



Asthma control: how it can be best assessed?

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Purpose of review

A control-based asthma assessment is recommended by guidelines, but questions remain about how to assess the level of asthma control, and how current control status relates to future risks and biomarkers of disease pathogenesis. This review summarizes recent published data relating to asthma control and describes the challenges created by currently available instruments.

Recent findings

The current literature continues to show the widespread use of various assessment instruments for asthma control, in particular those with composite scores. However, poor correlations exist between the different assessment tools, and these instruments lack diagnostic accuracy to differentiate uncontrolled asthma. Whereas the concept of asthma control has been extended to add an assessment of future risks to the clinical control, clinical asthma control as measured by current available assessment tools does not necessarily relate to the intrinsic disease activity which is typically characterized by inflammation in asthma.

Summary

The application of asthma control assessment represents an improvement in asthma management. The measurement of underlying disease activity potentially by biomarkers to assess disease control will lead to an improved assessment of the overall control of asthma, and further studies addressing this are needed.

Keywords

asthma control, biomarker, comorbidity, exacerbation, inflammation

INTRODUCTION

The assessment of asthma control and a control-based management strategy have been widely accepted and incorporated in asthma guidelines [1,2]. A variety of tools are available to measure asthma control in both clinical trials and clinical practice. Recent data suggest that there may be some dissociation between the different assessment tools, and a limited correlation between the control status as measured by current available assessment instruments with inherent characteristics of the disease and various clinical manifestations. Furthermore, the concept of asthma control has been recently extended to include an assessment of future risk in addition to the previous focus on the current impairment from asthma [1,2]. Future risk has been identified to include the risk of severe asthma exacerbations, loss of lung function, as well as long-term side effects of therapies. Whereas these recent developments represent maturation of the asthma control concept, an improved approach to asthma control that addresses these findings and incorporates current evidence and leads to improved asthma management is lacking.

Therefore, in this review, we summarize recent data on the assessment of asthma control and give a perspective on the future direction of work optimizing the assessment of asthma control.

TERMINOLOGY

Asthma control is defined as the extent to which the various manifestations of asthma have been reduced or removed by treatment [1]. In the clinical setting, a graded classification system is used to characterize

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KEY POINTS

- The agreement between some assessment instruments of asthma control is poor.
- The identification of uncontrolled asthma using composite scores with current established cut-off points is problematic due to the low sensitivity.
- An assessment of overall asthma control involves the evaluation of clinical control, disease activity/control and the consideration of asthma-related comorbidities.
- Current status of clinical control and exacerbation risk are different components of overall asthma control that are not necessarily related.

asthma control status and to guide stepwise treatment. ‘Optimal’ asthma control status is applied to patients who have none or minimal symptoms of asthma and no or minimal impairment of functional status. ‘Uncontrolled’ asthma is recognized when patients fall short of the optimal level of control, and an intermediate status indicating a ‘suboptimal’ or partial control level can also be applied to grade the degree of loss of control (Table 1). This classification system, which is largely based around symptom frequency, also forms the basis of current global asthma management guidelines [2].

The aspect of the asthma control concept was addressed in a recent study by Janssens *et al.* [3[¶]]. Cluster analysis was used to identify subgroups of asthma control based on the measures of symptoms, activity limitation, rescue medication use and pulmonary function. Three clusters were identified

which were ‘well controlled asthma’, ‘poorly controlled asthma’ and a third cluster of patients with an intermediate level of control between ‘well controlled’ and ‘poorly controlled’ asthma. A similar grading system of asthma control has also been used in the Global Initiative for Asthma (GINA) guidelines [2], and therefore this study confirmed the guideline approach to asthma control classification.

The terminology that is used to describe the asthma control classification system among different academic societies and studies is, however, variable, as shown in Table 1. This can lead to some confusion and difficulties in understanding and comparing control status across the literature, and therefore there is a need for future work to harmonize the terminology that is used for the different categories of asthma control, making it standardized and unified. In this review, we have used the terminology defined by GINA [2].

ASSESSMENT TOOLS

A range of assessment tools for asthma control have been developed, and the following is a review of recent literature on these tools according to the assessment types.

Composite scores

Several assessment instruments using composite scores have been developed such as the Asthma Control Test (ACT), the Asthma Control Questionnaire (ACQ) and the Asthma Treatment Assessment Questionnaire (ATAQ). Each has also been assigned threshold scores which relate to different levels

Table 1. Terminology used among different assessment systems of asthma control

	Optimal	Worst		
Global Initiative for Asthma (GINA)	Controlled	Partly controlled	Uncontrolled	
Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ)	Well controlled	Not well controlled	Uncontrolled	
The Gaining Optimal Asthma Control (GOAL) study	Totally controlled	Well controlled	Uncontrolled	
Expert Panel Report 3 (EPR3), American National Heart, Lung and Blood Institute	Well controlled	Not well controlled	Very poorly controlled	
French Clinical Asthma Practice Guideline	Optimal controlled	Acceptable controlled	Unacceptable controlled	
New Zealand Patient Outcomes Management Survey (POMS)	Optimal controlled	Sub-optimal controlled	Not well controlled	Markedly out of control
British Guideline on the Management of Asthma	Complete controlled	Inadequate controlled		

of asthma control, and is believed to have priority and be preferred in different settings such as research/clinical practice, primary/secondary care and clinical trials/real-world setting [1]. The consistency between these assessment tools was evaluated in previous studies [4], where the agreement was shown to be poor to moderate. Jia *et al.* [5^{***}] compared the diagnostic performance of the ACT and ACQ in a systematic review which included 21 studies and 11 141 asthmatic patients. This research demonstrated that both the ACT and ACQ had good sensitivity and specificity in differentiating well controlled and not well controlled asthma. However, both asthma control assessment tools failed to identify uncontrolled asthma accurately. This study also identified that when the cut-off points were determined using a non-prespecified area under the curve (AUC) method, then these new cut-off points were capable of improving the diagnostic performance of the tests, to a level better than currently established values.

Ko *et al.* [6] subsequently found that a higher ACT cut-off value of 19 or less showed an improved sensitivity but reduced specificity compared with the established cut-off point of 15 or less for identifying uncontrolled asthma. This is expected given the reciprocal relationship between sensitivity and specificity. Similarly, an ACQ cut-off point of at least 1 was shown to better discriminate uncontrolled asthma in a real-world setting [7]. In children with asthma, a positive correlation between the score of the Children's Asthma Control Test (C-ACT) and GINA criteria has been observed [8–10]; however, several recent studies have demonstrated an inconsistency in uncontrolled asthma as defined by established C-ACT cut-off value (≤ 19) and GINA criteria [10–13], with C-ACT tending to underestimate uncontrolled asthma.

Therefore the cut-off point selection for the assessment tools with numeric scores seems to be challenging, and it may be necessary to consider the test performance in different settings. The use of these composite scores to identify uncontrolled asthma can be problematic in both adults and children with asthma, and the application of the results using certain cut-off points should be made cautiously. Further validation of the existing assessment tools is required. These findings also suggest a hypothesis that in the assessment of asthma control, there may be a need to develop and use different tools for different purposes, for example, ACT/ACQ to confirm well controlled asthma, and other assessment tools to detect uncontrolled asthma. The path to the assessment of asthma control also appears to be thorny because there is no 'gold standard' for

asthma control levels. The comparisons of these assessment instruments were made with GINA criteria being the reference; however, the GINA criteria are a consensus-based scheme [2]. The introduction of the future risk concept offers the possibility of validating the asthma control tools against this outcome, and initial results are promising [6].

New composite scores

Given the limitations of the classic composite scores as stated above, several recent studies have proposed some novel instruments for control assessment. These are largely based on symptoms and attempt to accommodate different settings. The Active Life with Asthma (ALMA) tool was developed aiming to provide a structure for a primary care asthma review [14], as was the Royal College of Physicians three questions (RCP3Q) morbidity score [15] and the mobile phone-based assessments [16,17]. Each of these has been compared to the classic assessment tools of the ACT or ACQ, but in general, there were no strong correlations between the measurements. Therefore, additional evidence is required to support the validity of these newer tools and define their use.

Symptoms-based assessments

Asthma symptoms perceived by patients themselves are important components and constitute a substantial weight in almost all the assessment instruments for asthma control. However, the specific symptoms that are perceived to be important by patients are unexpectedly different from those considered important by clinicians [18]. Patients' perception of control level is not paralleled with those defined by physicians using objective tools [19–21], particularly in uncontrolled asthma [22]. Patients with asthma are more likely to overestimate their asthma control, leading to a high risk of being undertreated potentially due to unwillingness to be adherent to prescribed medications. On the other hand, Rudell *et al.* [23] recently found that the understanding of asthma control in patients also extends beyond the usual clinical manifestations of respiratory symptoms and lung function. There is therefore inconsistency in the level of asthma control assessed by guidelines, composite scores and the patients' perspective.

Accordingly, one would assume that treatment adjustment based on symptoms and objective tools would lead to different outcomes in asthma management where the latter approach would show its superiority; however, this assumption seems to be spurious in terms of achieving asthma control. The approach of adjusting inhaler use based on symptoms [Single Inhaler Maintenance

and Reliever Therapy (SMART)] [24,25] to asthma management maintains achieving a similar level of asthma control when compared with fixed doses of inhaled corticosteroid/long-acting beta agonists (ICS/LABA) combination as controller and short-acting beta agonists as reliever. Indeed, in all assessment systems, either guideline criteria or those based on composite scores, the weight of each symptom compared to other items such as rescue medication use, physiological and biomarker measurement is undetermined, and more evidence is required to address how to incorporate symptom evaluation in the assessment of asthma control and the clinical consequences.

Biomarker-based assessment

Asthma is now recognized as a heterogeneous disease with wide variability in natural history, pathogenesis and thereafter the response to treatment. Alternative therapies have become available for asthma treatment with the advances in biotechnology, such as omalizumab (anti-IgE monoclonal antibody) and montelukast (a leukotriene receptor antagonist). Biomarkers may be quite important in this context as they reflect the biological/pathogenic processes and underlying disease activity.

The call for biomarker determination to assess disease activity and improve diagnosis and treatment of asthma is emphasized by the observation of a poor correlation between the multiple domains of asthma, including symptoms, physiological

characteristics and inflammation [1,26], and the discrepancy between surrogate makers and clinical asthma control as measured by current available instruments. Recent studies have examined this and found that whereas more patients with uncontrolled asthma had sputum eosinophilia compared with those with generally controlled asthma, the association between sputum eosinophils and asthma control was weak [27^{***}]. Melosini *et al.* [28] also found that pulmonary function and airway inflammation as assessed by sputum eosinophil count or fractional exhaled nitric oxide (FeNO) were not related to the ACT score in adults with asthma. Similarly in children with asthma, airway inflammation measured by FeNO showed poor accuracy in the differentiation of not well controlled asthma [29]. Furthermore, airway inflammation, either eosinophilic or neutrophilic predominant, persists in a large proportion of patients with well controlled asthma [28,30]. The significance of this is unclear. The finding that airway inflammation is not well correlated with clinical control of asthma may suggest that the measurement of a pathogenic process, particularly airway inflammation, beyond an assessment of clinical control, provides additional information of inherent disease activity (Fig. 1).

EXACERBATION RISK FOR ASTHMA CONTROL ASSESSMENT

The focus of asthma assessment has clearly shifted from a severity classification to a control-based

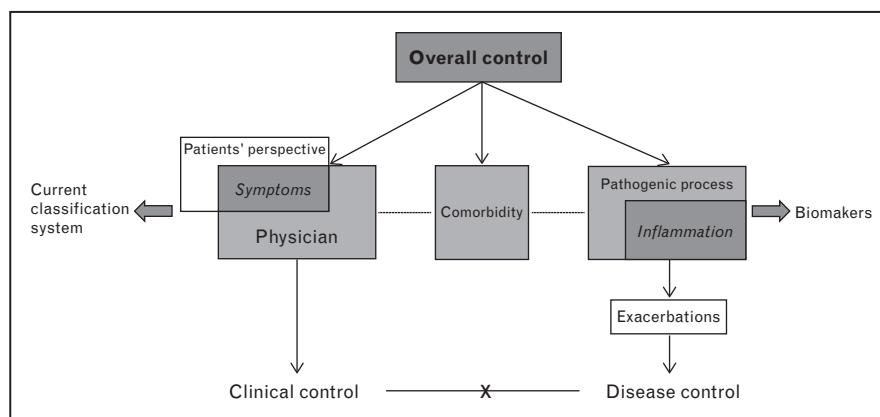


FIGURE 1. Illustration of the components of overall asthma control: overall asthma control can have multiple dimensions including clinical control, disease control and asthma-related comorbidity. Asthma symptoms perceived by patients are important components of physician assessment of asthma control, and constitute a substantial weight in current asthma control classification systems, whereas other criteria are also involved in the systems, for example, pulmonary function and medication use. These form the basis of an assessment of clinical control of asthma. Inflammation is the predominant characteristic of the pathogenic changes of asthma, and is a significant predictor of future exacerbations. It reflects the level of disease activity; therefore the measurement of inflammation is a marker of disease control. However, clinical control as measured by current instruments is poorly correlated with disease control/activity. Asthma-related comorbidity can worsen asthma control through a symptom misattribution effect or aggravate the pathogenic process.

strategy [2]. Current evaluation of asthma control is exclusively made according to the impairments that patients experience, for example, daytime and nocturnal symptoms, interference with activity, abnormality of lung function and rescue medication use. However, several recent guidelines and statements [1,2] extend the concept of asthma control by adding a domain of future risk, in particular, exacerbation risk, to the impairment assessment. Therefore, an assessment of exacerbation risk is an important component when looking into asthma control in both clinical practice and research.

Current control and exacerbation risk, however, appear to be different components of overall asthma control and are loosely associated (Fig. 1). Previous studies have shown that the baseline level of asthma control can predict subsequent exacerbations and asthma-related events [6,31], but it seems controversial in children where C-ACT failed to predict loss of asthma control in the future [11,32]. It is worth noting that patients with generally well controlled asthma are also at risk of exacerbations [33], indicating that other factors may be involved where inflammation can be an important predictor [33]. Inflammation, reflecting the intrinsic activity of the disease, is independently associated with current control status [28,30], and as stated above, persistent inflammation exists in patients with well controlled asthma [28,30]. In fact, previous studies have demonstrated the important role of inflammation in future exacerbations [34,35]. Several strategies of treatment adjustment to reduce exacerbations have been tested and compared to a regular physician-driven strategy which is largely based on an assessment of clinical control. Treatment adjusted according to sputum eosinophils significantly reduced exacerbation rate [36,37], whereas the FeNO-driven strategy had mixed effects [36–38]. Additionally, these clinical trials of inflammation-guided asthma treatment demonstrate an inconsistency between clinical asthma control and exacerbation risk, where the effect of inflammation-guided treatment on clinical asthma control is not in line with the benefit of exacerbation reduction [35,38].

Thus, an incorporation of measurement of airway inflammation, despite the technical difficulty in clinical practice, is presumably helpful in an improved overall asthma control assessment. Unfortunately, current well accepted tools for asthma control assessment fail to integrate any useful surrogate markers of inflammation or inherent disease activity to assess an overall control of asthma. An Asthma Intensity Manifestations Score (AIMS) developed by Schatz *et al.* [39[■]], integrating ACT, forced expiratory volume in 1 s, FeNO and Expert Panel Report 3 (EPR3) steps, seems to be promising

in this context and was shown to linearly correlate with adverse outcomes in the following year. The AIMS is considered a separate construct to clinical asthma control as it accesses the inherent severity of asthma and incorporates the assessments of functional status and inflammation, linking both clinical control and future exacerbation risk. It is a good starting point to show how the concept of asthma assessment has developed from an evaluation of clinical severity, to clinical control level, and now should involve assessment of the inherent disease severity. How to assess asthma control incorporating both the domains of impairment and exacerbation risk is still a question that challenges the current knowledge of asthma control and should be addressed in future studies.

COMORBIDITY

The most frequently studied asthma comorbid conditions include obesity, rhinitis, gastroesophageal reflux disease and obstructive sleep apnoea [40]. It is well recognized that these asthma-related comorbidities are associated with poor asthma control [41,42], but are rarely addressed in current classification systems for control assessment. It is notable that comorbidity is one of the modifiable factors among predictors related to asthma control [43]; therefore an improved recognition and intervention of asthma comorbidity will contribute to a comprehensive and better assessment and achievement of asthma control. However, some confusion exists regarding how comorbidity affects asthma control. The question is whether it is via symptom misattribution or through specific pathways that the comorbidity causes worsening of asthma control. Examples are obesity and gastroesophageal reflux disease. Limited physical activity due to obesity may aggravate the perception of dyspnoea and increase symptoms in obese asthmatic patients, and it is difficult to tell if the symptoms are due to asthma or the comorbidity. An intervention study by Farah *et al.* [44] showed that obesity is related to poor asthma control and accounts for the majority of residual symptoms after ICS treatment, independent of inflammation measured by FeNO and lung mechanics. It is also possible that neutrophilic airway inflammation and systemic inflammation [45,46] may be involved in the interaction between obesity and poor asthma control. Rhinitis, which is considered a condition that shares common inflammatory mechanisms with asthma, is also known to complicate the management of asthma. Treated rhinitis is associated with not only reduced asthma symptoms [47] but also reduced asthma-related emergency visits [48]. It is likely that

asthma-associated conditions complicate the disease *per se* through multiple aspects (Fig. 1).

CONCLUSION

The approach of asthma control and a control-based management strategy has been associated with overall improvement in mortality and morbidity from asthma. However, many unanswered questions remain regarding how to best assess overall asthma control level. Current instruments for control assessment are not consistent between each other, and the identification of uncontrolled asthma using composite scores is problematic due to a low sensitivity. Disease control by minimizing the underlying pathogenic process, which can be determined by relevant biomarkers, appears to be a different component from clinical control as measured by current assessment systems. Thereby an incorporation of biomarker measurement will help in estimating exacerbation risk, constituting another important domain of the overall asthma control. More data and effort are needed regarding a better assessment approach of overall asthma control, which integrates the evaluation of clinical control, disease control and comorbidity, aiming at an improved assessment and management of asthma.

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Conflicts of interest

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