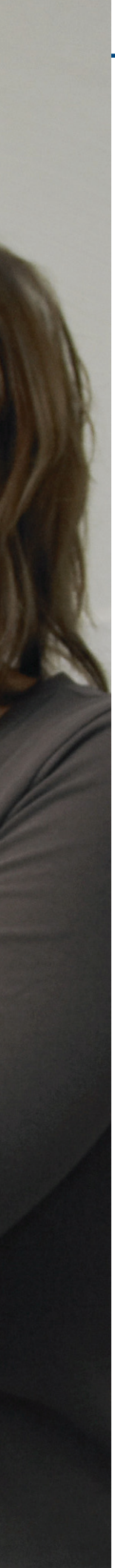
Key points

- Asthma control is the most important dynamic indicator of the current status of the patient's level of disease.
- Asthma control can be monitored by a range of methods, from physiological measures to patient questionnaires.
- It is desirable to use a composite measure, including lung function measurements, symptom scores and quality-of-life indices.



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Asthma control: evidence-based monitoring and the prevention of exacerbations

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Educational aims

- To define optimal asthma comtrol.
- To describe the strengths and weaknesses of objective and subjective measures of asthma control.
- To suggest the best tool for assessing asthma control.

Summary

Recent guidelines have advocated a change in approach to asthma management, with a focus on control rather than severity. However, the concept of asthma control has different meanings to healthcare professionals, patients, regulators and health insurers. Consequently, there is a range of measures of control. Traditional measures of lung function are an important indicator of severity, but are insufficient as an index of asthma control. Similarly, levels of inflammation and bronchial hyperresponsiveness have their advantages and limitations as measures of asthma control. From a more subjective point of view, tools such as asthma questionnaires can provide a valuable insight into patients' perception of their condition. It therefore seems sensible to propose that indices of asthma control be sought that combine the benefits of the above approaches in a way that allows a satisfactory classification of asthma control.

Despite the availability of highly effective pharmacotherapy, poorly controlled asthma is reported in up to 70–95% of patients in western Europe and the Asia-Pacific region [1, 2]. Nonetheless, the 2002 Global Initiative for Asthma (GINA) report stated: "it is reasonable to expect that in most patients with asthma, control of the disease can and should be achieved and maintained" [3]. To meet this challenge, the 2006 GINA report not only incorporated updated scientific information but also described a development of this theme (table 1) [4]. Components that contribute to an assessment of control include: 1) daytime symptoms; 2) limitation of activities; 3) nocturnal symptoms and nocturnal awakenings; 4) the use of rescue medications; and 5) objective assessment of lung function. Interestingly, the 2006 GINA guidelines recommend a change in approach to asthma management, with asthma control, rather than asthma severity, being the focus of treatment decisions [5].

The proposed control-driven approach involves an iterative cycle of assessment, treatment and adjustments to maintain asthma control, with control as the target. This paradigm shift for asthma care reflects progress in the pharmacological care of patients [4].

In addition, the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines from the USA noted that ongoing monitoring of the degree of asthma control is essential in allowing patients to achieve the goals of asthma therapy [6]. They have also noted that when asthma is not controlled, it is associated with increased asthma burden, decreased patient quality of life (QoL), and increased use of healthcare resources [6]. The NAEPP guidelines describe three levels of

Table 1 Levels of asthma control

Level of control	Characteristics					
	Daytime symptoms	Limitations of activities	Nocturnal symptoms/ awakening	Need for reliever/ rescue treatment	Lung function (PEF or FEV_1)#	Exacerbations¶
Controlled (all of the following required)	None (twice or fewer per week)	None (twice or fewer per week)	None	None (twice or fewer per week)	Normal	None
Partly controlled (any measure present in any week	More than twice a week	Any	Any	More than twice a week	<80% pred or personal best (if known)	One or more per year
Uncontrolled	Three or more features of partly controlled asthma present in any week					One in any week+

PEF: peak expiratory flow; FEV_1: forced expiratory volume in one second; % pred: % predicted. #: lung function is not a reliable test for children aged ≤5 yrs; ¶: any exacerbation should prompt a review of maintenance treatment to ensure that it is adequate; +: by definition, an exacerbation in any week makes that an uncontrolled asthma week. Modified from [4] with permission from the publisher.

Box 1 Components of asthma control from NAEPP guidelines.

- Frequency of patient symptoms.
- Frequency of night-time awakenings.
- Interference with normal activity.
- Frequency of short-acting β_2-agonist use for symptom control.
- FEV_1 or PEF levels.
- Scores on validated asthma questionnaires.

FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow.

asthma control: well controlled, not well controlled, and poorly controlled. Components of control in these 2007 NAEPP guidelines are listed in Box 1.

It is clear that asthma control is the most important dynamic indicator of the current status of the patient's level of disease, and is the most useful index in judging the need for adjustments in the patient's treatment plan. While severity is important in initial treatment planning, it is not useful as an index of fluctuations in the intensity of the patient's asthma. Assessment of the level of control involves a balanced evaluation of several variables. It should involve subjective information involving patient symptoms and level of function, as well as an objective measure of lung function, such as spirometry.

What is asthma control?

Currently, asthma control is measured in ways defined by healthcare professionals (*e.g.* use of reliever medication, lung function and need for unscheduled healthcare). Conversely, there are real differences in what asthma control means, depending on the specific person who defines or describes it. To the patient, asthma control means no symptoms that interfere with normal lifestyle, no exacerbations, normal quality of life, no missed school or work, and no side-effects. To care-givers (parents), it additionally means that the child is able to get to school and there is no interference with sleep. However, to the primary care provider it is few exacerbations, no unscheduled visits and no hospital admissions (maintenance of peak expiratory flow (PEF)). Finally, to the respiratory specialist it is no symptoms, maintenance of lung function (forced expiratory volume in one second (FEV_1)), few exacerbations and no admissions (decreased bronchial hyperresponsiveness (BHR) and decreased inflammation). Obviously, the regulatory authorities ask for improvement in morning PEF, or FEV_1, and symptom scores (and QoL), but in the case of the health insurer it is simply low healthcare costs (emergency department visits, hospitalisations and drug costs).

The big issue that explains and justifies these discrepancies is linked to the fact that the diagnosis and assessment of asthma has not yet been standardised. In effect, standardisation has not occurred because of wide interindividual variation in the natural history of asthma, symptoms produced and response to therapy, and also because objective physiological measures of the disease often do not correlate with symptoms, resulting in diverse clinical end-points. It is fundamental to highlight that, although asthma is routinely classified as intermittent, mild, moderate or severe, the severity of asthma changes over time. Consequently, asthma control can be expected to change over time. This clearly indicates that asthma control should be assessed at every clinical encounter, and management decisions should be based on the level of asthma control. Unfortunately, this is not what usually happens in real life and, in any case, specialists still are trying to define the best monitoring strategy for optimal control of disease. Many parameters and outcomes have been suggested for measuring asthma control, all with strengths and weaknesses (figure 1) [7].

Physiological measures: insight into clinical outcomes from evaluation of lung function?

Spirometric measures, principally FEV1, have long been used as markers of the degree of airways obstruction. The NAEPP has endorsed the use of objective measures of lung function to assign a severity rating to patients with asthma [6]. The purpose of such a severity rating is to guide asthma therapy, and the major assumption underlying it is that different levels of FEV1 (expressed as % predicted) suggest particular risks of adverse disease outcomes. Airflow obstruction (measured by FEV1) seems to be one of the most significant predictors of subsequent acute care [8]. This finding underscores the importance of obtaining spirometric data to identify patients at risk [9]. Moreover, an examination of the clinical trials literature examining asthma therapies suggests that improvements in FEV1 are mirrored by improvements in clinical asthma outcomes such as symptoms, health-related QoL, rescue medication use and healthcare utilisation [10–16].

Nonetheless, several significant limitations indicate that spirometry alone is not a sufficient measurement of asthma control. Some marked individual variations in symptoms are independent of FEV1, and symptomatic and functional responses to therapy may also be independent of FEV1 [6]. A re-analysis of data from two large, randomised controlled clinical trials found large within-patient variability and no more than a moderate correlation between changes in FEV1 and daily symptom scores [17]. Following treatment, subjective improvement in asthma symptoms may occur without improvement in the level of airway obstruction [18]. Possible reasons for this discordance might be uncovered by considering what FEV1 is actually measuring *versus* what we know about the pathophysiology of asthma. Two significant components in the pathogenesis of asthma, namely inflammation and small peripheral airway reactivity [19], might not be gauged adequately by FEV1. The discrepancy between events taking place within the tissue and what lung function studies can actually measure might account for discordance between lung function and clinical outcomes. Symptoms might be influenced by accumulation of eosinophils and other inflammatory cells in the distal lung. Intriguingly, recurrent exacerbations in severe asthma have been associated with enhanced airway closure during stable episodes [20]. Improvements seen in asthma symptoms might occur primarily because of dilation of small airways, which leads to decreased air trapping [21]. FEV1 is relatively insensitive to changes in small airway calibre and thus might disproportionately represent larger airways [21].

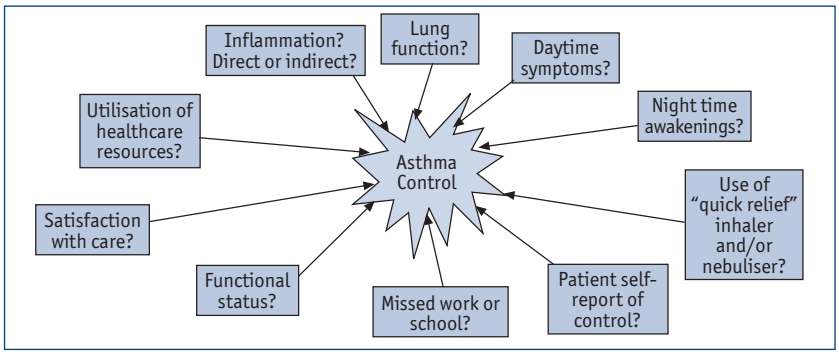

Figure 1
Measurement of asthma control.

It is obvious that other physiological endpoints, such as lung volumes and measures of distal lung inflammation, should be considered in asthma. These might better reflect the changes occurring in the small peripheral airways and alveolar tissue [22]. It should not be forgotten, though, that FEV1 still has advantages as a clinical marker in this disease (table 2).

Applying new research in the clinic

As inflammation determines prognosis in asthma, there is a need to measure it. Bronchial biopsy has been the historical means of measuring inflammation but it is invasive and unsuitable for repeated use. Therefore, noninvasive methods have been developed based on study of the cellular and soluble mediator content of induced sputum, as well as analysis of the exhaled constituents of breath and circulating activation markers of eosinophils.

Table 2 FEV1 as a clinical marker in asthma

Advantages
On average predicts function and prognosis
Reproducible measure
Responsiveness to various therapies well established
Limitations
Marked individual variation in symptoms independent of FEV1
Symptomatic and functional response to therapy may be independent of FEV1
May not reflect changes in asthma control over time, which could lead to long-term functional decline or increased frequency of exacerbations

It has been documented that a treatment strategy directed at normalisation of the induced sputum eosinophil count reduces asthma exacerbations [23]. Moreover, monitoring and normalising sputum cell counts was found to benefit patients with moderate-to-severe asthma by reducing the number of eosinophilic exacerbations, although it had no influence on the frequency of noneosinophilic exacerbations, which were the most common type [24]. The implication for clinical practice from these studies is that the additional measurement of inflammation might confer an educational advantage: knowing that inflammation is present in the airway might improve provider practice and patient adherence. In any case, a retrospective analysis demonstrates that in subjects with clinically stable asthma with normal pulmonary function using inhaled corticosteroids (ICS), measurement of sputum eosinophil counts before and 2 weeks after ICS discontinuation identifies individuals who can safely discontinue ICSs, as assessed on the basis of asthma stability over the subsequent 14 weeks [25].

It is well known that patients with asthma produce higher levels of exhaled nitric oxide (eNO) [26]. Nitric oxide is produced by a variety of cell types such as airway epithelial cells, alveolar macrophages and eosinophils. This explains why eNO is correlated with sputum eosinophilia and BHR. It is intriguing that corticosteroids may reduce eNO directly by inhibiting inducible nitric oxide synthase [27] or indirectly by suppressing proinflammatory cytokines. Thus, in effect, treatment with ICS reduces eNO in most patients with asthma [28]. It has been suggested that eNO measurements can guide treatment in chronic asthma. A first longitudinal study by JONES *et al*. [29] showed the usefulness of eNO fraction (F_{eNO}) monitoring for predicting and diagnosing loss of asthma control. Furthermore, a 1-year follow-up, randomised study caused increased interest in monitoring F_{eNO} in asthma patients by demonstrating that F_{eNO}-guided asthma therapy reduced ICS doses without compromising asthma control [30]. Although a more recent study may slightly temper this enthusiasm [31], all these data suggest that F_{eNO} may be a valuable indicator in the longitudinal assessment of asthma control. However, a more recent paper has documented that the overall ability of F_{eNO} to reflect asthma control is reduced in patients using high doses of ICSs [32].

There is no doubt that there are advantages in using eNO as a biomarker in asthma because it is reliable, noninvasive and easily measured (table 3).

Table 3 eNO as a biomarker in asthma

Advantages
Reliable, noninvasive and easily measured
Positive predictive value for loss of asthma control is 80–90% [28]
Response of eNO to ICS is dose dependent and reproducible [33]
Limitations
Nonspecific marker that is increased in conditions other than asthma (e.g. bronchiectasis and viral infections)
Several factors can affect eNO measurements (e.g. cigarette smoking, spirometric manoeuvres, sputum induction and alcohol)
There is a wide range of eNO levels in patients with asthma
eNO levels are often normal in ICS-treated patients and thus would have less utility in that patient group [34]
Expensive

Assessing asthma control using BHR

Inflammation is associated with structural changes in the airways, and one of the major functional consequences of airway inflammation and remodelling is considered to be BHR [35]. In effect, BHR is a hallmark feature of asthma [36]. It results in airflow limitation and asthma symptoms following exposure to stimulus [36]. BHR can be assessed by direct stimuli (*e.g.* methacholine) that act on airway smooth muscle and by indirect stimuli (*e.g.* adenosine monophosphate) that act by releasing mediators.

There is no doubt that by suppressing inflammation within the airways, adequate treatment improves asthma control and BHR [37]. For this reason, it has been suggested that by including BHR in asthma management, the control of the disease might be improved [38]. In fact, it has been documented that that ICS dose titration guided by BHR reduced the asthma exacerbation rate 1.8-fold, improved lung function and reduced remodelling in airway biopsy specimens from adult asthmatics [38]. Asthma treatment guided by BHR showed no benefits in terms of number of symptom-free days, but produced a better outcome in terms of pre-bronchodilator FEV_1 in allergic asthmatic children, especially those characterised by low symptom scores despite BHR [39].

The utility of BHR as a marker in asthma is linked to the fact that asthma severity is related to the severity of BHR, and BHR can be utilised as a diagnostic tool for asthma (table 4).

It is fundamental to bear in mind that direct bronchial responsiveness is influenced only

slowly, and to a modest extent, by the repeated administration of inhaled steroids [40]. Indirect challenges may more closely reflect acute changes in airway inflammation and be clinically relevant markers for the assessment of the clinical course of asthma [39]. Moreover, some indirect challenges, *e.g.* hypertonic saline and mannitol, can be combined with the assessment of inflammatory cells by induction of sputum [40].

BHR has also important limitations, as detailed in table 4. Improvement in lung function usually precedes and reaches a plateau before the reduction in BHR [41]; and the time course of normalisation of BHR is long [42, 43]. Moreover, it has recently been documented that for most subjects, control of BHR was maintained when treatment was directed toward control of clinical parameters [44].

Table 4 Utility of BHR as a marker in asthma

Advantages
Asthma severity is related to the severity of BHR
BHR can be utilised as a diagnostic tool for asthma
Testing for BHR in routine practice is relatively easy, and results can be obtained in 15–20 min
Limitations
BHR can be abnormal even in the absence of asthma symptoms or when lung function is normal
Baseline FEV_1 <60% pred or <1.5 L is a relative contraindication to performing BHR testing
Time course of normalisation of BHR is long
Expensive

Asthma control questionnaires

An increase in bronchial symptoms has been reported to be an essential aspect of true loss of asthma control. Obtaining symptom scores and insights into rescue medication use and QoL issues form a significant part of the focused asthma visit. This provides a snapshot, which, if recorded over time, will present an overview of the patient's asthma and show whether the patient's status is controlled or impaired. Any measure of symptom control needs to be multidimensional in order to overcome the effects of patients underestimating their symptoms.

Several questionnaires are currently in use to specifically assess asthma control on the basis of patients' symptoms, rescue medication use and limitation of daily activities in adults and children. The asthma control questionnaire (ACQ), the asthma therapy assessment questionnaire (ATAQ) and the asthma control test (ACT) are possibly the most utilised [45]. These questionnaires often correlate significantly with certain objective measurements of asthma control.

The seven-item ACQ, which was developed from of a list of symptoms ranked by 100 asthma clinicians who were members of guidelines committees in 18 countries, covers the five most important symptoms, use of β_2-agonist and airway calibre, and has been widely validated and shown to have strong evaluative and descriptive properties [46, 47]. One recent study has shown that ACQ was also effective in differentiating between "well controlled" and "not well controlled" asthma, as defined by the GINA/National Institutes of Health guidelines [48].

The ATAQ, which was developed for use in population-based disease management, is a self-administered population-based tool that shows a strong correlation with QoL indices and is used mostly for assessing acute asthma healthcare utilisation [49, 50].

The ACT, which was developed by triangulating a 22-item survey of 471 patients with specialist-assessed asthma control after spirometry, is a short and simple patient-based, five-item questionnaire, which does not encompass pulmonary function tests, requires no calculations and includes a question on the patient's view of control, thus giving a useful insight into the patient's perspective [51]. It takes <30 s to complete if the patient has experience with it. The ACT shows high internal consistency and good concordance with specialists' ratings of asthma control, based on spirometry [51, 52] and ACQ scores [52]. The psychometric properties and screening accuracy of ACT are also comparable to those of the ACQ [53], suggesting that this is a useful tool for the primary care setting.

More recently, the asthma control scoring system (ACSS) has been developed for the assessment of asthma control on the basis of clinical, physiological and inflammatory (induced sputum eosinophilia) parameters [54]. Initial investigations indicate that the ACSS has good test–retest reliability for all three parameter scores as well as

Table 5 Comparison of three asthma control questionnaires

Question topic	ACT	ATAQ	ACQ
Limits daily activities	✓	✓	✓
Shortness of breath	✓		✓
Disrupts sleep	✓	✓	✓
Salbutamol use	✓	✓	✓
Effect on global control	✓		✓
Frequency of wheeze			✓

Table 6 Utility of questionnaires for defining asthma control

Advantages
Obtaining symptom scores and insights into rescue medication use and quality of life issues form a significant part of the focused asthma visit
It provides a snapshot, which, if recorded over time, will present an overview of the patient's asthma and show whether the patient's status is controlled or impaired
Limitations
The influence of perceived control of asthma on health outcomes
They are generally retrospective and assess health status over extended time periods, so they are unable to accurately assess rapid or fluctuating changes in disease pathology
None of them assesses exacerbations
The majority of these tools are available mostly in the research setting or select specialist practices
Clinicians may not have the time or personnel required for administering such questionnaires
It is difficult to ensure an accurate translation of a numeric score into a corresponding degree of asthma control
The scoring system used may not necessarily be meaningful to the practitioner or patient
These tools are late indicators of loss of asthma control, reflecting the occurrence of symptoms rather than their imminent arrival

the global scores. Moreover, the ACSS scores are moderately correlated with ACQ and the mini asthma QoL questionnaire scores, although these findings need to be validated further.

Comparing the three major asthma control questionnaires, it is possible to observe that the three common questions on the impact of asthma on daily activities, the effect of asthma on sleep and the need for salbutamol, are constant between all three tools, whereas shortness of breath and global control of asthma are questions in two of them (table 5).

It has been highlighted that using such findings to guide therapeutic decisions is not easy [55]: the impairment in QoL associated with poorer control could be the consequence of both physical symptoms and lower lung function (which are improved by treatments) and higher therapeutic pressure (which may increase side-effects and patients' constraints) [56].

Apart from this critical point, it is important to stress that while questionnaires for defining asthma control have advantages, they also have an important limitations that are mainly linked to perceived control of asthma, which is defined as the individual's perception of their own ability to deal with asthma and its exacerbations, and is a psychological factor that may have an important impact on adult asthma outcomes (table 6) [57].

A specific limitation to the QoL questionnaires is that they are generally retrospective and assess health status over extended time periods; unfortunately, this precludes an accurate assessment of rapid or fluctuating changes in disease pathology [7]. By using questionnaires in conjunction with conventional measures, such as PEF, individual and overlapping factors are monitored simultaneously to provide a more comprehensive view of asthma control. Evidence supporting the use of the questionnaires in combination with objective measurements came from recent data demonstrating that distinct components of severity versus control could not be found using questionnaires alone [58]. In any case, a major limitation of the currently available asthma control tools is that none of them assesses exacerbations, an essential component of the asthma control strategy [45]. Another potential limitation to using control assessment questionnaires in general is ensuring accurate translation of a numeric score into a corresponding degree of asthma control [7]. Furthermore, busy clinicians may not have the time or personnel required for administering such questionnaires, and the scoring system used may not necessarily be meaningful to the practitioner or patient. Unfortunately, the majority of these tools are available mostly in the research setting or in select specialist practices [49], although a postal mailing of the ACQ seems to be an effective approach for tracing asthma patients who need medical attention [50]. It also traces patients who would otherwise not have consulted their family physician. The ACQ seems to be a useful starting point for healthcare professionals in family practice to improve the level of asthma symptom control in their patient population [59]. In any case, it has to be stated that these tools are late indicators of loss of asthma control, reflecting the occurrence of symptoms rather than their imminent arrival.

Assessing asthma control

The assessment of asthma control has become pivotal in the management of asthma. It is now obvious that a multifaceted approach to the assessment of asthma control is needed for most patients. It has been suggested that, in contrast to conventional end-points of clinical trials, such as FEV_1, the use of a composite measure incorporating a range of clinically relevant end-points provides a more complete view of the overall level of asthma control for the individual patient [60] and is likely to correlate with patient perception of control or freedom from disease [61].

An ideal measure of asthma control may be regarded as having the following characteristics:

simple; practical; meaningful; applicable to patients, clinicians and researchers; reflecting long-term asthma control; discriminatory; and responsive to change. Unfortunately, no ideal measure of asthma control exists; there is no single test that is simple, practical, meaningful, discriminatory, responsive to change, reflective of short- and long-term control, and applicable to patients, clinicians and researchers.

Although several standardised measures of asthma control exist, no direct comparisons of the performance and properties of these control measures have been published. The available instruments appear more similar than dissimilar. All share the common trait of assessing multiple aspects of asthma control, which is believed to provide better discrimination than a single measure [62].

Actually, the correct assessment of asthma control is like the connection of a jigsaw puzzle that requires the assembly of numerous small, often oddly shaped, interlocking and tessellating pieces (figure 2). An accurate assessment of asthma control should include multiple objective (*i.e.* pulmonary function tests) and subjective measures (*i.e.* symptoms and QoL). Measures of airway inflammation and airway hyperresponsiveness may also be helpful, although they are currently less practical to obtain [7].

Completing a jigsaw puzzle takes time but, unfortunately, a typical consultation in general practice involves identifying the patient's presenting problem, hypothesising possible aetiologies, examination, performing and arranging investigations, decisions on further management, addressing preventative medical issues (such as immunisations and advice on lifestyle) and sometimes referral for specialist advice or care, all within time slots of 6–12 min [63]. This is a true bias, because the level of control achieved and the time taken to do so depend upon the asthma measures utilised [64], with more time required to attain control using composite measures [65].

It is, therefore, useful to proceed on two parallel but different tracks in the assessment of asthma control. We must identify simple and rapid validated tools for the general practitioner, but we still do not know which is the best tool, although it is likely that an asthma control measure such as the ACT used in conjunction with spirometry provides the physician with a comprehensive assessment and permits better management of the patient with asthma. In any case, clinicians should be conscious of the bias that may occur when estimating changes in asthma control and know that it is much more accurate to measure asthma control at each visit using a validated instrument, than to rely solely on clinical judgement [66].

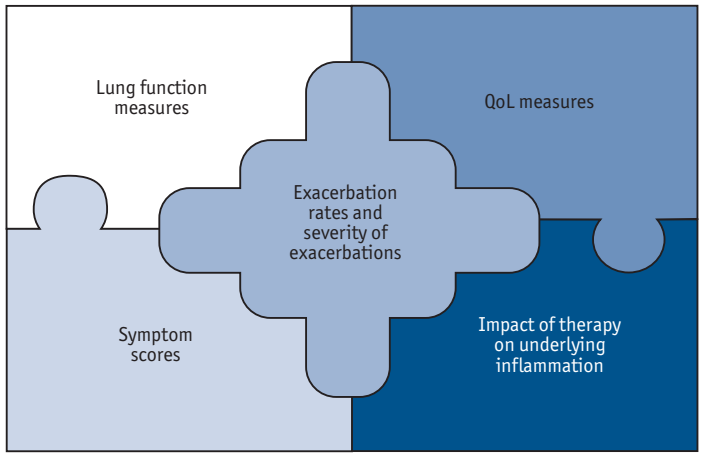

Figure 2
Assessing of asthma control is like solving a jigsaw puzzle

In contrast, the specialist will devote all his or her time and knowledge to determining the actual presence or absence of asthma control using a composite measure incorporating lung function measures, symptom scores, QoL measures and markers that can determine the impact of therapy on underlying inflammation. Exacerbation rates and severity of exacerbations are also important, although there are difficulties in differentiating the words "asthma control" and "exacerbation" [67]. Most observers use the term "exacerbation" to imply a worsening of asthma which is relatively acute (usually a few days and certainly <1 week) and this word represents a contrast with "control" which is usually a longer-term description of either asthma symptomatology or adequacy of treatment (usually reflecting a time period of >1 week). By the very nature of its shorter timescale, exacerbations are usually defined by using a combination of subjective day- and night-time symptoms and objective parameters, such as peak flow, use of treatment or spirometry, but others have used the term to include need for unscheduled healthcare. The latter is a particularly difficult interpretation because it is so clearly influenced by differences in healthcare systems and geography.

The use of a composite measure incorporating lung function measures, symptom scores, QoL measures and markers that can determine the impact of therapy on underlying inflammation will always be desirable for the proper classification of asthmatic patients. It will be mandatory in all cases when the general practitioner fails to assess asthma control, and especially in those cases in which simpler instruments seem to indicate a likely lack of such control.

Educational questions

1. Do lung function and BHR improve at the same time?
2. Why is it preferable to dissociate asthma control and severity?
3. Are the questionnaires currently in use specifically to assess asthma control capable of predicting exacerbations?

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Suggested answers

1. No, the improvement in lung function usually precedes and reaches a plateau before the reduction in BHR.
2. By dissociating asthma control and severity, the clinician may focus on the level of control during each encounter, independent of asthma medication.
3. No, because they are late indicators of loss of asthma control, reflecting the occurrence of symptoms rather than their imminent arrival.