Asthma: diagnosis and management in adults

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Abstract

Asthma is a common respiratory disorder characterized by chronic airway inflammation and airway hyperresponsiveness. It typically presents with a constellation of symptoms including wheeze, shortness of breath, chest tightness and cough. It is increasingly recognized as a heterogeneous disease with distinct clinical and molecular phenotypes based on clinical, inflammatory cell and cytokine profiles. Diagnosis, however, remains principally clinical, supported by objective evidence of variable airway obstruction and/or airway hyperresponsiveness. Management aims to minimize current symptoms and prevent future deterioration, in particular acute exacerbations. Pharmacological treatment is principally inhaled therapy (a corticosteroid and β-adrenoreceptor agonist), prescribed in a stepwise fashion in accordance to disease severity. Non-pharmacological management, principally patient education (but also smoking cessation and allergen avoidance if applicable), plays an equally important role. Although most asthmatic patients achieve stability with inhaled treatment, a minority remain symptomatic despite maximal therapy. Anti-immunoglobulin E therapy is effective for some but not all patients with severe asthma, reflecting its significant heterogeneity. Current research therefore focuses on the accurate identification of disease phenotype and potential biomarkers so that appropriate targeted therapy can be given.

Keywords Airway hyperresponsiveness; airway inflammation; asthma; inhaled corticosteroids; methacholine challenge; omalizumab

Key points

- Asthma is a heterogeneous disease with an evolving number of phenotypes
- Asthma remains a clinical diagnosis, supported by objective evidence of airflow obstruction
- When the diagnosis is uncertain, other investigations such as bronchial provocation and reversibility testing, may be helpful
- Pharmacological management of asthma is largely unchanged, with the addition of tiotropium and omalizumab in selected cases
- Non-pharmacological approaches are important in achieving good asthma control
- New biological therapies targeting specific asthma phenotypes are in advanced clinical development

A common and heterogeneous disease

Asthma is one of the most common respiratory diseases, with an estimated 300 million people suffering from asthma worldwide and a rising prevalence in developed countries. In the UK, approximately 5.4 million people are currently given treatment for asthma: 1.1 million children (1 in 11) and 4.3 million adults (1 in 12). The healthcare and socioeconomic costs are significant, with the National Health Service spending an estimated £1 billion per annum on the treatment and care of asthmatic patients. Despite this, more than 50% of patients suffer at least one exacerbation (acute worsening of symptoms often necessitating hospitalization) over the course of a year, with over 1000 deaths per year in the UK alone. Furthermore, treatment is usually long term and associated with adverse effects. It is therefore imperative that patients are diagnosed accurately to ensure appropriate, and avoid inappropriate, treatment.

One of the main challenges is the heterogeneity of asthma. It has long been recognized that asthma can present at different stages of life, with varying severity and treatment response. This is now believed to reflect differing underlying pathological processes and has driven efforts to cluster and distinguish distinct clinical 'phenotypes' and molecular 'endotypes' based on demographics, clinical features and inflammatory cell and cytokine profiles.[1]

Definition and hallmark features

The Global Initiative for Asthma (GINA) definition endeavours to encompass the core clinical features and pathological hallmarks distinguishing asthma from other respiratory conditions. Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Classically, chronic airway inflammation in asthma was thought be primarily driven by eosinophils as a result of heightened T helper type 2 adaptive response to various allergens. However, it is now recognized that the innate epithelial immune system may be equally important. Chronic inflammation ultimately leads to structural changes in airway morphology, termed remodelling. Another cardinal feature is airway hyperresponsiveness, defined as heightened pharmacological sensitivity and reactivity of the airway smooth muscle to bronchoconstrictor stimuli. It is associated with variable airflow obstruction and is positively associated with disease severity.

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The exact mechanism is unknown, although mast cell infiltration and interaction with the smooth muscle layer appear to play a role.

Diagnosis

A diagnosis of asthma is established by identifying a characteristic pattern of clinical symptoms and signs in the absence of an alternative diagnosis, and is supported by objective measurements of variable airflow obstruction. A detailed clinical assessment is therefore vital. Figure 1 provides an example of the diagnostic work-up of a patient suspected of having asthma.

Clinical history and examination

In adults, asthma typically presents as a constellation of respiratory symptoms including wheeze, shortness of breath, chest tightness and cough. An isolated cough is seldom caused by asthma, although cough-variant asthma is a possibility. Caution should be taken as descriptors of symptoms differ with age and culture. It is also paramount to establish the pattern of symptoms in terms of variability over time and in severity. Night-time and early morning 'dips' are suggestive of asthma.

Furthermore, triggers of symptom exacerbation should be sought. Common precipitants include allergens, cold air, exercise, medications (aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], β-adrenoreceptor blockers) and viral infections (particularly the common cold). In adults of working age, an occupational history and symptom variability and intensity during work days and holiday should be assessed to exclude occupational asthma. A history of other atopic conditions such as hay fever or eczema and/or a family history of asthma or atopy further increase the likelihood of asthma.

In the absence of an acute exacerbation, physical examination is frequently uninformative but offers an opportunity to exclude mimicking disorders. The most common feature is expiratory polyphonic wheeze caused by the variable degree of obstruction within the small airways. This is often only audible in forced expiration. Chronic obstructive pulmonary disease (COPD) and acute left ventricular failure (sometimes termed cardiac asthma) can present in similar fashion, but other distinguishing features are usually present. Other conditions that can present with expiratory wheeze include tracheomalacia, inhaled foreign body and upper airway dysfunction, although these typically present as a monophonic wheeze. Importantly, inspiratory crepitations and stridor are not features of asthma. Table 1 summarizes the clinical features and differential diagnoses of asthma.

Assessment of airflow obstruction

Although the diagnosis of asthma may be apparent from the clinical history alone, objective evidence of variable airflow obstruction is recommended. Spirometry, when calibrated correctly and used by well-trained operators, is preferred to peak expiratory flow (PEF) as it provides greater accuracy in identifying airflow obstruction and is less effort-dependent. Airflow obstruction is quantified by the forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio, with a reference range of 0.75–0.80. An FEV_1/FVC ratio <0.70 is considered to indicate obstruction and supports a diagnosis of asthma.

It is important to note, however, that the absence of airflow obstruction in an asymptomatic patient with a history suggestive of asthma does not exclude asthma, and additional investigations may be required as outlined below. Spirometry is also helpful in deciding the plan of investigation in patients with intermediate probability of asthma following clinical assessment (Figure 1). If spirometry demonstrates an obstructive pattern, bronchodilator reversibility testing is recommended to confirm variable airflow obstruction and exclude other obstructive lung diseases such as COPD. However, if spirometry is normal or near normal, reversibility testing may not help diagnosis as there is little room for improvement. In such cases, measurement of airflow variability over time (Table 2) and airway hyperresponsiveness are the preferred next steps.

Assessment of airway hyperresponsiveness

Bronchial hyperresponsiveness can be assessed by bronchial provocation testing; this is frequently helpful in patients with an intermediate probability of asthma whose spirometry results are normal. The methods chosen (Table 2) usually depend on local expertise, patient capability and preference.

Assessment of eosinophilic airway inflammation and allergy tests

In a minority of patients, the diagnosis of asthma remains unclear despite the history and lung function measurements. Moreover, some patients with a previous diagnosis of asthma appear to have uncontrolled disease despite inhaled and/or systemic corticosteroid treatment. In such settings, assessment of airways inflammation can be very informative.

Until recently, this required induction of sputum to measure the eosinophil count; however, this procedure is both time-consuming and technically difficult. Consequently, a number of biomarkers of airway eosinophilic inflammation are currently in use, including blood eosinophil count and fractional concentration of exhaled nitric oxide (FeNO). However, other non-asthmatic conditions can be associated with increased blood eosinophils (eczema) and/or FeNO (allergic rhinitis), while smoking is known to decrease FeNO. Therefore, measurements of airway inflammation should only be interpreted in the context of other co-morbid conditions and clinical tests.

Finally, evidence of atopy, denoted by either positive skin-prick testing or measurement of specific immunoglobulin E (IgE) concentrations, increases the likelihood of asthma in a patient with typical respiratory symptoms. Again, it is neither diagnostic nor specific for asthma.

Special circumstances

Although the diagnostic work-up is broadly similar in most patients, there are a few exceptions (Table 3). Most of these patients should be assessed in specialist centres.

Confirming the diagnosis of asthma in patients already on maintenance therapy

It is not uncommon to see a patient who is already on maintenance therapy but whose diagnosis is uncertain; this may be because of a lack of expected response to treatment or because of other clinical features such as a significant smoking history that make COPD a possibility. In such cases, assessment is

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