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Key Points

- Asthma is a heterogeneous syndrome ranging from mild disease with barely noticeable symptoms to very severe disease with constant symptoms that may greatly hinder patients' quality of life.
- The aim of asthma treatment is control of asthma and the prevention of risk of exacerbations and fixed airflow limitation.
- Asthma management must be individualised; tailored not only to the severity of the disease but importantly, to the phenotypic characteristics of the patient and modified according to response to treatment.

Educational Aims

- To inform readers about the current understanding on the treatment of asthma.
- To highlight the usefulness of phenotypes in treating asthmatic patients, especially those with severe disease.
- To introduce the issues of severe asthma management and future planning.

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Clinical asthma phenotypes in the real world: opportunities and challenges

Asthma is a common, chronic and heterogeneous syndrome, affecting people of all ages, all races and both sexes. It may range from mild disease with barely noticeable symptoms, to very severe disease with constant symptoms that greatly hinder the life of the patient. Guidelines issued by various medical societies provide guidance on how to diagnose and manage asthmatic patients. It is now increasingly recognised that asthma management must be individualised, tailored not only to the severity of the disease but to the phenotypic characteristics of each patient. The aim of asthma treatment is control of asthma and the prevention of risk of exacerbations and fixed airflow limitation. Asthma control can be easily assessed clinically through simple screening tools such as the use of validated questionnaires and spirometry. The use of inflammatory biomarkers can be an alternative approach that, however, requires more time and resources. Asthma treatment involves the use of controllers, mainly inhaled corticosteroids and long-acting β_2-agonists, and relievers, mainly rapid-acting β_2-agonists. Controller medications reduce airway inflammation, lead to better symptom control and reduce the risk of future exacerbations. Reliever (rescue) medications alleviate symptoms and prevent exercise-induced bronchoconstriction. Treatment must be based on a "stepwise approach" in order to achieve good control of symptoms and to minimise future risks of exacerbations. That is, less treatment for mild disease, more treatment for severe, uncontrolled disease. Once good asthma control has been achieved and maintained, treatment should be stepped down. In severe asthmatics, phenotypic characterisation becomes more clinically useful and add-on treatment such as anti-immunoglobulin E monoclonal antibodies may be required. Despite our better understanding of asthma, there are still patients who will not respond to treatment and remain symptomatic. Dissemination of guidelines and national plans allowing early diagnosis of asthma as well as access to specialised primary and secondary care for asthmatic patients, personalised treatment and continuity of care may lead to excellence in care and controlled asthma for the majority of patients. Education of the patient in asthma is also very important, as in every chronic disease, as the patients live with the disease every day while they visit a healthcare professional a few times a year. Future planning for new treatments should focus on the needs of such severe asthma patients.

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An overview of treatment of asthma and introduction to issues of severe asthma management and future planning http://ow.ly/RbYc1

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Introduction

Asthma is a common, chronic and heterogeneous syndrome, affecting people of all ages, all races and both sexes. It may be mild, barely noticed by the patient, or it may range all the way to very severe disease, greatly hindering the life of the patient, causing constant symptoms, inability to perform daily activities, poor quality of life, severe and life threatening attacks and even death.

Millions of people suffer from asthma worldwide, are under regular medical care and receive treatment which is based on a step-wise approach: milder disease requires few and low-dose medications, while more severe disease requires more medications and higher doses. There are national and international guidelines such as those from the Global Initiative for Asthma (GINA), the National Asthma Education and Prevention Program (NAEPP) and the British Thoracic Society (BTS) [1–3], which provide guidance on how to diagnose and manage asthmatic patients. What has, however, become apparent in recent years is that asthma management must be individualised: tailored not only to the severity of the disease but also, importantly, to the phenotypic characteristics of the patient. Phenotypic characteristics may be easily recognisable clinical ones such as asthma that is induced by exercise or infection, linked with obesity, perimenstrual or characterised by frequent exacerbations or by peripheral eosinophilia. Asthma phenotypes may also be much more complex and may require a dedicated lab and specialised centre to characterise, as with cellular or biochemical markers in induced sputum or in bronchial biopsies; and these characteristics are mostly used in clinical trial settings and in research. For the successful clinical management of most patients, a good understanding of the clinical characteristics is enough to provide education and life-style advice and to base treatment on the phenotype as well as the severity and control of the disease.

Advice on healthy diet, regular exercise, smoking abstinence and avoidance of triggers, such as allergens or through work exposure, is very important and may be enough for patients with very mild asthma. For those with more frequent symptoms, medications are required. The most important medications are inhaled corticosteroids (ICS) and β_2-agonists. ICS are used to manage bronchial inflammation and therefore to prevent exacerbations and β_2-agonists provide relief of breathlessness through bronchodilation. β_2-agonists are available as either short-acting (SABA) or long-acting (LABA), with some LABAs being rapid acting (*e.g.* formoterol) which can be used for acute symptom relief due to their rapid onset of action, and others having a slow onset of action *e.g.* salmeterol. Not all patients need both ICS and LABA in fixed combination and some patients may require no regular medication or need other medication classes either as monotherapy or, usually, as add on treatment.

Some years ago, Haldar *et al.* [4] published an important paper describing clinical characteristics and linking them to ICS and bronchodilator treatment response. In this article, we use the example of that paper to illustrate the clinical thinking behind individualised management.

Treatment and control

Definition of control and ways to assess it

The aim of asthma treatment is control of asthma. Control of asthma is achieved when the various manifestations of asthma such as symptoms and limitations in daily activities are eliminated or greatly reduced either spontaneously or by treatment [1, 2, 5]. According to current recommendations, therefore, it is important to determine the appropriate, and lowest, level of treatment that achieves control [1, 2].

Two domains are included in the definition of control and are important for the patient and the physician. First, the assessment of current level of clinical control, including the presence of symptoms, the ability to carry out everyday activities and the overall quality of life, and second, the assessment of future risk to the patient, including future loss of control, exacerbations, accelerated decline in lung function, and side-effects of treatment [5, 6].

In everyday practice, asthma control can be assessed through simple screening tools that are particularly useful in primary care settings (table 1), such as the consensus-based "Royal College of Physicians Three Questions", or by categorical symptom control tools, such the consensus-based GINA symptom control tool [1]. More importantly, several numerical composite scores have been developed to assess asthma control. Examples include the Asthma Control Questionnaire (ACQ). [7], the Asthma Control Test (ACT) [8] and the Asthma Control Scoring System (ACSS) [9]. These have the advantage of being easy for both patients and healthcare providers to understand and record, and they are available in many languages. Moreover, they have proven to be user-friendly in self-management programmes [10] and more sensitive than categorical tools in detecting changes in symptom control [1].

An alternative approach in asthma control evaluation involves the use of inflammatory biomarkers in the blood, sputum, bronchial tissue or exhaled breath condensate. The idea is to obtain an objective measurement of airway inflammation that may correlate to disease activity and even predict exacerbation, as opposed to symptoms, which are subjective and may be under- or over-estimated by patients. While there are studies showing promising results [11, 12], this

approach is time-consuming, more expensive, and requires special equipment and trained personnel; therefore, it is neither recommended nor feasible for everyday practice. Biomarkers are utilised in cases of severe asthma monitoring and in specialised centres [13]. One measure that is easy to apply and seems to have a clinical application is peripheral blood eosinophilia which, when associated with sputum eosinophilia, is a marker of severe and uncontrolled disease [14].

The second domain of asthma control includes assessment of the risk of adverse outcomes, and particularly exacerbations, fixed airflow limitation and side effects of medications. Exacerbations, defined as the acute or sub-acute worsening in asthma symptoms and lung function, already imply an increased risk of future loss of control [15–17], so a current exacerbation or a history of more than one exacerbation in the previous year increases the risk of uncontrolled asthma. Additionally, there are independent factors that increase the risk of future exacerbations, including poor adherence, incorrect inhaler technique and smoking. Furthermore, asthma patients are at risk of an accelerated decline in their lung function and even of developing airflow limitation that may not be fully reversible [18].

The majority of patients using low and moderate doses of asthma medication will not experience any side effects other than hoarseness [19]. Patients on higher doses, however, may demonstrate systemic adverse events that may include impaired growth in children, decreased bone mineral density, skin thinning and bruising, and adrenal suppression [20, 21].

The role of spirometry remains fundamental in the assessment of asthma control, since it provides an objective and reproducible measure of airflow limitation [5]. Reduced lung function expressed by a low forced expiratory volume in 1 s (FEV_1), particularly when <60% of predicted, is an independent predictor for future risk of exacerbations [22–25] as well as for accelerated decline in lung function, even in the absence of symptoms [26], possibly due to untreated airway inflammation [27, 28]. However, it must be noted that spirometry varies greatly over time and therefore treatment changes should not be based on spirometry alone [1]. Moreover, spirometry alone should not be used to guide treatment as some patients may show stable fixed airflow obstruction not associated with inflammation, and therefore do not require high-dose anti-inflammatory treatment.

There are multiple reasons for poor asthma control. These include 1) factors related to the physician, including asthma misdiagnosis, lack of knowledge of current guidelines or even failure to implement self-management plans in treating asthma patients [29]; 2) factors related to the patient, including socioeconomic factors, poor adherence to medication, life-style factors such as smoking, lack of physical exercise or a poor diet, and incorrect use of inhalation devices [29–31]; 3) factors related to disease severity including a history of hospitalisation or intensive care with ventilation due to an asthma exacerbation [1] and the presence of comorbidities including allergic rhinitis [32], gastro-oesophageal reflux disease (GORD) [33], obstructive sleep apnoea [34] and psychopathological comorbidities [35]; and 4) exposure to environmental triggers, such as allergens, environmental or work-related irritants and smoke [36].

Table 1 *Parameters used in the questionnaires by which physicians evaluate asthma control*

Questionnaire	Parameters
Royal College of Physicians "Three Questions" tool	Presence of daily symptoms Limitation in daily activities Trouble sleeping
Asthma Control Questionnaire	Self-assessment of morning symptoms Limitation in daily activities Night awakening Shortness of breath Self-reported presence of wheezing Use of reliever medication# Pre-bronchodilator FEV_1#
Asthma Control Test	Shortness of breath Limitation in daily activities Night awakening Use of reliever medication Self-assessed level of control
Asthma Control Scoring System	Presence of daily symptoms Limitation in daily activities Night awakening Use of reliever medication PEF % predicted FEV_1 % predicted ΔPEF % predicted Sputum eosinophilia¶

PEF: peak expiratory flow; ΔPEF: change in PEF. #: used in extended seven-question versions; ¶: optional.

Asthma treatment and management

Asthma treatment involves two main categories of medications, controllers and relievers. Controller medications (mainly ICS and ICS/LABA in combination) reduce airway inflammation, lead to better control of symptoms and reduce the risk of future exacerbations. Reliever (rescue) medications (SABA and formoterol) relieve symptoms and prevent exercise-induced bronchoconstriction. In patients receiving treatment with formoterol and either budesonide or beclomethasone preparations in one inhaler device, the same medication may be used as reliever. More severe/uncontrolled asthma patients may require "add-on therapies".

Treatment must be based on a "stepwise approach" (figure 1) [1] in order to achieve good control of symptoms and to minimise future risks of exacerbations, fixed airflow limitation and medication side effects. Once good asthma control has been achieved and maintained for 3 months, treatment should be stepped down. In patients with persisting symptoms or exacerbations despite therapy, a review of the history, diagnosis, exposure to triggering factors and comorbidities as well as adherence to treatment and inhaler technique must be undertaken. These factors should be assessed and corrected before any change in medications [1].

For patients with mild asymptomatic asthma or with occasional daytime symptoms of short duration, with no nocturnal symptoms and with normal lung function, as-needed inhaled SABA is the most appropriate therapy for the relief of symptoms [1]. However, for patients who present more frequent symptoms or exacerbation risk factors, a low dose of ICS is necessary [37–39]. Studies suggest that treatment with low-dose ICS reduces asthma symptoms and the risk of exacerbations and asthma-related death, and increases lung function and improves the quality of life [37, 38, 40, 41] Leukotriene receptor antagonists (LTRAs) are another option in controller treatment but studies suggest that LTRAs provide inferior efficacy compared with ICS [42] thus the recommendation favours ICS as first-line treatment.

For patients who are not well controlled using ICS as maintenance treatment plus as-needed SABA, ICS/LABA as controller plus SABA as relief or low-dose ICS/formoterol as both maintenance treatment and reliever is recommended. Studies suggest that adding LABA to the same dose of ICS improves asthma symptoms and reduces the risk of exacerbation [43]. Another option might be to increase ICS to medium dose but the evidence suggests that it is less effective than the addition of LABA [44–46]. The addition of LTRAs or low-dose sustained-released theophylline is also an option but again is less effective [47, 48].

Increase to medium-dose ICS/LABA is recommended for patients who receive low/medium-dose ICS/LABA and still suffer uncontrolled asthma [49], despite the increased risk of side effects [44, 45]. In these cases, it may also be beneficial to add a third controller, such as LTRA or sustained-released theophylline in order to achieve control [38, 50, 51]. Recently, it was shown that tiotropium by soft mist inhaler may be used as add-on therapy for adults with uncontrolled asthma or with a history of exacerbations. Studies suggest that the addition of tiotropium to patients who receive only ICS or medium/high-dose ICS/LABA improved symptoms, improved lung function and increased the time for first severe exacerbation [52–54].

Which treatment should we use for the patient with moderate–severe asthma? The role of phenotypes

As shown by Haldar *et al.* [4], some asthma patients have concordant asthma *i.e.* inflammation and symptoms increase in parallel and this is how we used to think about asthma (figure 2). In this group of patients, who probably form the majority, a step-wise approach as described in all guidelines is relevant and usually leads to the desired outcome of control: the worse the symptoms, the higher the ICS dose. However, there are patients who have discordant disease and have lots of symptoms with little evidence of eosinophilic inflammation. In these patients, increasing the dose of ICS will only lead to side effects and the medications needed may include more bronchodilators, anti-leukotrienes, low-dose azithromycin or other possible solutions, such as bronchial thermoplasty in severe asthma. Conversely, there are patients who show high eosinophilic inflammation with very few symptoms and these patients need high doses of ICS but little bronchodilation. In cases of severe discordant eosinophilic asthma, oral steroids or monoclonal antibodies, such as anti-immunoglobulin E (anti-IgE) or anti-interleukin 5 (anti-IL5) may be needed [55,

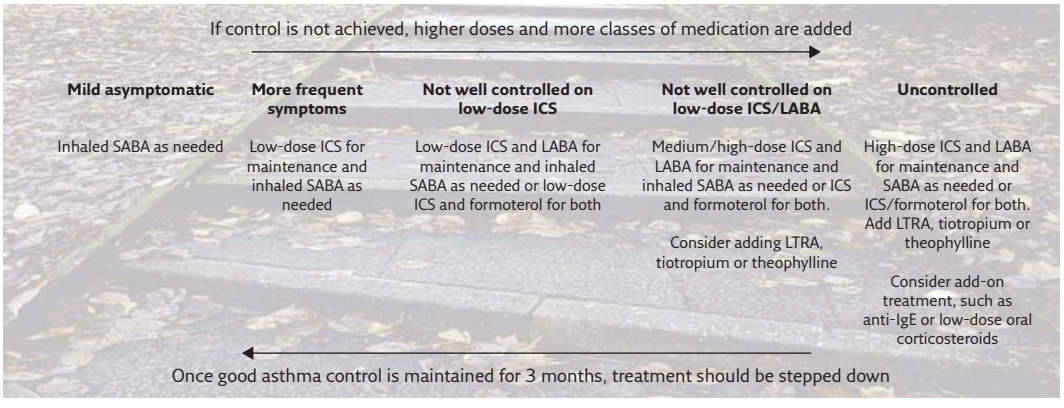

Figure 1 *Stepwise approach to the treatment of asthma. If control is not achieved with low-dose medication, higher doses and more classes of medication are prescribed in order to control asthma symptoms. Moreover, doses are kept at the minimum level that achieves good control in order to minimise future risk.*

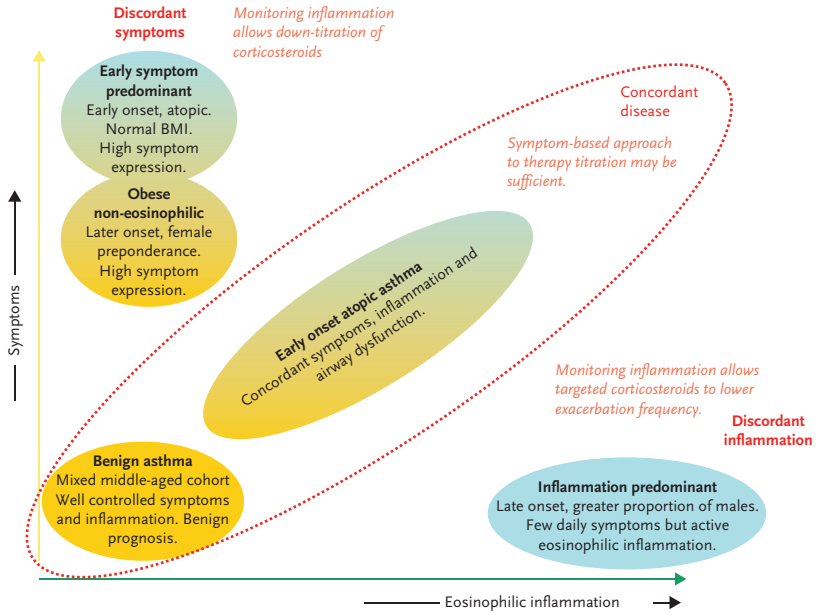

Figure 2 *Asthma phenotypes identified using cluster analysis plotted according to their relative expression of symptoms and inflammation. The axes represent symptoms and inflammation. The disease is concordant when symptoms and inflammation increase in parallel. However some patients have discordant disease, i.e., a lot of inflammation requiring high doses of ICS but few symptoms, requiring little bronchodilation. And some patients have a lot symptoms but with little inflammation and therefore require bronchodilation but low ICS doses. So one size does not fit all! BMI: body mass index. Adapted from [4] with permission from the publisher.*

56]. Thus, it is important to assess the individual patient and provide personalised management based on the patient's specific clinical characteristics and responses. This does not necessarily require elaborate biomarker measurements and specific tests but rather a good history, medical review and sound clinical judgement.

Problems with severe asthma

The European Respiratory Society (ERS)/ATS statement on severe asthma defines severe asthma as asthma which requires treatment with high-dose ICS/LABA and add-on controllers or systemic CS for ≥50% of the previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this treatment [13]. In these severe asthma patients, a personalised treatment approach and evaluation and follow up by a specialised team is recommended. The ERS/ATS statement describes specific phenotypes, poses research questions and links new and future treatments with specific phenotypes. Management of severe asthma is beyond the scope of this review; however, it must be mentioned that anti-IgE treatment is recommended for severe allergic asthma, the use of methotrexate is not recommended, anti-fungal treatment is only recommended for the treatment of allergic bronchopulmonary aspergillosis and bronchial thermoplasty should only be used in the context of a clinical study. So far, no biomarkers are recommended in for use in routine clinical practice. At the time of publication, there is not enough evidence regarding the use of macrolides in severe asthma.

Are there unanswered questions today?

We have come a long way in understanding and managing asthma over the last 30 years. It is now widely accept that asthma is characterised by bronchial responsiveness and inflammation in which many cells and mediators play a role but which is usually a T-helper cell type 2 driven, eosinophilic inflammation. The majority of these patients will respond well to currently available treatment and lead unhindered, normal lives.

However, there is ~10–15% of patients who will not respond to treatment and who have symptoms and consequent disability caused by uncontrolled disease. We need to assess the true number of these severe, uncontrolled, high-risk patients, clarify the mechanisms that lead to this severe, non-response to treatment state, and design and produce new medications. In order to do this, we need to involve the patients and ask for their input: what are their needs, which are their priorities and what solutions do they require? New medications, especially so-called "biological" agents, require a lot of effort in research and development which is very expensive and, as a result, come at a high price especially when they are designed for few patients and orphan diseases [57]. So, in any planning for new needs and treatments in severe asthma, we need concerted action including healthcare professionals from primary to tertiary care, the industry, patients and policy makers. It is important to have new medications but it is also important to have medications that can be reimbursed by healthcare systems and sustained for the long term.

Important questions that help us assess a patient we see for the first time

What is the age of onset?

Early onset asthma is usually allergic and responds well to steroids. Asthma that is associated with infections during the first 3 years of life presents with wheezing and can either disappear or persist with age. Late-onset asthma affects ~4–8% of those above the age of 65 years and may easily be misdiagnosed and inadequately treated. Often, it is not associated with atopy and it is less clear whether allergic exposure and sensitisation play the same role in the development of disease in adults as they do in children. ICS therapy is recommended for patients with persistent late-onset disease.

Which are the most important symptoms?

Wheeze is a symptom that usually responds to broncho-dilatation while cough may imply the need for anti-inflammatory medication. In all cases, alternative diagnoses such as vocal cord dysfunction or GORD must be considered if the patient does not respond to asthma treatment.

When do the symptoms appear and does this influence treatment?

Symptoms appearing on exertion usually require more relief medication while night-time awakenings imply the need for ICS.

Has the patient linked his symptoms to specific exposure?

The patient may say that their symptoms appear in the spring, suggesting spring allergy, or when entering an uninhabited house, suggesting allergy to mites or moulds, or with viral infection, at work, after exercise *etc*. It must be stressed that patients do not always recognise such links and need to prompted by specific questions which would include conditions at work, smoking, lifestyle and many others. Avoidance of specific triggers should be advised and stressed. The stepping up of medication in specific seasons or circumstances should be recommended. Specific immunotherapy may be an option for patients with clinicaly relevant monosensitivitiy to allergens and mild–moderate disease and anti-IgE treatment for more severe cases.

Are there other important diseases/comorbidities?

Always ask for symptoms of upper airway disease, assess severity and provide appropriate treatment. Local steroids and LTRAs can work in both cases and provide good disease control. Psychological status of the patient should always be considered as psychomorbidity is a major risk for uncontrolled asthma. Psychiatric/psychological help may be required. Thyroid function and perimenstual exacerbations should be examined and managed. Smoking cessation programmes should be offered and recommended to smokers and advice from a dietitian to obese patients. Although not always achievable, smoking cessation and loss of excess weight lead to better asthma control.

Do we need a biomarkers?

There is no universally accepted biomarker that is easy to use, applicable and meaningful in clinical practice. Examining for atopy and peripheral eosinophilia is important in the original work-up and, in severe asthma, may suggest specific treatment (*e.g.* anti-IgE, anti-IL5). Exhaled NO is relatively easy to measure and increased levels may imply an upcoming exacerbation but its use is not universally recommended. Many other markers in the blood, tissue, sputum and exhaled air have been tested but still remain in the research setting and specific high output severe asthma centres.

Conflict of interest

None declared.

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