

What are the best estimates of pediatric asthma control?

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Purpose of review

To evaluate asthma outcome measures in the face of the variable nature of asthma. The outcome measures are divided into objective and subjective clinical measures, humanistic measures such as quality of life, and costs of asthma control.

Recent findings

Objective measures of asthma include those traditionally used such as spirometry, peak expiratory flow rate, and airway hyperresponsiveness. Recently, more attention has been geared towards markers of inflammation including exhaled nitric oxide and sputum eosinophils. Subjective measures of asthma control include patient-derived parameters such as number of wheezing episodes, nocturnal symptoms, exercise-induced symptoms, short-acting β -agonist use, steroid bursts, emergency-department visits, and hospitalizations. Asthma-related quality of life is related to asthma morbidity, and patients with better baseline quality of life have improved outcomes. Asthma-related costs include direct costs mostly comprised of hospitalizations and emergency-room visits, and indirect costs including school absenteeism.

Summary

There is no ideal outcome measure for evaluating pediatric asthma control, but each of these outcome measures must be used together to evaluate a patient at each outpatient visit. Patient-centered measures of asthma control must also be further incorporated into office visits for improved asthma management.

Keywords

asthma control, asthma outcomes

Introduction

Asthma is the most common chronic disorder of childhood with 9 million children under 18 years affected. The prevalence of asthma in the USA increased 160% between 1980 and 1994 in children under 5 years [1]. Asthma is characterized by reversible airflow obstruction and airway hyperresponsiveness (AHR). Despite the underlying pathophysiology of asthma many different phenotypes exist, making asthma a spectrum of disease. This inconsistency of asthma as a disease is most clearly manifested in the variable response of patients to therapy. In a study of 86 asthmatics, a good response to treatment with inhaled corticosteroids (ICS) was best correlated with the forced expiratory volume in 1 s (FEV₁) and blood and sputum eosinophils counts [2*].

In 2002, the National Asthma Education and Prevention Program (NAEPP) updated the guidelines for the diagnosis and management of asthma. These guidelines use clinical symptoms, peak expiratory flow rate (PEFR) variability, and FEV₁ to classify a patient's asthma severity and outline an asthma treatment plan [3]. Asthma severity is established by the guidelines prior to the initiation of treatment and reflects primarily the underlying severity of asthma, which may change only slowly over time. Asthma control is closely related to asthma severity but reflects a relatively short-term evaluation of the adequacy of patient management. Asthma control takes into account asthma severity as well as medical adherence, allergen avoidance, and the patient's perception of their asthma status. Determining asthma control allows for adequate adjustment of therapy. Asthma control is the ultimate outcome of patient management and allows identification of patients at risk of exacerbation [4**].

A patient's perceptions of asthma control also varies from that of guideline-determined, controlled asthma. In one study, 21% of parents described their children's asthma as very well controlled, and yet the child had visited the emergency room or required an acute outpatient visit for asthma in the last 3 months [5*]. In a retrospective study of 63 patients with asthma, almost 75% of asthmatic patients on controller medications had an episode of uncontrolled asthma over a 3-year period [6]. With varying asthma phenotypes, poor asthma-control perception, and growing costs of asthma, adequate asthma-control measures are necessary. Especially in children with asthma, outcome measures must be designed to identify children at risk for worsening of symptoms and progression of the disease into adulthood [7*].

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Abbreviations

AHR	airway hyperresponsiveness
eNO	exhaled nitric oxide
FEV ₁	forced expiratory volume in 1 s
HRQOL	health-related quality of life
ICS	inhaled corticosteroids
PAQLQ	pediatric asthma quality of life questionnaire
PEFR	peak expiratory flow rate

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In this review, clinical outcome measures of asthma, including objective measures such as spirometry, PEFR, and AHR, and biomarkers including exhaled nitric oxide (eNO) and sputum eosinophils are evaluated as well as subjective clinical measures, humanistic measures, and costs of asthma control. These asthma outcome measures together should provide a more complete picture of asthma control.

Objective clinical outcome measures: spirometry/peak expiratory flow rate

Spirometry and specifically FEV₁ have been used traditionally as an outcome measure in asthma reflecting large airway obstruction. In a retrospective study of 13 842 children [8], a progressive decrease in the number of asthma exacerbations was associated with an increase in FEV₁. In this study, FEV₁ was shown to be an independent predictor of asthma exacerbations, and children with a FEV₁ < 60% were twice as likely to have an asthmatic attack in the subsequent year than children with FEV₁ > 80% [8]. Another study of 698 adults in the USA and 195 adults in the Netherlands [9•] revealed that FEV₁ could also predict the risk of asthma exacerbation in the following 3 years.

Nevertheless, there have been no randomized control trials monitoring FEV₁ changes with asthma control, and it has been argued that FEV₁ is a poor marker of ongoing asthma inflammation [10]. It has been observed that eNO levels do not correlate with FEV₁ but do correlate with AHR [11]. Limitations of FEV₁ were also seen in the Childhood Asthma Management Program (CAMP) study where the baseline mean FEV₁ of enrolled patients was > 93% but one-third of those patients had required a steroid burst in the preceding 6 months [9•].

PEFR has been used widely due to its ability to screen airway obstruction in a simple and inexpensive manner. PEFR has also been shown previously to correlate with FEV₁, but it did not correlate well with β -agonist use or daytime symptom score [12]. In a randomized control trial of 168 children, patients who used a PEFR meter when symptomatic had a lower asthma severity score, fewer symptom days, and less health-care utilization than children who used PEFR daily or evaluated subjective symptoms alone [13]. Daily peak-flow monitoring has not been shown to be more effective than symptom monitoring alone in achieving asthma control, and PEFR can be insensitive to small-airway obstruction and airflow limitation [10,14••].

Daily use of PEFR has been perceived as not useful by most families and is an unrealistic expectation for children [15]. There is also a wide variation of PEFR on different charts, and there is a need for global standardization of PEFR [16•]. A study of asthmatic children

keeping peak flow diaries revealed the accuracy of recording at 56% during the first week, declining to < 50% over the subsequent 4 weeks [17]. PEFR has diurnal variation and significant day-to-day variation. It is difficult to use for children under 5 years of age, and a single measurement may be inaccurate. PEFR may be an important part of self-management plans for acute attacks along with proper education and symptom monitoring [10].

Airway hyperresponsiveness

AHR measures the exaggerated airway response to exogenous stimuli, which is a hallmark of asthma. AHR has been thought to reflect airway inflammation because it strongly correlates with inflammatory cell counts on bronchoalveolar lavage, but it may also correlate with the overall severity or remodeling in asthma [10,11].

AHR is often used for diagnosis of asthma. In a 2-year randomized control trial of 75 adults with asthma, when AHR was used to guide anti-inflammatory treatment, the patients had fewer exacerbations and more pronounced improvement of inflammatory changes in bronchial biopsy specimens than patients treated based on FEV₁ alone [18]. Nevertheless, AHR measurement is more technically difficult and time consuming, requiring 45–60 min to perform [10].

Exhaled nitric oxide

eNO, a noninvasive marker of airway inflammation, reflects increased expression of inducible nitric oxide in epithelial and inflammatory cells in the airway. It has been shown to correlate with sputum and peripheral eosinophilia, IgE levels, and AHR as a marker of inflammation, but does not correlate well with FEV₁ [19,20•]. eNO has also been shown to correlate with small-airway inflammation in mild asthma [21•]. It has been demonstrated to be higher in steroid-naïve asthmatics and during acute attacks. eNO has been shown to be higher in patients with insufficiently controlled asthma, and eNO levels are responsive to ICS therapy. eNO can be used in diagnosing the loss of asthma control as ICS are withdrawn and may be used to predict the risk of future asthma exacerbations [22•,23•,24•]. eNO can also help distinguish asthma from other disorders such as chronic obstructive pulmonary disease [25].

A recent randomized control trial of 97 asthmatics demonstrated that use of eNO measurements on a regular basis allowed a 40% reduction in maintenance doses of ICS needed to control asthma [26•]. In a study of 40 children with asthma on controller therapy with ICS, eNO was measured 2 and 4 weeks after discontinuation of ICS. eNO was found to be higher in children who were about to relapse [27•]. A prospective trial was performed

to evaluate the predictive value of eNO in diagnosing asthma. Using ROC curves, they demonstrated that eNO was a better test than exercise and equal to methacholine challenge as an aid in diagnosing asthma in patients presenting with non-specific respiratory symptoms [28[•]].

eNO levels are not specific to asthma and can also be increased in sinus disease and upper respiratory tract infections. The levels of eNO may also be falsely elevated if the patient has recently completed spirometry, exercised, or had a meal [29[•],30[•]]. The procedure has been found to be difficult in preschool children who must exhale slowly at a steady rate for 10–15 s [31[•]]. Costs of an eNO machine and establishing appropriate diagnostic cut-off values are still challenges at the present time.

Sputum eosinophils

Sputum induction has been used as a surrogate marker for airway inflammation, and higher sputum eosinophil counts have been seen in children with uncontrolled asthma over healthy children even in the presence of normal lung function. In 117 children in the CAMP study, sputum eosinophil counts correlated with other markers of inflammation including peripheral eosinophils and AHR. Children who required steroid bursts in the study had higher sputum eosinophil counts than those who did not require steroid bursts [32^{••}]. A study of 74 adults with asthma demonstrated that adjusting treatment regimens to 'normalize' sputum eosinophil counts reduced the number of asthma exacerbations and hospitalizations [33]. Sputum eosinophils may also serve as a potential marker for loss of asthma control.

Obtaining induced sputum requires technical expertise and may take on average 3 hours. In one study, 8% of children had bronchospasm after sputum induction even after pretreatment with albuterol [32^{••}].

Subjective clinical outcome measures

Subjective measures include patient-derived parameters such as number of wheezing episodes, nocturnal symptoms, exercise-induced symptoms, short-acting β -agonist use, steroid bursts, emergency-department visits, hospitalizations, and impact of asthma on daily life. In a recent review of hospital admissions in 31140 adult asthmatics, emergency-department visits and hospitalizations were strongly associated with preceding short-acting β -agonist prescription refills suggesting that these refills may be used as a marker for asthma morbidity [34^{••}].

A randomized control trial of 90 children comparing symptom monitoring and PEFr in asthma self-management plans found no differences in daily symptom score, lung function, quality of life, or health-service use between those who used symptoms alone to guide

asthma treatment and those who used PEFr [35]. In another study of 100 children and their parents, subjective symptom perception was compared to PEFr as a measure of present asthma severity. Children and parents were found to be inaccurate one-third of the time overall [36].

In a study of 12 children (6–14 years) with mild to moderate asthma, wheeze monitoring was used to determine asthma activity using an automatic wheeze-detection device overnight. Wheeze monitoring was found to provide quantitative, noninvasive information on nocturnal wheezing which correlated with both FEV₁ and AHR [37].

In a systematic review of risk factors associated with fatal or near-fatal asthma, increased short-acting β -agonist, oral steroids, and hospital admissions due to asthma all correlated with fatal or near-fatal asthma [38].

Humanistic outcome measures

Patient's perceptions of asthma control often vary from guideline-defined severity or clinician's rating of control. The primary concern for most patients is the burden of the disease on daily activities and the health-related quality of life (HRQOL) [39[•]]. In a cross-sectional study of data from 163 773 adult asthmatics, patients with self-reported asthma had more age-adjusted physically unhealthy days (6.5 versus 2.9 days), mentally unhealthy days, and days with activity limitation in the previous 30 days when compared with those without asthma [40].

Validated psychometric tools are needed to provide reliable and reproducible methods to measure subjective aspects of asthma control. Many generic and disease-specific validated tools are available to measure HRQOL including the generic quality-of-life short-form 12 (SF-12) and the pediatric asthma quality of life questionnaire (PAQLQ). These tests encompass four major domains, including physical and functional status, psychologic status, social interactions, and economic factors. In one study of 2854 patients, comparing various validated tests demonstrated that asthma symptom frequency is a major factor that influences patient's perceptions of their asthma burden. Other important factors included whether their asthma symptoms bother or interfere with daily activity. A history of previous asthma exacerbations is also a major concern for a patient's asthma control perception, and it is not measured by any of the tests [41[•]].

It has been previously shown in a study of 3482 asthmatics that better baseline asthma-specific HRQOL was associated with a decreased risk of asthma-related emergency-department visits or hospitalizations over

12 months [42]. Most of these tools are geared towards adults or the caregiver in pediatrics. A cross-sectional study of 185 adolescents with asthma (11–17 years) was performed using the PAQLQ. The results revealed that poor emotional quality of life was common in adolescent asthmatics and related to hospitalizations, emergency-department visits, and school absenteeism [43[•]]. Frequent mental distress was prevalent among 3226 asthmatic patients in the Behavioral Risk Surveillance System resulting in increased physical distress, activity limitation, and anxiety [44[•]].

A study evaluating the HRQOL in asthmatic patients evaluated 12 111 participants and found three modifiable factors associated with poor HRQOL. These factors were smoking status, physical activity, and body mass index. Among patients with poor HRQOL the elderly, female, poorly educated, and low-income patients were more prominent [45].

It has not been demonstrated clearly whether clinical parameters of lung function translate into improvements in HRQOL. In a retrospective study of patients with asthma of varying severities, patients were assessed with the Juniper Asthma Quality of Life Questionnaire. The study revealed that lung function was not an independent predictor or determinant of HRQOL at any asthma severity whereas intensity of shortness of breath predicted HRQOL at all levels of asthma severity [46].

HRQOL measurements should become routine parts of asthma control evaluation, but they currently remain a research tool. These measurements have drawbacks including most measures are parent directed in the pediatric setting and are prone to respondent expectations and biases. Psychosocial factors may alter responses including socioeconomic status, recent stressors, or tendency towards anxiety or depression. These measures must also be used in conjunction with other asthma outcome measures to determine asthma control.

Economic outcome measures

Health-care costs in asthma are primarily a concern for managed care organizations. Most direct costs of asthma result from physician services including outpatient visits, emergency-department visits, and hospitalizations. Patients with severe or difficult-to-treat asthma account for a larger share of health-care costs than do patients with well-controlled asthma. Twenty percent of patients with asthma have frequent exacerbations, but they account for 80% of total direct costs of asthma [47^{••}]. Identifying the patients at risk of hospitalization not only decreases asthma costs but also preventable hospitalizations. In a study of 230 hospitalized children with asthma, 93% were non-white, 74% had public insurance, and 44% were cited by the inpatient physician as

preventable, primarily caused by non-compliance and poor follow-up [48].

Asthma-control questionnaires

Recently, several validated tools have been designed to focus more on global asthma control in the short-term including the Asthma Therapy Assessment Questionnaire (ATAQ), the Asthma Control Questionnaire, and the Asthma Control Test [49[•],50] (Table 1). The ATAQ questionnaire has been cross-sectionally, prospectively and retrospectively validated to predict past and future health-care use for asthmatics. In this questionnaire, individuals scoring a 3–4 were at 3.5 times increased risk of future exacerbations above those with a score of 0 [4^{••}]. The Childhood Asthma Control Test is a seven-item assessment of asthma control completed by the child and parent/caregiver. It is designed to identify children (4–11 years of age) whose asthma is inadequately controlled (Fig. 1). The score ranges from 0 to 27 with higher scores indicating better asthma control. A score of 19 or less indicates inadequately controlled asthma. The Childhood Asthma Control Test has been validated against clinical measures of asthma control in a cross-sectional study of 344 patients and their caregivers [52].

Conclusion

In conclusion, there is no ideal outcome measure for asthma control. An ideal outcome measure must be simple and practical to perform in the clinical setting. It must reflect both short and long-term control and identify patients at risk of worsening [39[•]]. Each outcome measure has its advantages and disadvantages, as outlined previously. With further focus on the spectrum of asthma and variable asthma phenotypes, we must aim to use these outcome measures in conjunction with one another to achieve optimal asthma control. Patient-centered measures of asthma must be further incorporated into office visits for asthma and in evaluation of asthma control. Asthma education plans for each patient must be designed to empower patients and families to become involved in their health care and prepare for acute situations. These plans can help prevent acute-care visits and decrease anxiety associated with a diagnosis of asthma.

Table 1 Comparison of asthma-control questionnaires

	Asthma Control Test	Asthma Therapy Assessment Questionnaire	Asthma Control Questionnaire
Limits daily activities	Yes	Yes	Yes
Shortness of breath	Yes	No	Yes
Disrupts sleep	Yes	Yes	Yes
Albuterol use	Yes	Yes	Yes
Effect on global control	Yes	Yes	No
Frequency of wheeze	No	No	Yes

Adapted from [51].

This test will provide a score that may help your doctor determine if your child's asthma treatment plan is working or if it might be time for a change.

Step 1 Let your child respond to the first four questions (1 to 4). If your child needs help reading or understanding the question, you may help, but let your child select the response. Complete the remaining three questions (5 to 7) on your own and without letting your child's response influence your answers. There are no right or wrong answers.

Step 2 Write the number of each answer in the score box provided.

Step 3 Add up each score box for the total.

Step 4 Take the test to the doctor to talk about your child's total score.

If your child's score is 19 or less, it may be a sign that your child's asthma is not controlled as well as it could be. No matter what the score, bring this test to your doctor to talk about your child's results.

Have your child complete these questions.

1. How is your asthma today?

 0 Very bad	 1 Bad	 2 Good	 3 Very good
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2. How much of a problem is your asthma when you run, exercise or play sports?

 0 It's a big problem, I can't do what I want to do.	 1 It's a problem and I don't like it.	 2 It's a little problem but it's okay.	 3 It's not a problem.
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3. Do you cough because of your asthma?

 0 Yes, all of the time.	 1 Yes, most of the time.	 2 Yes, some of the time.	 3 No, none of the time.
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4. Do you wake up during the night because of your asthma?

 0 Yes, all of the time.	 1 Yes, most of the time.	 2 Yes, some of the time.	 3 No, none of the time.	☐
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Please complete the following questions on your own.

5. During the last 4 weeks, on average, how many days per month did your child have any daytime asthma symptoms?

5 Not at all 4 1-3 days/mo 3 4-10 days/mo 2 11-18 days/mo 1 19-24 days/mo 0 Everyday

6. During the last 4 weeks, on average, how many days per month did your child wheeze during the day because of asthma?

5 Not at all 4 1-3 days/mo 3 4-10 days/mo 2 11-18 days/mo 1 19-24 days/mo 0 Everyday

7. During the last 4 weeks, on average, how many days per month did your child wake up during the night because of asthma?

5 Not at all 4 1-3 days/month 3 4-10 days/month 2 11-18 days/month 1 19-24 days/month 0 Everyday

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 136–137).

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