

REVIEW

The ADMIT series – Issues in Inhalation Therapy.

1) The goals of asthma treatment: can they be achieved?

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Summary

The widespread use of inhaled corticosteroids (ICS) since the early 1970's has meant that asthma is generally better controlled in comparison with previous decades. Nevertheless, recent patient interview surveys indicate that there is still a lot to gain in terms of abolishing daytime and nocturnal symptoms, and asthma exacerbations. It is important to use the terms asthma 'control' and asthma 'severity' in a correct way. Whereas asthma control reflects fluctuation in symptoms and lung function (or lack of them) over time, asthma severity reflects both asthma control and the need for medication. Thus, 'severity' is a property of the disease which reflects the degree of pathophysiological abnormality, whereas 'control' refers to the reduction of the clinical manifestations of disease achieved by treatment – thereby reflecting the adequacy of treatment. This introductory review, the first of a series of review papers to be published in this journal by the ADMIT team (see Appendix), discusses briefly our present knowledge of asthma control, its components, factors that may limit patients' ability to achieve optimal asthma control, and instruments to measure asthma control.

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Introduction

The introduction of inhaled corticosteroids (ICS) in the early 1970's – and their subsequent widespread use – has meant that asthma is generally better controlled for most patients particularly in comparison with previous decades.¹ Nevertheless, recent patient interview surveys indicate that there is still a lot to gain in terms of abolishing symptoms which can impede normal daily activities, normal leisure activities, and activities at school or work. Furthermore, nocturnal symptoms, recurrent symptoms, or asthma exacerbations, are present more frequently than sometimes assumed by the physician.

'Asthma control' is a frequently used but poorly defined term when assessing efficacy in international studies.^{2,3} In view of the fact that many patients treated with apparently efficacious therapy frequently complain of symptoms, it is pertinent to consider what other factors may have a role in the failure of individual patients to achieve full control of their symptoms. Consequently, one may question if asthma control is indeed achieved in these patients, and – if it isn't – what reasons there may be for patients not achieving optimal disease control.

This introductory review, the first of a series of review papers to be published in this journal by the ADMIT team (see Appendix), discusses briefly our present knowledge of asthma control, its components, and factors that may limit patients' ability to achieve optimal asthma control.

How is asthma control defined?

Optimal control of asthma should encompass lack of day- and night-time symptoms, no asthma exacerbations, no need for rescue medication, normal peak expiratory flow (PEF) rates, and no unwanted side effects from medication (see Table 1).^{4,6} Clearly this is the ideal, but not all patients with asthma can achieve these levels of disease control. Asthma severity

subdivisions and levels of control have been described in the guidelines from the Global Initiative for Asthma (GINA)⁵ and the National Asthma Education and Prevention Program (NAEPP),⁶ each of which include consideration of each of the aforementioned items (see Tables 2 and 3).⁵⁻⁷ Subdivision of patients into those with 'total control' and 'well-controlled' asthma have been proposed and applied in recent studies (for example, the GOAL study⁸), and, although not validated in large scale epidemiological studies, this categorisation is appealing to the clinician and might appear to be a useful instrument.

European respiratory societies have provided guidelines for the achievement of asthma control. Interestingly, British⁹ and French¹⁰ guidelines stipulate that asthma control can be qualified as being acceptable for a patient by taking into account not only symptoms, PEF and lung function, use of rescue medication and exacerbations (Table 4), but also the patient's aspirations and goals, the adverse effects of drugs and also the inconvenience of taking them. This view of asthma control – with a level of achievement varying from one patient to another – can be very useful in clinical practice; it allows a balance between the aims of the clinician (total control) and the aspirations and expectations of patients.

Asthma exacerbations are a manifestation of, and can help define, *poor* asthma control. However, there have been many different definitions of asthma exacerbations used in research studies over the years.² Various criteria used to define exacerbations include: the presence of subjective day- and night-time symptoms such as dyspnoea, cough and wheeze; objective measures such as PEF or forced expiratory volume in one second (FEV₁) readings; healthcare utilisation measures such as the need for hospitalisation, accident and emergency (A+E) or emergency room (ER) attendance, emergency general practitioner (GP) or practice nurse consultation; and acute treatment changes such as the prescribing of oral

Table 1. Goals of asthma therapy according to GINA⁵ and NAEPP⁶ guidelines.

National Asthma Education and Prevention Program (NAEPP) guidelines	Global Initiative for Asthma (GINA) guidelines
Prevent chronic and troublesome symptoms	Achieve and maintain control of symptoms
Maintain (near) "normal" pulmonary function	Maintain pulmonary function as close to normal levels as possible
Maintain normal activity levels (including exercise and other physical activities)	Maintain normal activity levels, including exercise
Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits and hospitalisation	Prevent asthma exacerbations
Provide optimal pharmacotherapy with minimal or no adverse effects	Avoid adverse effects from asthma medications
Meet patients' and families' expectations of and satisfaction with asthma care	Prevent development of irreversible airflow limitation
	Prevent asthma mortality

Table 2. Classification of asthma severity according to symptoms as per the Global Initiative for Asthma guidelines (GINA).⁵

Frequency of asthma symptoms	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Daytime	<2 times/week	≥2 times/week	Every day (≤2 times/day)	3 times daily
Night time	2 times/month	≥2 times/month	≤2 times/week	Most nights
Severe episodes in past 12 months	≤1 time/week	≥2 times/week	Every day	Every day
Exercise induced symptoms in past 12 months	≤1 time/week	≥times/week	Every day	Every day
Symptom frequency in typical week	≤2 times	3-6 times	7-20 times	8-21 times

Table 3. Levels of asthma control.⁵

Characteristic	Controlled (all of the following)	Partly controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV ₁)	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year	One in any week

Table 4. Criteria defining acceptable asthma control.¹⁰

Criterion	Value or frequency
Day-time symptoms	<4 days/week
Night-time symptoms	<1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school	None
Use of short-acting β ₂ -agonists	<4 doses/week
FEV ₁ or PEF	>85% of personal best
PEF diurnal variation (optional)	<15%

steroids or use of nebulised bronchodilators. In their analysis of the 425 asthma exacerbations which occurred during the FACET study,¹¹ Tattersfield *et al*¹² defined severe exacerbations as the need for a course of oral corticosteroids or a reduction in morning PEF of 30% on two consecutive days. Exacerbations identified by the need for oral corticosteroids were associated with more symptoms and smaller changes in PEF than those identified on the basis of PEF criteria alone.

Finally, an ERS/ATS Joint Taskforce, under the

chairmanship of Helen Reddel and Robin Taylor, is currently working on providing consensus recommendations on standard definitions and data collection methods for assessing asthma control, asthma severity and exacerbations in future clinical trials.² Importantly, this report (which is about to be submitted for publication^{2a}) will permit better definition of asthma control and will help develop rational goals for asthma treatment.

Difference between severity and control

Some confusion may arise regarding the terms asthma 'control' and asthma 'severity'. Whereas asthma control reflects fluctuation in symptoms and lung function (or lack of them) over time, asthma severity reflects both asthma control and the need for medication. For example, one would not say that a patient is suffering from mild asthma if he/she is taking regular high dosages of inhaled corticosteroids and other add-on drugs such as long-acting beta-agonists (LABA), even if control of the disease is satisfactory. Recently, Bateman,¹³ and Stoloff and Boushey,¹⁴ have described 'severity' of a disease as a property of the disease which reflects the grade of pathophysiological abnormality, whereas 'control' refers to the reduction of the clinical manifestations of disease

Table 5. Asthma questionnaires to assess asthma control.⁴

ACQ	Includes 6 Questions and the FEV ₁ . Five questions are those rated most important by a survey of 100 clinicians in 18 countries. The sixth question concerns rescue inhaler use
ACT	Includes 5 questions that most closely correlate patients'symptoms with their specialists'evaluations of control
AQLQ	Includes 32 questions in 4 domains (symptoms, activity limitations, environmental stimuli and emotional function) that measure the functional problems that are most troublesome to adults with asthma
ATAQ	Assesses 4 measures of control over a 4-week period and scores 1 point for each-self-perceived control, missed activities, nighttime waking and use of rescue inhalers
AQ30	Includes 30 questions which determine everyday life health status estimates in patients with asthma. Questions answered "Yes" = 1 and "No" or "N/A" = 0; a total score of 0 = no asthma and 30 = very severe asthma. Correlates with AQLQ and clinical variables
ABP	Measures asthma distress by bother; patient's confidence of asthma knowledge, perception of the quality of care, and confidence in managing asthma attacks

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AQLQ = Asthma Quality of Life Questionnaire; ATAQ = Asthma Therapy Assessment Questionnaire; AQ30 = Asthma Questionnaire 30; ABP = Asthma Bother Profile.

achieved by treatment – thereby reflecting the adequacy of treatment.

How can asthma control be measured?

Asthma control comprises several domains which are partly interrelated. Day- and night-time symptoms can be recorded by patients using symptom diaries, PEF readings can be recorded by patients themselves, and PEF and FEV₁ readings can be measured in the consulting room. Data can be collected on healthcare utilisation measures – such as hospital attendance and emergency GP and nurse consultation – and on the prescribing of acute courses of oral steroids or nebulised bronchodilators.

Another set of measures includes surrogate markers of inflammation, such as hyperreactivity to methacholine or histamine, and markers in (induced) sputum such as the number of eosinophils and exhaled nitric oxide (NO) levels. At present, these markers are not included in routine clinical assessment of control, although measurement of exhaled NO levels is becoming more feasible.¹⁵

Several questionnaires have been developed to measure asthma control – see Table 5.⁴ A frequently used example is the Asthma Control Test (ACT)¹⁶ as shown in Table 6.

Can asthma control be achieved?

As shown in Table 1, the GINA guidelines specify eight goals for the long-term control of asthma: minimal chronic symptoms, minimal exacerbations, no emergency visits, minimum need for as-required beta-2-agonists, no limitations of daily activities, near-normal PEF, PEF circadian variation of less than 20%, and minimal adverse effects from asthma medication.

However, several recent surveys have shown that asthma control is not achieved in a large number of patients. The Asthma Insights and Reality (AIR) surveys aimed to assess control of asthma and the current state of asthma management with respect to the GINA guidelines. The AIR surveys were the Asthma in America survey in the United States in 1998, the Asthma Insights and Reality in Europe (1999), followed by surveys in Asia-Pacific and Japan in 2000 and in Central and Eastern Europe in 2001.¹⁷ In all participating regions, asthmatic patients performed equally poorly against the various GINA goals, with a consistently high proportion of subjects reporting daytime, night-time, and exercise-induced symptoms. A remarkable finding across all regions was the discrepancy between the numbers of reported symptoms and patients' perception of their asthma control. The surveys indicate that 32-49% of patients experiencing severe symptoms, and 39-70% of patients with moderate symptoms, believed their current level of asthma control to be 'good or 'complete'. Rabe and coworkers¹⁷ noted that there was a tendency for patients to overestimate control and underestimate severity, suggesting a willingness to accept symptoms and lifestyle limitations as unavoidable consequences of their disease. This might, in part, be responsible for the poor outcomes seen elsewhere in these surveys because patients who consider their symptoms controlled are unlikely to seek further medical advice.

Which factors may limit asthma control and how can they be eliminated?

Many factors may contribute to inadequate asthma control. A number of issues are listed in Table 7. Assuming that asthma

Table 6. Asthma Control Test: Items and scores.¹⁶

Asthma Control Test™

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
0	0	0	0	0
1	2	3	4	5

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	Once a day	3 tot 6 times a week	Once or twice a week	Not at all
0	0	0	0	0
1	2	3	4	5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or twice	Not at all
0	0	0	0	0
1	2	3	4	5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
0	0	0	0	0
1	2	3	4	5

5. How would you rate your asthma control during the past 4 weeks?

Not controlled at all	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled
0	0	0	0	0
1	2	3	4	5

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is the correct (and only) diagnosis, the underlying severity of the disease may prevent achievement of optimal control in some patients. Even in the well-conducted GOAL (Gaining Optimal Asthma control) study only 40% of all patients reached predefined levels of optimal asthma control and only 60-70% reached the level of 'well-controlled' asthma.⁸ It is important to remember that a significant proportion reached these degrees of control only with high dosages of ICS

(fluticasone) which are associated with local side effects and systemic effects such as cortisol suppression.¹⁸ This demonstrates the difficulties in getting the balance right in terms of attaining the goals of asthma treatment by achieving asthma control but at the same time limiting the potential for ICS side effects.

The physician should consider whether all bronchial triggers have been identified, including exposure to unknown

Table 7. Issues to consider if asthma is not under control.

A	Is it really A sthma?	Consider other diagnoses, e.g. hyperventilation, vocal cord dysfunction, Churg-Strauss syndrome, carcinoid
B	Are all B ronchial triggers known?	Exposure to unknown triggers at work, hobby, rhino-sinusitis, gastro-oesophageal reflux (GORD), intolerance to medications
C	Is C ompliance optimal?	Does the patient use the medication at the prescribed dosages?
D	Can the patient handle the D evice?	Is the patient able to use the device correctly?
E	Is E very small airway reached?	Does the anti-inflammatory medication reach the peripheral compartment of the lung?

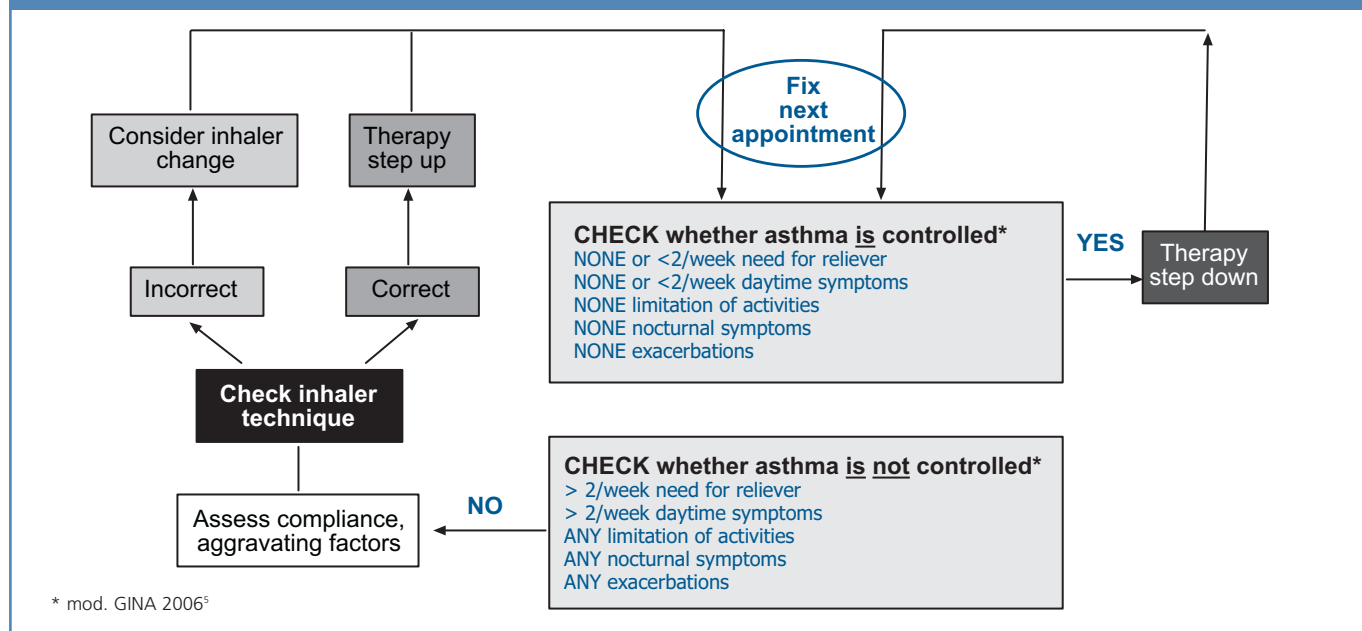
triggers at work or when doing other activities such as hobbies, rhino-sinusitis, gastro-oesophageal reflux (GORD), and intolerance to medications. It is important to check whether or not the patient is able to use the inhaler device correctly, and in some patients with nocturnal awakenings and/or severe asthma it may be of clinical importance to ensure that the anti-inflammatory medication reaches the peripheral compartment of the lung.

Compliance with, and adherence to, treatment schedules should be checked and re-checked. The subject of patient compliance with asthma treatment is complex. Issues include the need for discussion between the patient and healthcare professionals concerning the patient's health beliefs and the various explanatory models that can be used, conceptualisation of asthma as a short term acute intermittent illness rather than the medical model of a persisting inflammatory process, and the goals and willingness of patients to trade off inconvenience against benefit.¹⁹⁻²² These issues will be addressed in more detail in forthcoming ADMIT papers.

Treatment strategy: the ADMIT protocol

Recently, the ADMIT Group has proposed a practical algorithm in order to improve the instructions given to the patient regarding optimal use of their inhaler.²³ Figure 1, an asthma therapy adjustment flow chart, shows the way in which the healthcare professional can monitor and check the patient's use of inhaled medication and make treatment changes according to various criteria. At each consultation, the physician or nurse should check that the patient has few symptoms, is leading a normal life, performs regular exercise, is on low-dose relief medication, and is not taking any additional medication. If all these conditions are met then therapy should be stepped down according to treatment guidelines, and another appointment should be scheduled for a symptom check. If, however, the patient answers 'no' to any of the checklist questions then compliance and aggravating

Figure 1. Achieving asthma control: Recommendation for therapy adjustment. Modified from the original published in *Respiratory Medicine*²³ with permission from Elsevier



factors should be assessed. Most importantly, inhalation technique should be assessed. If inhalation technique is incorrect and cannot be corrected adequately, a change in inhaler device should be considered. If, on the other hand, inhalation technique is correct then asthma therapy should be stepped up according to treatment guidelines and another appointment scheduled in order to check symptoms.²³

Conclusion

Using several scoring systems, it appears that large numbers of patients do not achieve acceptable levels of asthma control. There is a wide range of explanations for this, including inaccurate diagnosis, failure to identify triggers, poor compliance, and incorrect use of inhaled medication. The latter can easily be improved by following strict algorithms to direct optimal choice and usage of an inhalation device.

Forthcoming ADMIT papers

A forthcoming series of papers on Issues in Inhalation Therapy will appear in this Journal over the next year. The series will focus on inhalation treatment in adults and children with obstructive airways diseases. Future themes include: the aims of therapy in patients with asthma and COPD; the characteristics of inhaled medication including side effects and their use in daily practice in stable and unstable disease; compliance issues; ways to optimise inhaler use; inhalation issues in children; inhalation devices in COPD; reasons to choose a specific device first; and the actions to be taken prior to altering an inhaled drug or its dosage.

Conflict of interest declaration – the ADMIT Working Group

The Aerosol Drug Management Improvement Team (ADMIT) is a consortium of European respiratory physicians with a common interest in promoting excellent delivery of inhaled drugs for asthma and COPD. It is supported by an unrestricted educational grant from MEDA AB. Members of ADMIT receive a small honorarium for attending meetings from MEDA AB and travel expenses are reimbursed.

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