Outcome Measures in Childhood Asthma

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ABSTRACT. Although evidence suggests that asthma onset occurs early in childhood, many standard asthma outcome measures are either impractical or unreliable in preschool-aged children. In this population, for instance, patient history and symptom reports rely on the observations of caregivers, who tend to underreport their child’s asthma symptoms. Furthermore, the use of conventional measures of pulmonary function such as spirometry may be impractical in very young children. Recent clinical studies have used a variety of techniques to measure symptoms, pulmonary function, and cellular mediators of inflammation. Outcomes such as discontinuation and exacerbation rates, frequency of daytime and nocturnal symptoms, and caregiver assessments of quality of life can be useful measures in evaluating outcomes in young children with asthma. Some measures, such as plethysmography and inflammatory marker analysis, may be suitable options for assessing pulmonary function and predicting asthma susceptibility in preschool-aged children. Indeed, altered levels of inflammatory markers, including immunoglobulin E, interleukin-10, and exhaled nitric oxide, may be useful tools in diagnosing asthma, evaluating interventions, and assessing future risks for asthma symptomatology in very young children. Whether 1 or more of these outcome measures will prove useful clinically in improving the diagnosis and management of childhood asthma remains uncertain, although early research results are encouraging. Pediatrics 2002;109:393–398; outcomes, asthma, pediatric, diagnosis, treatment.

ABBREVIATIONS. ENO, exhaled nitric oxide; DWAS, days without asthma symptoms; FEV₁, forced expiratory volume in 1 second; sRAW, specific airway resistance; LTRA, leukotriene receptor antagonist; IgE, immunoglobulin E; IL-10, interleukin-10; RSV, respiratory syncytial virus; NO, nitric oxide.

Accumulating evidence indicates that asthma onset occurs early in childhood, often before the age of 2 years.¹ It is critical to identify children with asthma so that effective treatment can be initiated early to prevent the irreversible airway remodeling that can be characteristic of chronic disease. Identifying which outcome measures are suitable in young children with asthma can be a formidable task in clinical trials, however. Generally, outcome measures in asthma are based on changes in symptoms, pulmonary function, quality of life, or the direct and indirect costs of this disease, but perspective often influences which outcome measure is most relevant. From a societal perspective, for example, the economic burden of asthma on the patient and on the health care system is a legitimate concern and thus an appropriate outcome measure. For children with asthma and their families, however, symptom severity and frequency, as well as quality-of-life measures, are outcomes with more immediate relevance because these measures assess the impact of asthma on day-to-day activities.

The choice of an outcome measure is also at least partially driven by the time scale of interest. A bronchodilator challenge test can reflect minute-to-minute changes in airway function, whereas measures of asthma symptomatology can indicate changes that occur over days, or, as in the case of the impact of environmental influences, even longer—weeks or months. In clinical trials, typical measures of symptomatology, especially in mild asthma, include an evaluation of nocturnal and breakthrough symptoms as well as an assessment of the frequency of wheezing after normal activities. Assessments of pulmonary function using plethysmography, and airway hyperresponsiveness using challenge testing, are beginning to be used to measure outcomes in mild asthma. Moreover, increases in certain markers of inflammation, such as the eosinophil level and exhaled nitric oxide (ENO), reflect poor disease control and may be useful outcome measures in these patients as well. Finally, evaluating the effects of early intervention on asthma progression in children will require years of outcome monitoring and evaluation. In clinical trials, these outcomes may include the frequency of acute exacerbations, often reflected by an increased need for corticosteroids, progressive changes in pulmonary function, and changes in the rates of asthma-related mortality, hospitalizations, and emergency department visits.

Despite the above array of outcome options, identifying outcome measures that are of value in making an accurate diagnosis or in evaluating the benefits of treatment in young children with asthma remains particularly difficult. All too often, standard symptom reports and the pulmonary function testing that are used successfully in adult asthma patients prove unreliable or impractical in very young children with asthma. Although the comprehensive battery of outcome measures used in the Childhood Asthma Management Program¹⁵ (children aged 5–12 years) should be used in long-term studies of controller medications in persistent asthma, not all of the mea-

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sures would be possible in children 2 to 5 years old. This article will review some of the challenges and explore novel approaches to measuring outcomes and disease control in young children with asthma.

CHALLENGES TO MEASURING ASTHMA OUTCOMES

Among preschool-aged children, differentially diagnosing asthma presents an ongoing challenge because its symptomatology often mimics that of other respiratory disease. Additionally, a diagnosis of asthma in young children is based often on only 1 or 2 patient contacts with a caregiver, despite the fact that symptom presentation and pulmonary function vary considerably in young children with asthma. Thus, an accurate diagnosis requires an evaluation of longitudinal information gleaned from repeated patient contacts. Even with repeated patient contact, however, outcome measures in young children must be chosen carefully.

Because of their complexity, standard methods for measuring pulmonary function, such as spirometry, are often impractical in very young children. Direct reports from young children with asthma are unreliable, and clinicians rely on information obtained from caregivers whose reports frequently miss symptoms of exercise-induced asthma and dyspnea. As a consequence, these hallmark symptoms of asthma frequently go unreported. Complicating matters even further, reports of nocturnal awakenings attributable to wheezing or cough, a common asthma outcome measure in clinical studies, depend largely on whether these symptoms are severe enough to awaken the caregiver; thus, these symptoms tend to be underreported as well. The extent of this problem was highlighted in one study during which a microphone that would automatically record episodes of coughing at night was placed on the necks of children with mild asthma. Eighty percent of the children were actually coughing at night, but the caregivers reported only about 15% of these episodes, leaving an alarming 85% of the nocturnal coughing episodes unreported.

Recent clinical studies in children with asthma have used a variety of traditional and nontraditional techniques to measure symptoms, pulmonary function, and cellular mediators of inflammation in asthma. Some of these techniques are expected to show promise as valid outcome measures in pediatric asthma.

SYMPTOM AND QUALITY-OF-LIFE MEASURES

The goal of a randomized, multicenter, open-label, long-term (52 weeks) study of 2- to 6-year-old children was to examine the effects of nebulized budesonide compared with nebulized cromolyn in young children with mild-to-moderate asthma. Several measures proved useful for evaluating treatment outcomes. During this study, the rate of discontinuations successfully differentiated between treatment groups, with 8% and 20% of the children discontinuing treatment in the budesonide and cromolyn groups, respectively. Moreover, the asthma exacerbation rate differed significantly \((P = .001)\) between groups, with a mean exacerbation rate of 1.23 per year and 4.65 per year for the budesonide and cromolyn groups, respectively. Nighttime and daytime symptom rates also differed significantly between groups, with clear improvements seen in asthma symptom scores in the budesonide group (Fig 1). In addition, the caregiver’s quality-of-life score—measured on study weeks 8, 28, and 52—revealed significant differences between groups in terms of improvements in emotional status. Significantly greater improvements in emotional status scores were observed when the children received budesonide treatment. These results suggest that in young children with asthma, outcomes such as discontinuation and exacerbation rates, frequency of daytime and nocturnal symptoms, and caregiver assessments of quality of life can be useful measures.

DAYS WITHOUT ASTHMA SYMPTOMS (DWAS)

The use of a diary by caregivers of preschool children (2–5 years of age) included an assessment of DWAS as well as numerous other behaviors and symptoms characteristic of asthma. In the Pediatric Asthma Caregiver Diary, a DWAS was defined as a day free of daytime and nighttime asthma symptoms. In a group of unstable asthma patients (Fig 2), the percent of children experiencing a DWAS was rare initially, between 3% and 13% (mean 11.0%) but,
with subsequent addition of (or increase in) antiinflammatory therapy on days 8 to 21, the incidence of DWAS increased to 20% to 32%. In the group of stable asthma patients who were taking sufficient antiinflammatory medication from the beginning of the study, the percent of patients having a DWAS remained between 33% and 45% (mean: 37.0%) throughout the 3-week study. Figure 2 shows that the measurement of DWAS in preschoolers significantly ($P < .0001$) differentiated unstable from stable patients. This parameter can be a valid outcome measure of the control of asthma in preschool children.

**PULMONARY FUNCTION**

A discrete analysis of changes in forced expiratory volume in 1 second (FEV$_1$) evaluated the effects of beclomethasone and montelukast in a randomized, double-blind study of 895 adults with persistent asthma.5 This analysis not only included the mean percentage change from baseline in FEV$_1$ but also a histogram of discrete intervals of 10% change in FEV$_1$ from baseline for each drug. Both beclomethasone and montelukast produced significant mean improvements in FEV$_1$ compared with placebo, and the mean FEV$_1$ improvement was significantly greater with beclomethasone (13.1%) than with montelukast (7.4%; $P < .05$). The analysis of the discrete changes, however, showed that both treatments produced similar results. For both treatments, the distribution of discrete FEV$_1$ responses resembled a bell-shaped curve and not a bimodal distribution. With 50% of the beclomethasone patients above the +11% median response, 42% of the montelukast patients showed an improvement of 11% or greater in FEV$_1$ (Fig 3). This study suggested that measuring discrete responses of FEV$_1$ may be a more meaningful way to express changes of clinical importance than just representing the changes as means. Although children above 14 years of age were included in this study, it still may prove to be useful in studies that are entirely pediatric.

**PLETHYSMOGRAPHY**

To examine the feasibility of using a whole-body plethysmograph as a diagnostic tool for assessing the airway function in 38 asthmatic and 29 healthy children 2 to 5 years of age,6 specific airway resistance (sRAW) was measured from simultaneous airway volume and flow measurements. The plethysmograph required these young children to sit inside a clear acrylic chamber and breathe normally through only a mouthpiece connected to a flow meter. Most children felt comfortable going into the chamber without their parents. The results demonstrated the

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**Fig 2.** DWAS. The percentage of children (2–5 years of age) with a DWAS over a 3-week study is presented. The solid line represents children with stable asthma (receiving adequate antiinflammatory therapy throughout the study) and the broken line represents children with unstable asthma who only started receiving adequate antiinflammatory therapy on day 8. Adapted from Santanello et al.4

**Fig 3.** Distribution of treatment responses for FEV$_1$. In a study comparing the effects of beclomethasone with montelukast in 895 adults with persistent asthma, the distribution of discrete FEV$_1$ responses for both groups were represented by a bell-shaped curve, with about 50% of the beclomethasone and 42% of the montelukast patients showing improvement of $\geq$11% in FEV$_1$. Adapted from Malmstrom et al.5
value of sRAW as a diagnostic measure: it had a high sensitivity (68%) and specificity (93%–100%) for distinguishing asthmatic individuals from healthy control subjects (Table 1). Additionally, sRAW demonstrated excellent repeat reliability, with a correlation coefficient of 0.96 between the original and repeat measures. Therefore, sRAW may be a useful measure of airway function to use with young children.

In a separate study, a plethysmograph was used to assess changes in pulmonary function following specific asthma therapy.7 In this crossover study, 16 children 2 to 5 years of age were treated with either the leukotriene receptor antagonist (LTRA) montelukast or placebo. The sRAW after cold air and placebo increased 46%, whereas montelukast only permitted an increase of sRAW by 17% (P < .05; Fig 4).

These studies indicate that sRAW obtained using plethysmography may be useful both in establishing a diagnosis and in evaluating treatment outcomes in young children with asthma.

INFLAMMATORY MARKERS

Sensitization and Immunoglobulin E (IgE)

In a study of 817 infants 1 to 2 years of age with atopic dermatitis and a family history of atopic disease, the children were randomized to receive either cetirizine or placebo treatment for 18 months to determine if the prophylactic value of an antihistamine therapy prevented the subsequent development of asthma (as defined by 3 episodes of nocturnal cough with sleep disturbances or wheezing, separated by at least 7 days, in a clinical setting where asthma is likely and conditions other than allergy have been excluded).8 When analyzing whether asthma occurred, no significant difference was detected between the fraction of children in each group who developed asthma.

A subgroup analysis, however, revealed important differences when a group of children were categorized using a preselected indicator. When children were followed who, at baseline were sensitized to grass pollen or house dust mite, there were significant differences in the probability of their developing asthma when they received cetirizine versus placebo (Fig 5). The data in Fig 5 represent the progressive onset of asthma and the consequent probability of developing asthma in each group and are not represented by a single endpoint but presented graphically as a Kaplan-Meier estimate of the cumulative probability. The onset of asthma in each group clearly diverges in occurrence attributable to the intervention.

Whereas this study showed that atopic infants responded with less asthma when receiving cetirizine, it also presented a novel way in which to present an outcome, especially in infants who are very difficult to diagnose for asthma. This approach requires a clearly defined distinction or definition for inclusion in the analysis; in this case, it was a specific sensitization. But such an analysis could also use another indicator for inclusion such as the frequency of wheezing, nocturnal awakenings, or of needed emergency medical rescue. A specific randomized, place-

| TABLE 1. Baseline Characteristics and Lung Function (Mean ± Standard Deviation) Using Plethysmography |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                      | Asthmatic (n = 38) | Healthy (n = 29) | P Value         |
| Age, y                               | 4.6 ± 0.9        | 4.7 ± 0.9       | NS              |
| Sex, male/female                     | 23/15            | 6/13           | ?               |
| sRAW, kPa/s                           | 1.56 ± 0.47      | 1.23 ± 0.21    | <.001           |

NS indicates not significant.
Adapted from Nielsen and Bisgaard.6

Fig 4. Plethysmography as a diagnostic test for asthma. In a study of 16 children 2 to 5 years of age treated with montelukast or placebo, a significant reduction in the bronchoconstrictive response to cold air challenge was detected in the LTRA (montelukast) group, with sRAW increasing by only 17% compared with a 46% increase after placebo treatment. Adapted from Bisgaard and Nielsen.7

Fig 5. Occurrence of asthma in patients sensitized to house dust mite. A subgroup analysis of children 1 to 2 years of age with atopic dermatitis and a family history of atopic disease were randomized to either cetirizine or placebo. There was a significant reduction of the risk of developing asthma in cetirizine-treated children with IgE antibodies for grass pollen and house dust mite. Adapted from the ETAC Study Group.8
bo-controlled study with an unstudied therapy could determine if the therapy reduces the probability of subsequently developing asthma or another disease.

In infants receiving placebo who had an elevated level of total IgE, or specific IgE for grass pollen, house dust mite, or cat dander, an elevated risk for asthma was measured. For cetirizine-treated infants, the risk of developing asthma was reduced in those who began the study sensitive to grass pollen and house dust mite, but not to cat dander. Moreover, elevated total and allergen-specific IgE levels may be a predictor for asthma in some infants and may be a meaningful outcome measure when assessing the value of an intervention to prevent or delay the onset of asthma.8

Interleukin-10 (IL-10)

In young children, changes in the level of certain inflammatory mediators have been shown to be useful not only in diagnosing asthma but also in evaluating the antiinflammatory effects of asthma treatments. In one study, in vitro cytokine responses, particularly IL-10, were measured in whole blood cultures stimulated with lipopolysaccharide (100 ng/mL) and interferon-γ (20 ng/mL).9 This study included 50 children younger than 13 months of age hospitalized for respiratory syncytial virus (RSV), bronchiolitis, and associated recurrent wheezing, as well as 27 control children free of atopy or infection. Because the episodic wheezing associated with the RSV virus can occur months or even years after the infection,10 follow-up data were collected for 1 year after hospital discharge to evaluate the relationship between the presence of recurrent wheezing and a cytokine response, in vitro.

During the acute RSV phase, 24 hours after admission, IL-10 levels were comparable to those observed in controls (Fig 6)9; however, during the convalescent phase, 3 to 4 weeks later, IL-10 responses were significantly elevated in the RSV-infected group. All of the 27 RSV-infected children who developed wheezing during follow-up also had elevated IL-10 levels during the convalescent phase compared with those RSV-infected children who did not develop wheezing. The IL-10 responses during the convalescent phase correlated significantly with the frequency of subsequent wheezing episodes, implying that certain cytokine responses in vitro, such as elevated IL-10, may predict recurrent nonasthmatic wheezing in young children. Recent studies have shown that IL-10 levels actually are suppressed, when compared with healthy controls, in patients with atopic asthma and other conditions characterized by chronic inflammation of the airways.11,12 Reduced levels of IL-10 may play a role in the pathogenesis of chronic airway inflammation, and, as an outcome measure, the levels of this antiinflammatory cytokine may distinguish atopic asthma from other nonatopic wheezing conditions common in young children, such as wheeze secondary to RSV infection.

ENO

ENO, a marker of inflammation, can be used as an aid in the diagnosis of asthma and as an outcome measure in young asthmatic children. In a study that included children 6 to 11 years of age with mild-to-moderate asthma, baseline nitric oxide (NO) levels were significantly elevated in the children with asthma when compared with nonasthmatic children (Fig 7).13 During treatment with the LTRA montelukast, ENO levels significantly decreased. Two weeks after montelukast treatment ceased, however, NO levels returned toward baseline.

A separate, double-blind, 2-week crossover study examined the effects of montelukast treatment on NO levels in children 6 to 15 years of age also receiving inhaled corticosteroid or β-agonist therapy.14
When compared with placebo treatment, montelukast reduced NO levels by 20%—but did not normalize them. These results show that the addition of montelukast further reduces the inflammatory response in children receiving either β-agonist alone or combined with inhaled corticosteroid therapy. The level of ENO appears to be a sensitive marker of inflammation in these young patients and, therefore, ENO measurements may be a noninvasive objective outcome measure, not only in identifying the presence of inflammatory diseases like asthma, but also in assessing responses to treatment.

CONCLUSION

Until the pathophysiology of childhood asthma is more completely understood, asthma symptomatology such as coughing and wheezing is likely to continue as a primary outcome measure in young children with asthma. Because the symptom profile of other respiratory ailments can mimic asthma in young children, and treatment can mask the presence of asthma symptoms, symptom assessment alone is not a sufficient outcome measure. Indeed, no single outcome measure is likely to provide an accurate diagnosis or evaluation of asthma interventions. The results of recent, controlled clinical studies in asthma suggest that certain nontraditional measures such as sRAW and alterations in the levels of certain markers of inflammation, including IgE, NO, and IL-10, are inflammation-sensitive measures and can be used successfully in asthma diagnosis, assessment of asthma therapy, and in evaluating the risk for the eventual development of asthma in very young children.

Although these findings are certainly encouraging, whether one or a combination of these outcome measures ultimately will be of routine clinical value remains uncertain. As our understanding of the pathophysiology and cellular mechanisms of asthma in children continues to improve steadily, the likelihood of identifying reliable, valid, and practical outcome measures in young children with asthma improves as well.

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