inclusion of patients receiving current asthma treatment, selection bias, use of

Abbreviations used

AIA: Asthma in America
AIRE: Asthma Insights and Reality in Europe
CAMP: Childhood Asthma Management Program
EIA: Exercise-induced asthma
GINA: Global Initiative for Asthma
ICS: Inhaled corticosteroid
NAEPP: National Asthma Education and Prevention Program
PEF: Peak expiratory flow
PREPAC: Prevalence of Recurrent Respiratory Episodes in Preschool Children
START: Inhaled Steroid Treatment As Regular Therapy in Early Asthma

caregiver reports, and reliance on symptoms for severity categorization frequently occurring in these studies negate their usefulness in accurately determining the true prevalence of mild persistent asthma in children. Moreover, the prevalence and effect of exercise-induced asthma (EIA) are unclear. For some particularly active children, symptoms of EIA might constitute a burden consistent with that of mild persistent disease.

In addition to the lack of studies on the prevalence of mild persistent asthma, limited pediatric data are available regarding the prognosis of mild persistent disease and the possible pathophysiologic differences between asthma severities. Finally, the evidence base for the treatment of mild persistent asthma is limited, because many studies include children with mild to moderate persistent asthma, and most recommendations are based on extrapolation from adult data or data from children with moderate to severe asthma.

This review discusses the limitations and results of studies that have attempted to assess the burden of asthma in children, drawing attention to our very limited knowledge of the extent of mild persistent asthma in the pediatric population, and offering some beginning insight into the treatment of mild persistent asthma with inhaled corticosteroids (ICSs).

OVERALL BURDEN OF PEDIATRIC ASTHMA

Three recent large-scale surveys have been conducted in the United States and Europe to assess the overall

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burden of asthma and recurrent respiratory illness in children and adolescents. Although these surveys demonstrate that the goals of asthma therapy are not being met in children, they fail to provide specific data regarding the burden of disease in mild persistent asthma.

The Asthma Insights and Reality in Europe (AIRE) survey included 753 patients younger than 16 years with a physician diagnosis of asthma and who were currently using asthma medications or had asthma symptoms or attacks in the past year.¹ A similar survey conducted in the United States,² the Asthma in America (AIA) survey (www.asthmainamerica.com), included 721 children and adolescents younger than 16 years with current asthma. Caregivers provided responses to the survey for the children in both surveys. A third survey conducted in the United States and Europe, the Prevalence of Recurrent Respiratory Episodes in Preschool Children (PREPAC) survey, examined the prevalence and burden of recurrent lower respiratory symptoms in preschool-age children. Surveyors interviewed mothers of 9490 children age 1 to 5 years.³

The results of these surveys suggest that overall, there is a significant worldwide burden of asthma and respiratory illness in children and adolescents with and without current asthma treatment. According to the AIRE survey, more than one third (38%) of the patients had daytime symptoms at least once a week. Moreover, both the AIRE and the AIA surveys reported that more than 40% of children missed school because of their asthma.

In the PREPAC survey of 9490 young children, 32% suffered recurrent episodes (days) of troublesome lower respiratory symptoms (cough, noisy breathing, or breathlessness) in the past 6 months, 26% of them at least on a weekly basis.

Both the AIRE and AIA surveys reported that most children with asthma have symptoms of mild intermittent or mild persistent asthma. Moreover, evidence from conscripts in Israel suggests that two thirds of 17-year-old patients with asthma have mild disease.⁴ However, accurate classification of asthma severity in these studies is precluded by the survey designs, limiting our current knowledge of the true burden of mild persistent asthma in children.

DIFFICULTIES IN DETERMINING THE EXTENT OF MILD PERSISTENT ASTHMA

Factors that hinder the determination of the true extent of mild persistent asthma in children in epidemiologic surveys include lack of information of current treatment status, selection bias, use of caregiver reports, reliance on symptoms for severity categorization, and ambiguity in operationalizing categories of asthma severity.

Current treatment status

Criteria for the classification of mild persistent asthma based on clinical parameters before treatment are provided in Table I. According to the Global Initiative for Asthma

TABLE I. Criteria for mild persistent asthma*

Criterion	NAEPP, 2002	GINA, 2003
Symptoms	>2/wk but <1×/d	>1/wk but <1×/d
Nighttime symptoms	>2 nights/mo	>2×/mo
FEV ₁ or PEF†		
% Predicted	≥80	≥80
Variability, %	20-30	20-30
Exacerbations	—	May affect activity and sleep

*Criteria used to classify asthma severity in patients before treatment or before adequate asthma control is achieved.

†In adults and children older than 5 years; PEF and spirometry are not included in the criteria for children 5 years and younger.

(GINA) strategy for asthma management, asthma severity in untreated patients is classified according to clinical features (symptoms, exacerbations, activity limitations) and pulmonary function.⁵ Once treatment has begun, estimation of asthma severity must take into account the patient's medication regimen. Thus, a classification of moderate persistent asthma is appropriate for a patient with symptoms of mild persistent disease who is already receiving low-dose ICSs or an alternative controller therapy. Similarly, treatment guidelines from the National Asthma Education and Prevention Program (NAEPP)⁶ recommend asthma severity classification in patients before treatment or before adequate control of asthma is achieved. Although symptom burden can be considered a proxy for asthma severity, severity estimates were not adjusted for current medication use in available surveys. Failure to consider medication use can result in underestimation of disease severity and an overestimation of mild disease prevalence.

Selection bias

In both the AIRE and the AIA surveys, a physician diagnosis of asthma was a criterion for inclusion.^{1,2} Selection of patients who already had a physician diagnosis of asthma excluded patients with untreated or undiagnosed asthma. Those excluded from these surveys may be more likely to have mild persistent asthma and might skew asthma distribution to more severe disease.

Use of caregiver reports

All 3 surveys depended on caregiver descriptions of the symptoms of the child. Dependence on caregiver reports is subject to error because important differences exist between a caregiver's perception of a child's asthma and a child's own perception of asthma. A prospective cohort study in children age 7 to 17 years indicated that differences between a child's and a caregiver's perception of the child's symptoms, global assessment of asthma, and quality of life depend on the age of the child.⁷ Moreover, conceptual understandings of wheeze for parents of children with reported wheeze are different from epidemiologic definitions. Less than 50% agreement between parents' and clinicians' reports of wheeze and asthma was

reported in recent studies.^{8,9} A study of symptom reporting by parents and children with EIA found that the children's symptom perception related weakly to change in FEV₁ after exercise. Parents' perceptions of symptoms were unrelated to any physiologic measure of EIA in the child, and there was no significant relation between parent and child reports of symptoms.¹⁰

In preschool-age children, asthma is particularly difficult to diagnose on the basis of caregivers' symptom reports. The difficulty in diagnosing asthma in very young children is compounded by the similarity of asthma symptoms with those of commonly occurring recurrent infections. Such difficulty in diagnosing asthma in children also may contribute to inaccuracy in determining the true prevalence and severity of pediatric asthma.

Categorizing on the basis of symptoms

The use of asthma symptoms alone as a measure of disease severity is not without its limitations, in part because symptoms correlate poorly with objective measures of airway obstruction. In a prospective cohort study of 67 adult patients with persistent asthma, patient assessments of cough, dyspnea, wheeze, chest tightness, sputum production, and nighttime awakening correlated poorly with FEV₁ and peak expiratory flow (PEF).¹¹ At the initial clinic visit, airway obstruction was underestimated in 17% of patients and overestimated in 31% of patients on the basis of total asthma symptom scores. A study conducted in children with a history of recurrent wheeze, cough, shortness of breath, and intermittent acute exacerbations likewise showed a poor correlation between asthma symptoms and airway obstruction, supporting the need for variable outcomes to assess asthma in children.¹² On the other hand, many children with asthma have FEV₁ values within the normal range when their disease is stable, and FEV₁ may not correlate well with asthma severity in childhood. FEV₁ is generally normal even in children classified with severe persistent asthma on the basis of symptoms and medication use,¹³ suggesting a need for more appropriate measures to assess asthma severity.¹⁴

An additional factor to be considered when using asthma symptoms as a criterion for classifying asthma severity is that asthma severity varies over time. Short-term symptom recall (eg, within the past 4 weeks) may result in an asthma severity classification different from that based on long-term symptoms or activity limitations. In clinical trial populations of adult patients with asthma, large variability in outcomes was shown over a period of 12 weeks for single point in time measurements. The variability was reduced when measurements were taken at multiple time points and averaged, suggesting that changes in a single measurement at any one time point cannot be used to describe the state of the disease adequately.¹⁵ Similarly, individual patients were found to move frequently across severity categories over time.¹⁶ Variability in asthma symptoms over time may be best controlled for by assessing patient symptoms over multiple recall periods to obtain an average for long-term symptom burden. Fuhlbrigge et al¹⁷ based their determi-

nation of long-term symptom burden on recall of average weekly symptoms and frequency of asthma exacerbations over a period of 12 months.

Ambiguity in categories of asthma severity

Asthma disease severity will depend on how classification is operationalized.¹⁸ Use of global symptom burden (composed of both short-term and long-term symptoms and functional effect) shifted asthma severity from a mild intermittent to persistent classification in a significant proportion of adult patients in the AIA survey.¹⁷

Even when using the same outcome, criteria for assessing asthma severity may differ. For example, a patient experiencing daytime symptoms twice a week would be classified with mild intermittent asthma according to the NAEPP guidelines but with mild persistent asthma according to the GINA guidelines.

Studies have shown a variable prevalence of EIA in the pediatric population, with rates ranging from 3% in Ghana¹⁹ to 23% in Australia.²⁰ EIA may be particularly burdensome in an active pediatric population and might best be treated as a persistent form of disease. Unfortunately, EIA is often not recognized by children or their caregivers¹⁰ and is often not diagnosed by physicians. Children with EIA thus represent an underdiagnosed pediatric asthma population, with 1 study reporting no formal asthma diagnosis in more than 40% of children age 8 to 11 years, demonstrating hyperresponsiveness to exercise challenge.²¹ If one considers EIA a persistent form of asthma, then underdiagnosis of EIA may also contribute to the difficulty in quantifying mild asthma prevalence.

PROGNOSIS OF MILD ASTHMA IN CHILDREN

Studies suggest that lung function decline in children with asthma may occur predominantly in younger or preschool-age children.²²⁻²⁶ In general, patients with asthma appear to remain within a narrow span of disease severity—that is, studies do not suggest that mild asthma is the typical start in a progression to more severe disease. Available evidence suggests tracking of lung function by age, such that patients with more severe asthma early in life are at greater risk of lung function deficits throughout childhood and into adulthood.^{23,25,27} Among children (age 5-12 years) with mild to moderate persistent asthma enrolled in the Childhood Asthma Management Program (CAMP) study, lung function remained stable throughout childhood and adolescence whether or not patients received active treatment. However, a follow-up analysis of this patient population recognized that approximately 25% of the cohort had a loss in lung function of greater than 1% predicted FEV₁ per year during the 5-year study period, regardless of the assigned treatment arm.²⁸ Because lung function was not reported for children with mild versus moderate disease, it is difficult to determine asthma burden specific to children with mild disease. It will be important to determine whether this overall trend continues in the long-term follow-up of this

TABLE II. Pediatric studies of ICS treatment for mild persistent asthma

GINA criteria	CAMP, 2000 ²² (n = 1041)	Arets et al, 2002 ³³ (n = 68)	START, 2003 ⁴⁵ (n = 1974 age <11 y)
Currently using controller medication?	Some*	No*	No
Symptoms >1/wk but <1/d	Score ≥ 1 but <2†	~14% SFD; "mean symptom scores were low"	~66% SFD
Baseline FEV ₁ $\geq 80\%$ predicted (prebronchodilator)	93.9% $\pm$ 14.3%	104.1% $\pm$ 10.8% (fluticasone) 99.8% $\pm$ 17.0% (placebo)	85.0% $\pm$ 13.4% (budesonide) 85.5% $\pm$ 12.9% (placebo)

SFD, Symptom-free day.

*In the CAMP study, daily use of asthma medication, asthma symptoms at least 2 times weekly, or use of an inhaled bronchodilator was required for enrollment. For ≥ 6 months before enrollment, 27.6% of children had used cromolyn and 22.6% had used ICSs ≥ 2 times weekly. In the study by Arets et al,³³ 6 children had received maintenance treatment with ICSs.

†Diary symptom score; scale, 0 to 3.

study population now that study treatment has been discontinued. The loss in predicted pulmonary function in this population could be related to structural changes that occurred early at the onset of the disease, continuing inflammation, or various other reasons. If the loss is indeed a result of a structural change, it may not be reversible. If it is a result of ongoing inflammation, perhaps higher doses or earlier initiation of corticosteroids or alternative treatment strategies are necessary to prevent ongoing loss in pulmonary function.

RISK OF MILD ASTHMA

The risk of severe asthma exacerbations may be unrelated to the symptom severity. For this reason, mild asthma should not be considered a benign disease. Children with generally mild asthma symptoms can have life-threatening exacerbations. The majority of children hospitalized for asthma were classified as having mild intermittent (50%) or mild persistent (36%) asthma in a recent retrospective chart review of all pediatric asthma admissions to a local hospital.²⁹ According to a study examining the circumstances surrounding asthma-related deaths in patients 20 years old and younger in Victoria, Australia, 33% of deaths occurred in patients classified with mild asthma on the basis of reported symptoms, exercise capacity, medication requirements, and previous asthma attacks.³⁰

A recent study investigating genetic polymorphisms among Chinese preschool-age and school-age children found a higher frequency of the RANTES-28G allele among children with near-fatal asthma compared with children with mild to moderate asthma.³¹ Interestingly, the subgroup of children with mild asthma had a lower frequency of this allele than those with moderate asthma, suggesting a possible basis for differences in asthma severity.

TREATMENT OF MILD ASTHMA IN CHILDREN

Inhaled corticosteroid therapy is the preferred controller therapy for the treatment of mild persistent asthma in children.^{5,6} The benefits of ICS therapy for persistent

asthma in children are considered so well documented that placebo-controlled trials were recently discouraged.³² Still, most of the data supporting the preferred status of ICSs are derived from clinical studies in school-age children with moderate to severe asthma, and adults. In addition, most studies of mild persistent asthma in children also include children with moderate disease severity. The CAMP Research Group trial provided the most robust evidence for the efficacy of ICSs in school-age children with mild to moderately severe asthma.²² The CAMP trial randomized 1041 children age 5 to 12 years with mild to moderate persistent asthma to budesonide dry powder inhaler 400 μ g/day, nedocromil 16 mg/day, or placebo (Table II). After 4 to 6 years of treatment, the primary outcome, postbronchodilator FEV₁, showed no significant advantage of budesonide. However, children who received budesonide had 43% fewer hospitalizations ($P = .04$), 43% fewer courses of prednisone ($P < .001$), and 45% fewer visits for urgent care ($P < .001$) than children who received placebo. Although this trial included children with moderate asthma, 48% of those enrolled had mild disease,²⁴ suggesting the effectiveness of ICSs in reducing the morbidity associated with mild persistent asthma in children, although no subanalyses according to severity are available.

Although the effectiveness of ICS treatment based on objective measures of pulmonary function may be difficult to demonstrate in children with near normal pulmonary function, a limited number of clinical studies have demonstrated a significant reduction in asthma burden with ICS therapy in children with mild asthma (Table II). In the study by Arets et al,³³ 68 children age 5 to 10 years were randomized to receive fluticasone propionate 250 μ g twice daily via metered-dose inhaler with spacer or placebo for 12 weeks. Compared with placebo, children receiving fluticasone had significant improvements in symptom-free days, use of rescue β_2 -adrenergic agonist, wheezing, and pulmonary function. It should be noted that the high dose of fluticasone propionate used in this study should generally be restricted to use in children with severe persistent disease.

Inhaled corticosteroid treatment has shown a protective effect on exercise-induced symptoms in children and

adolescents with severe asthma.^{34,35} Although limited in number, studies assessing the effects of ICS use on exercise-induced symptoms in mild asthma have demonstrated that when used on a daily basis (not as needed before exercise), ICS therapy protects against exercise-induced bronchoconstriction in children with near normal pulmonary function. One randomized, placebo-controlled study evaluated the efficacy of budesonide dry-powder inhaler 100 or 200 μ g once daily in the morning, 100 μ g twice daily, or placebo for 12 weeks in 163 patients age 7 to 16 years with mild persistent asthma (mean characteristics: FEV₁, 103% predicted; postexercise fall in FEV₁, 10.4%), as reported in several articles.³⁶⁻⁴⁰ Compared with placebo, the fall in FEV₁ after exercise was significantly less with budesonide at study end. These studies highlight the potential for ICSs to diminish the burden of EIA in pediatric patients.

ADULT STUDIES INCLUDING ADOLESCENTS AND CHILDREN

With these exceptions, studies in mild asthma are limited to adult studies.⁴¹⁻⁴⁵ One such adult study in mild asthma included a subset of adolescents too small for subanalyses.⁴⁴ The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study included 3970 adult patients, 1974 patients age 5 to 10 years, and 1221 patients age 11 to 17 years with corticosteroid-naïve mild to moderate persistent asthma for less than 2 years. Subjects were randomized to receive budesonide dry powder inhaler 200 μ g (age <11 years) or 400 μ g (age $\geq$ 11 years) once daily or placebo plus their usual asthma therapy.⁴⁵ Subgroup analyses of pediatric patients and adolescents are awaited and will provide further insight into ICS treatment for children and adolescents with mild persistent asthma.

These studies illustrate the burden of mild and moderate persistent asthma. In 1 study, 33% of patients receiving placebo had a severe exacerbation, and asthma was poorly controlled on 14% of days.⁴⁴ Substantial morbidity also was demonstrated in the START study, in which 5.6% of patients in the placebo group had at least 1 severe asthma-related event—an event requiring admission or emergency department care for worsening asthma, or death caused by asthma—during 3 years of follow-up, and 0.7% had a life-threatening exacerbation. Among all patients, treatment with inhaled budesonide in addition to usual asthma therapy reduced the risk of a severe asthma-related event by 44% (hazard ratio, 0.56; 95% CI, 0.45-0.71; P < .0001).⁴⁵

CONCLUSION

This article has attempted to bring to light an important deficit in our knowledge of pediatric asthma—namely, the extent and burden of mild persistent disease. Although asthma surveys suggest a high prevalence of mild symp-

toms, these surveys do not accurately reflect disease burden. Use of additional markers of disease severity and further consideration of confounding factors are needed to determine accurately the distribution of asthma severities among patients and define the true burden of mild disease. Notwithstanding the potential discrepancy in terms of prevalence, pediatric patients with mild persistent asthma have symptoms on many days, are limited in their daily activities (along with their caregivers), and have exacerbations that require emergency intervention.

Exercise-induced asthma, which is often undiagnosed, may be particularly burdensome in a pediatric population. Unlike adults, children often do not have scheduled exercise, might be unable to recognize the need for pretreatment, can forget to carry their rescue inhalers with them, or may not have immediate access to their inhalers at day care or school. Efficacy of ICS therapy in EIA and circumstances that make the use of as-needed β_2 -adrenergic agonists impractical support daily controller therapy with ICSs for children with EIA.

Recent studies demonstrate the efficacy of ICSs in reducing the burden of mild persistent asthma in adults and children. Furthermore, there is some evidence to suggest that in mild persistent pediatric asthma, ICS treatment may improve symptoms and pulmonary function and decrease exacerbation rates. In pediatric patients in whom asthma is suspected, the frequency of exacerbations can guide the decision to begin long-term ICS therapy. As new data from the CAMP and START studies become available, the role of ICSs in reducing morbidity and mortality caused by mild persistent asthma and possibly altering the natural history of the disease can be further elucidated.

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