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Measures of asthma control

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Abstract

Purpose of review—Over the past decade, the concept of asthma control as distinct from asthma severity has been clearly defined. Well controlled asthma is the goal of therapy in all asthma patients. This review is a comprehensive description of the tools currently available for a methodical assessment of different aspects of asthma control in clinical practice and research.

Recent findings—Several questionnaires for assessing asthma control have been extensively validated in adults. In children, validation data are less extensive. Considerable overlap exists between asthma control measures and measures of asthma-specific quality of life. Asthma-specific quality-of-life questionnaires have been used as primary outcome measures in major clinical trials evaluating asthma therapy. Biomarkers that reflect eosinophilic inflammation of the airways are used as intermediate outcome measures to reflect the biological basis of asthma control. There is some controversy, however, over which biomarkers are best incorporated into therapeutic algorithms that attempt to achieve maximal asthma control while minimizing treatment intensity.

Summary—In designing clinical studies to evaluate different asthma therapies, researchers will find this review to be a useful resource in terms of choosing the appropriate tool for assessing asthma control. This is also a valuable resource for a methodical assessment of response to asthma therapy in routine clinical care.

Keywords

asthma; asthma control; biomarkers; quality of life; questionnaires

INTRODUCTION

Recent international guidelines for the assessment and monitoring of asthma have defined the concepts of asthma severity and asthma control [1,2]. Asthma severity is an inherent trait of the patient that reflects the intrinsic intensity of the disease process, which is more or less constant [1]. Asthma control is the degree to which manifestations of the disease are reduced or removed by therapy [1]. Asthma control is not intrinsic to the patient and can fluctuate over time. Two domains of asthma control are identified in the guidelines: current impairment and future risk [1,2]. Current impairment includes the extent of asthma

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Conflicts of interest

There are no conflicts of interest.

symptoms, the degree of activity limitation, and asthma-related quality of life. The risk domain of asthma control is defined by the presence of adverse outcomes such as exacerbations, accelerated decline in lung function, or treatment-related side effects. The clinical manifestations of asthma have wide patient variability in frequency and intensity. Hence no single asthma symptom is ideal for the comprehensive assessment of asthma control [2]. This review focuses on the methods currently available for assessing asthma control in clinical practice and in research.

ASSESSMENT OF ASTHMA SYMPTOMS AND ASTHMA-RELATED QUALITY OF LIFE

Typical asthma manifestations such as cough, wheeze, dyspnea, activity limitation, nocturnal awakening, and airway obstruction are characterized by marked variability. Consequently, they require frequent monitoring to document their occurrence and to assess their impact on patients. In asthma research, the methodical assessment of asthma symptoms and asthma-related quality of life is best achieved with standardized instruments, such as asthma diaries or asthma questionnaires [1,2]. Systematic monitoring of asthma symptoms with diaries and questionnaires may also have a place in routine clinical care.

Asthma diaries

Asthma diaries are designed to collect information about asthma-related events on a daily basis. The American Thoracic Society/European Respiratory Society guidelines recommend that the frequency and intensity of asthma symptoms as well as their impact on patient activities be included in asthma diaries [1]. In addition to questions assessing asthma symptoms, some diaries include questions about the occurrence of an exacerbation such as use of systemic corticosteroids for asthma or an unscheduled contact with a healthcare provider for asthma [3–5]. A measure of lung function such as peak expiratory flow rate (PEF) and/or spirometry (FEV1) is often included in asthma diaries [3,6–8].

Asthma diaries are considered a special form of questionnaire and thus require the same degree of validation and standardization as other asthma questionnaires [1]. A few asthma diaries such as the Pediatric Asthma Diary (PAD) [9], Pediatric Asthma Caregiver Diary (PACD) [5], the daytime and nocturnal asthma symptom diary scales [4], and the Asthma Control Diary (ACD) [6] have been validated for use in clinical practice and clinical trials. Despite the availability of these validated asthma diaries, many clinical trials use customized asthma diaries based on their specific research requirements [3,10]. There is a need to develop a standardized asthma diary that is broadly accepted for use in different clinical studies so as to facilitate the comparison of composite outcome measures across multiple studies.

One major benefit of asthma diaries is that they are not limited by patient recall and hence provide a more realistic assessment of asthma control. Another advantage is that adverse events are monitored and recorded in real time with an opportunity for timely intervention. There are potential concerns with the use of paper diaries including the risk of missing substantial amounts of data, retrospectively completed data, incorrect data, or fabricated data

[11–13]. A potential remedy is to use other means to collect more accurate and time-verified data such as telephone-administered diaries, online diaries, or handheld electronic diaries [13–15]. There are currently no standardized validated handheld electronic asthma diaries for use in clinical practice or clinical trials. Another concern with diary data in clinical trials is the large quantity of data collected per patient [1]. In analyzing data derived from asthma diaries, mixed model (or other equivalent) analyses should be used so as to account for the large quantity of longitudinal data [7,8,10,16].

Overall, there is little standardization in the methods used by different studies to report outcome data from asthma diaries [3,7,8,17]. Some studies report asthma control as either the proportion of symptom-free days [18] or the number of symptom-days per week [10]. There is an advantage to reporting diary-derived data using symptom-free days or symptom-days because this information can be useful in cost-benefit analyses. Other studies report the proportion of patients with at least one event [3]. This method measures the impact of treatment at the population level. It has the advantage of an uncomplicated power analysis during study design. The annualized rate of events [3] is another method for reporting diary-derived data in asthma research. This method takes into account the number of events in the population and thus has a greater bearing on healthcare resource use. Its shortcoming is that a small group of patients may account for a large number of events. Time to first event [19] is also used to report asthma diary-derived data especially in studies designed to assess the effect of therapy on disease progression. In clinical studies, asthma events from diaries have also been reported as a composite variable. In a recent study, several individual events from asthma diaries were combined into a multidimensional variable of poor asthma control and used as the primary outcome [3]. In that study, an episode of poor asthma control (EPAC) was defined by the occurrence of at least one of the following events: a significant increase in frequency of rescue medication use for asthma symptoms, the occurrence of an unscheduled contact with a healthcare provider for asthma, use of systemic corticosteroids for asthma, or a significant drop in lung function from baseline [3].

Questionnaires for assessing control of asthma symptoms

Asthma symptom questionnaires combine several individual variables to generate a composite score [1,20,21]. The goal is to provide a complete evaluation of asthma-related manifestations over a defined period, typically between 1 week and 1 month [22–26]. Asthma questionnaires are either self-administered [27] or completed by a healthcare provider during clinic or study visits [23,25,26]. Questionnaire items typically relate to the frequency and impact of daytime symptoms, night-time symptoms, activity limitations, as well as a measure of lung function [1,2,20]. There is no consensus regarding which items should be included in questionnaires designed to assess asthma control. The choice of items included in current asthma questionnaires is based on expert opinion, focus group discussions, or both [23,25–27]. A list of questionnaires used to assess control of asthma symptoms is presented in Table 1. In adults, the Asthma Control Questionnaire (ACQ) [27] and the Asthma Control Test (ACT) [25] are well validated and frequently used in clinical trials. The ACT is available in the public domain for free and can be used in clinical practice. The ACQ requires permission from the company that holds the copyright before it can be used in research or in clinical practice. In children, the Childhood Asthma Control

Test (c-ACT) [28] is well validated for assessing asthma control in children aged 4–11 years. The ACQ [27] has also been validated for use in assessing asthma control in children aged 6–16 years [29■].

Data obtained from asthma questionnaires are usually expressed as a composite score. Composite scores from asthma questionnaires allocate the same weight to all items even though some symptoms may have more impact on individual patients than others. There has been an attempt with the Asthma Symptom Utility Index (ASUI) [30] to integrate the patient's preferences for various asthma-related manifestations. The ASUI is not extensively validated and a minimally important difference (MID) has not been defined.

Asthma questionnaires have been most useful in evaluating the efficacy of various therapeutic interventions for asthma in the context of clinical trials [3,7,10,17,22,31]. Composite scores from asthma questionnaires are more easily analyzable than asthma events from diaries. However, diary-derived outcome measures are more clinically interpretable and are therefore more meaningful to the clinician and the patient. One limitation of asthma questionnaires is that they do not adequately assess the risk domain of asthma control because exacerbations, treatment-related side effects, and lung function decline are not included in these interval questionnaires [1]. However, in one study, a low ASUI score (more symptoms) was predictive of an exacerbation and an EPAC occurring within the next month [32]. Another limitation of asthma questionnaires is their dependence on patient recall [33]. The recall period of 1–4 weeks is somewhat arbitrary and the accuracy of patients in distinguishing different timeframes has not been determined [6,32]. McCoy *et al.* [32] showed that a 2-week recall of asthma symptoms was essentially the same as a 52-week recall in terms of predicting a subsequent exacerbation or an EPAC. Another concern with asthma questionnaires is that patients may improve adherence to medications in the days before a clinic visit and thus scores may not represent true asthma control over a longer period [6,34]. Asthma control questionnaires evaluate the goals of care from the perspective of healthcare providers and expert panel guidelines. Hence, they fail to include the patient's perspective by not assessing the impact of the disease on their daily activities and overall quality of life.

Questionnaires for assessing asthma-related quality of life

One of the goals for controlling asthma-related impairment as stated in the EPR-3 2007 guidelines is to meet the patient's expectation of satisfaction with asthma care [2]. Asthma-related quality-of-life questionnaires assess the impact of asthma symptoms on the patient's daily activities as well as the patient's perspective on the overall effectiveness of asthma therapy [1]. Asthma-related quality-of-life instruments assess emotional, social, and occupational impairments [35–38]. However, other domains of general quality of life such as mental health, occupational satisfaction, income, creativity, and so on are not assessed in asthma-related quality-of-life questionnaires. A list of questionnaires currently used to assess asthma-related quality of life is presented in Table 1. Among adults, the Asthma Quality-of-Life questionnaire (AQLQ) [36], the Mini-AQLQ [35], the AQLQ-Mark [39], Living with Asthma Questionnaire (LWAQ) [40], and the Asthma Questionnaire-20 (AQ20) [41] are frequently used. The St. George's Respiratory Questionnaire (SGRQ) [42], which is

a general respiratory disease quality-of-life questionnaire, is also used in asthma research. Generic health status questionnaires such as the SF-36 quality-of-life questionnaire [43] and the SF-12 questionnaire [44] have been used in asthma patients as well. The Pediatric Asthma Quality-of-life Questionnaire (PAQLQ) [45] and the Pediatric Asthma Caregivers Quality-of-life Questionnaire (PACQLQ) [37] are two available questionnaires for assessing asthma-related quality of life in children.

Asthma-related quality-of-life questionnaires have emerged as an important tool for assessing asthma therapy in recent clinical trials [46■■,47■■]. The primary outcome measure in a recent randomized controlled trial to evaluate the effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma was the change in AQLQ score from baseline [46■■]. The study showed that a larger proportion of patients who underwent bronchial thermoplasty compared to placebo had a statistically significant and clinically meaningful improvement in the AQLQ score of 0.5 points or greater. On the basis of these results, the device used for bronchial thermoplasty has been approved by the Food and Drug Administration (FDA). Likewise, the mean MiniAQLQ score was the primary outcome measure in a recent open-label trial to evaluate the effectiveness of leukotriene-receptor antagonist (LTRA) versus inhaled glucocorticoids as initial treatment for asthma [47■■].

Measurement properties to consider when choosing asthma questionnaires

According to published quality criteria for review and comparison of health status questionnaires, the key measurement properties to consider when selecting asthma questionnaires include validity, reliability, responsiveness and interpretability [48,49]. The cost and copyright restrictions also need to be considered [50].

Validity

Validity is the degree to which an instrument actually measures what it purports to measure [48,49]. In selecting an asthma questionnaire, the dimensions of validity to consider include content validity, face validity, construct validity, criterion validity, and predictive validity. Content validity is the extent to which all the components assessing asthma control or asthma-related quality of life are comprehensively sampled by the items in the questionnaire. Face validity is a type of content validity which involves a review of the contents of the questionnaire by an expert panel to determine if the items included seem appropriate. Construct validity evaluates whether an asthma questionnaire correlates with other asthma variables or asthma outcome measures in a predictable manner, such as correlation of asthma questionnaire scores with FEV_1. Construct validity is also referred to as convergent validity or discriminant validity. Criterion validity refers to the extent to which scores on a questionnaire correlate with a ‘gold standard’ instrument used to measure the same construct. Some authors use physician assessment of asthma control or other validated asthma control tools as the ‘gold standard’ measure of asthma control [51]. Others have argued that there is no ‘gold standard’ for measuring asthma control and thus criterion validity cannot be assessed [50]. Predictive validity is a form of criterion validity that examines an instrument’s ability to predict a subsequent event, such as the ability of an asthma questionnaire to predict the occurrence of an exacerbation during a defined period of time.

Reliability

Reliability is defined as the degree to which an instrument is free from random error [48,49]. In evaluating the reliability of asthma questionnaires, the internal consistency reliability and the test-retest reliability are used. Internal consistency reliability evaluates the extent to which the individual items on the questionnaire are correlated. It is estimated by calculating the Cronbach's coefficient alpha. Values of Cronbach's alpha between 0.70 and 0.95 generally indicate good internal consistency. Reproducibility or test-retest reliability quantifies the degree to which repeated measurements in stable asthma patients provide similar results. The intraclass correlation coefficient (ICC) and the Kappa coefficient (κ) for continuous data and categorical data, respectively, are used to assess test-retest reliability. An acceptable standard is typically a value of ICC or k at least 0.75.

Responsiveness

Responsiveness is the ability of an instrument to detect clinically important changes over time [48]. It is a measure of longitudinal validity and assesses the extent to which changes in questionnaire scores will correlate with changes in another measure of asthma control, such as specialist's rating of asthma control, changes in FEV_1, or changes in other validated asthma questionnaires over a defined period of time.

Interpretability

Interpretability is the degree to which a qualitative meaning can be assigned to the scores obtained from a questionnaire [48]. In addition to a statistically significant change in questionnaire scores, a minimal level of change in the score that is consistent with a real benefit is needed. The minimally important difference (MID) is the smallest change in score on a questionnaire that is clinically meaningful and would lead a clinician to consider a change in treatment [48,51]. The MID of a questionnaire is calculated by distribution-based (statistical) or anchor-based approaches [36,48,52].

Surrogate methods for assessing asthma control

Assessing asthma control is traditionally based on improvement in symptoms, rescue medication use, lung function and quality of life. Abnormal exaggerated inflammatory response in the airways plays a key role in the pathophysiology of asthma [53■,54]. Therefore, measuring the degree of airway inflammation is an important adjunct to the assessment of asthma control. Direct evaluation of the airways with bronchoscopy is invasive and therefore not ideal for frequent monitoring of airway inflammation. Analysis of induced sputum is a standardized minimally invasive technique for evaluating lower airway inflammation [55,56]. The procedure is labor-intensive and requires technical expertise [57]. The number of eosinophils in induced sputum is increased among asthmatic patients compared to nonasthmatic individuals [58]. Some studies have shown that high baseline sputum eosinophilia predicts good response to corticosteroid therapy [59,60]. Use of sputum eosinophil counts to guide asthma therapy reduces exacerbation rates compared to standard clinical assessment alone [61–64]. Analysis of induced sputum for eosinophilia therefore represents a valuable noninvasive method for assessing airway inflammation in asthma.

Nonetheless, widespread use of induced sputum analysis in clinical practice for assessing asthma control is still limited because of technical challenges.

Other noninvasive surrogate methods of assessing airway inflammation include measurement of the fractional concentration of nitric oxide in exhaled breath (FeNO), analysis of exhaled breath condensate (EBC), measurement of urinary leukotrienes, and measurement of serum eosinophilic cationic protein (ECP) (Table 2).

CONCLUSION

In summary, the clinical manifestations of asthma vary in frequency and intensity. Therefore, a standardized approach to the assessment of asthma control is necessary. In this review, we described the methods currently used to assess asthma control in clinical practice and research. These include asthma diaries, asthma questionnaires, and surrogate markers of airway inflammation.

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

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 92–93).

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KEY POINTS

- Asthma control is a multidimensional construct that measures the degree to which the goals of asthma therapy are achieved.
- Asthma control may be measured by standard questionnaires, which have strengths and weaknesses. The most widely used are the ACQ and the ACT.
- Asthma quality of life and asthma symptom utility scores are closely related indicators of asthma control, but attempt to take into account the impact of disease on a person's physical, social, psychological, and spiritual well being.
- Biomarkers may be used as surrogate outcome measures to assess the biological substrate of asthma control.

Table 1.

Questionnaires used for assessment of asthma control

Questionnaires for assessing control of asthma symptoms in adults			Questionnaires for assessing control of asthma symptoms in children			Questionnaires for assessing asthma-related quality-of-life		
Instrument[a]	Age range (years)	MID points[d]	Instrument[b]	Age range (years)	MID points[d]	Instrument[c]	Age range (years)	MID points[d]
ACT	≥12	3	c-ACT	4–11	NA	AQLQ-Juniper	17–70	0.5
ACQ	≥12	0.5	ACQ	6–16	0.5	MiniAQLQ	17–70	0.5
ATAQ	≥18	NA	c-ATAQ	5–17	NA	AQLQ-Marks	Adults	NA
ACSS	≥18	NA	CAN	2–14	NA	AQ20	Adults	NA
ASUI	Adults	NA	Breathmobile	2–14	NA	PAQLQ	7–17	0.5
LASS	18–64	7	PACT	1–18	NA	PCAQLQ	NA	0.5
ACCI	≥17	NA	FSAS	3–17	NA	AIS-6	18–56	4
SASCQ	≥12	NA	Quiz	1–17	NA	ITG-ASF	Adults	NA
30 s	≥19	NA	RCP	6–15	NA	ABP	Adults	NA
PCAQ	≥18	NA	TRACK	2–14	NA	SGRQ	Adults	NA
			SASCQ	≥12	NA	LWAQ	Adults	NA
						SF-36 or SF-12	Adults	NA

[a]Tools for assessing asthma control in adults. 30 s, Thirty second Asthma Test; ACCI, Asthma Control and Communication Instrument; ACQ, Asthma Control Questionnaire; ACS, Asthma Control Score; ACSS, Asthma Control Scoring System; ACT, Asthma Control Test; ASUI, Asthma Symptom Utility Index; ATAQ, Asthma Therapy Assessment Questionnaire; LASS, Lara Asthma Symptom Scale; PCAQ, Perceived Control of Asthma Questionnaire; SASCQ, Seattle Asthma Severity and Control Questionnaire.

[b]Tools for assessing asthma control in children. Breathmobile, Breathmobile Assessment of Asthma Control; c-ACT, Childhood Asthma Control Test; CAN, Asthma Control in Children; c-ATAQ, ATAQ for Children and Adolescents; FSAS, Functional Severity of Asthma Scale; LASS, Lara Asthma Symptom Scale; PACT, Pediatric Asthma Control Tool; Quiz, Asthma Quiz; RCP, Royal College of Physicians Three Questions; SASCQ, Seattle Asthma Severity and Control Questionnaire; TRACK, Test for Respiratory and Asthma Control in Kids.

[c]Tools for assessing asthma-related quality-of-life (adults and children). ABP, Asthma Bother Profile (22 items – 15 ‘bother’, 7 ‘self-management’); AIS-6, Asthma Impact Survey-6 (6 items); American version); AQ20, Asthma Questionnaire-20; AQLQ(S)-Juniper, AQLQ short version = MiniAQLQ, AQLQ-Marks; AQLQ, Asthma Quality of Life Questionnaire - Juniper = AQLQ(L) long version; ITG-ASF, ITG-Asthma Short Form; LWAQ, Living With Asthma Questionnaire (68 items); PAQLQ, Pediatric Asthma QOL Questionnaire; PCAQLQ, Pediatric Asthma Caregivers QOL Questionnaire; SF-36, Medical Outcomes Survey Short Form 36; SGRQ, St. George’s Respiratory Questionnaire (50 items).

[d]The minimally important difference (MID) for the questionnaire.

Table 2.

Surrogate biomarkers for assessment of asthma control

	Fractional concentration of nitric oxide in exhaled breath (FeNO)	**Exhaled breath condensate (EBC)**	**Urinary cysteinyl leukotriene E4 (LTE4) levels**	**Measurement of eosinophilic cationic protein (ECP)**
Source of biomarker	Excess nitric oxide (NO) is produced in the airways of asthmatic patients when L-arginine is oxidized to L-citrulline by the action of the inducible isotype of nitric oxide synthases (iNOS) [54,65]	EBC consists mainly of water vapor and bio-molecules from the aerosolized airway lining fluid [66]	Cysteinyl leukotrienes (CysLt) are produced in airway inflammatory cells by the action of 5-lipoxygenase on arachidonic acid [67], LTE4 is a stable end product of this pathway [67]	Eosinophilic cationic protein (ECP) is one of four major cationic proteins released by activated eosinophils in the airways of asthmatic patients [68]
Procedures for measurement	Procedures for quantifying FeNO have been standardized [69–71]	With the exception of EBC pH and H_2O_2, the techniques for analysis of EBC biomarkers are not well standardized [66]	Urinary LTE4 it is analyzed using liquid chromatography, tandem mass spectrometry, or enzyme immunoassays [67]	Commercially available immunoassays are used to measure ECP
Correlation with asthma severity and asthma control	Levels of FeNO directly correlate with sputum eosinophil counts and bronchoalveolar lavage (BAL) fluid eosinophilia [72–74]	Lower EBC pH levels indicate poor asthma control and pH levels increased after anti-inflammatory therapy [78–80]	High urinary LTE4 levels are also associated with acute asthma exacerbations [85,86]	Serum ECP levels increase during asthma exacerbations in children [88]
	NB. Some studies have been inconclusive [75–77]	EBC levels of IL-4, RANTES, 8-isoprostane, and CysLTs decrease with better asthma control [81–84]	High urinary LTE4 levels predict good response to leukotriene receptor antagonist therapy in asthma [87]	Sputum ECP levels are also elevated in adult asthmatics with poorly controlled asthma [89]
Pros	Newer devices for FeNO measurement are relatively cheap and the procedure is easy to perform thus multiple repeated tests can be performed.	Many cytokines and arachidonic acid derivatives can be analyzed from EBC	It is a cheap, reliable, indirect, noninvasive method for assessing airway inflammation especially in clinical research	ECP levels are measured in serum, sputum, saliva, nasal lavage fluid, bronchoalveolar lavage fluid, and urine
Cons	Studies evaluating the efficacy of tailoring asthma interventions based on FeNO levels compared to clinical symptoms have not shown a substantial reduction in exacerbations or better asthma control [90,91■,92,93,94■■]	Quantity and composition of the condensate is affected by the physical properties of the device used [95–98] Collection and analysis of EBC sample is time consuming and costly	Its role in assessing asthma control in clinical practice is yet to be determined	Its role in assessing asthma control in clinical practice is not yet determined