Chronic severe asthma in adults

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Abstract

Patients with chronic severe asthma remain symptomatic despite intensive treatment with high-dose inhaled corticosteroids and long-acting β_2-adrenoreceptor agonists; they therefore frequently require systemic corticosteroids. These patients experience substantial morbidity, reduced life expectancy and high use of healthcare resources. Patients should be assessed for treatment adherence, potential asthma triggers, coexisting or alternative diagnoses and undertreatment. A stepwise pharmacological treatment approach should be combined with facilitation of adherence and inhaler technique, non-pharmacological treatments where appropriate and supported self-management. Specialist asthma services may start additional treatments (e.g. monoclonal antibody therapy, bronchial thermoplasty) in patients with persistent poorly controlled asthma.

Keywords Bronchial thermoplasty; difficult-to-control asthma; exacerbations; mepolizumab; omalizumab; phenotypes; severe asthma

Key points

- Patients who have uncontrolled asthma on British Guideline on the Management of Asthma step 4 or 5 treatment should be referred to a 'difficult asthma' service for assessment
- Ensure the diagnosis of asthma is correct, especially if there is a lack of response to standard asthma therapy
- Adherence to asthma treatments is very important in managing severe asthma
- Identify coexisting conditions and aggravating factors that may be amenable to treatment
- Encourage smoking cessation and weight reduction
- Any patient taking long-term oral corticosteroids should carry a corticosteroid warning card
- Under specialist supervision, biological therapies (omalizumab), bronchial thermoplasty and immunosuppressants can be considered for patients with persistent poorly controlled asthma

Burden of disease

Chronic severe asthma is defined as persistent symptoms and/or frequent exacerbations despite treatment with high-dose inhaled corticosteroids (ICS) and inhaled long-acting β_2-adrenoreceptor agonists (LABAs) (step 4 of the British Guideline for the Management of Asthma), or the need for continuous or frequent use of oral corticosteroids (step 5).[1]

The prevalence of severe asthma is estimated to vary from 4% to 10% of the population with asthma. Two-thirds of patients are female. Patients with severe asthma have reduced life-expectancy and substantial morbidity because of poor control and the adverse effects of high-dose corticosteroids. Severe asthma persists in most patients.

Evaluation of the patient

Patients with uncontrolled asthma on step 4 or 5 treatment should be referred for assessment at a service specializing in difficult asthma. It is important to distinguish severe asthma from 'difficult-to-control' asthma caused by reasons other than disease severity.[1] A systematic evaluation of patients includes:

- confirmation of the diagnosis of asthma
- identification of the cause(s) of persistent poor control
- development of a patient-specific management plan.

Confirmation of the diagnosis of asthma

At initial assessment of difficult-to-control asthma, ensure the diagnosis is correct before escalating treatment. The national guidelines outline an algorithm to diagnose asthma using clinical probability, measurement of airway obstruction and response to treatment.[1] Fractional exhaled nitric oxide (FeNO) measurements can provide supporting evidence (Table 1).[2] Additional investigations may be required to diagnose and evaluate alternative diagnoses and co-morbidities (Table 1).

Differential diagnosis

In adults, the differential diagnosis includes:

- chronic obstructive pulmonary disease
- bronchiectasis
- cardiac failure
- pulmonary thromboembolism
- vocal cord dysfunction
- dysfunctional breathing
- endobronchial lesions.

One or more of these conditions can coexist with asthma.

Cause(s) of persistent poor asthma control

The cause(s) of persistent poor asthma control should be investigated. They include poor adherence to asthma medication, unidentified trigger factors, coexisting co-morbidities and undertreatment.

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Investigations in patient with chronic severe asthma considered at a tertiary referral centre

Baseline investigations in all patients	
Spirometry including reversibility and transfer factor	To document variable airflow obstruction and identify features not consistent with asthma
Peak expiratory flow	To provide evidence of variable lung function. To identify occupational asthma in relevant patients
Chest X-ray	To exclude other diagnoses
Oxygen saturation	Low baseline saturations prompt consideration of conditions other than asthma, e.g. COPD
Additional investigations:	
Blood eosinophil count	Elevated in eosinophilic asthma
Total serum IgE and radioallergosorbent test	To provide evidence of allergic sensitization
Aspergillus serology	Elevated concentrations prompt consideration of allergic bronchopulmonary aspergillosis and fungal sensitization in association with asthma
Antineutrophil cytoplasmic antibody	If pulmonary vasculitis considered, e.g. eosinophilic granulomatosis with polyangiitis (Churg—Strauss syndrome)
Immunoglobulins and functional antibodies	To exclude immunodeficiency if recurrent infections are a prominent feature
Blood prednisolone and cortisol concentrations	To assess adherence to treatment, if applicable
Blood theophylline concentrations	To assess adherence to treatment, if applicable
Bronchial provocation testing	To provide evidence of airway hyperresponsiveness, especially if baseline spirometry fails to confirm an asthma diagnosis
FeNO	Associated with eosinophilic inflammation and corticosteroid responsiveness. Used to support (FeNO $\geq$40 ppb) or rule out a diagnosis of asthma in patients with intermediate probability of asthma and normal spirometry
Sputum cytology	Determines inflammatory phenotype (eosinophilic versus non-eosinophilic/neutrophilic). Sputum eosinophil counts can guide corticosteroid treatment
High-resolution CT scan of the chest	To exclude other diagnoses, e.g. bronchiectasis, interstitial lung disease
CT of the sinuses and nasal endoscopy	To assess presence of sinus disease
Electrocardiogram, echocardiogram	To exclude cardiac failure (wheeze due to 'cardiac asthma')
Bronchoscopy	To look for tumours or foreign bodies
D-dimer/CT pulmonary angiogram	To exclude recurrent pulmonary embolism
Polysomnography	To exclude sleep apnoea
Laryngoscopy during attack	To confirm vocal cord dysfunction

COPD, chronic obstructive pulmonary disease; CT, computed tomography.

Table 1

Adherence to asthma treatment and inhaler technique

Poor adherence to treatment is one of the most important reasons for poor asthma control.[3] It is very hard to detect poor adherence to treatment from the history alone. Adherence can be assessed by reviewing the prescription refill frequency and measuring circulating blood prednisolone concentrations in patients taking oral corticosteroids. A trial of a parenteral depot corticosteroid may establish whether persistent symptoms are caused by poor compliance with inhaled and/or oral corticosteroids. Around half of patients have poor inhaler technique irrespective of the device used.[1]

Trigger factors

Triggers such as allergens, occupational agents and non-steroidal anti-inflammatory drugs (NSAIDs) induce asthma attacks only in people sensitive to these stimuli. Triggers such as exercise, cigarette smoke, infections and β-adrenoreceptor blockers can induce symptoms in all individuals with asthma (Table 2).

Co-morbidities

Co-morbidities (Table 2) can contribute to poor asthma control and reduced quality of life in severe asthma. They require additional assessment (see Table 1).

Phenotypes of severe asthma

Several phenotypes of severe asthma are recognized based on clinical, physiological or immunological variables used to help classify asthma as well as predict and monitor response to therapy (Table 2).

Management

Management aims to achieve good asthma control and minimize treatment burden, especially from oral corticosteroid use. However, it is often difficult to achieve this in severe asthma. Patients with severe asthma should be reviewed at a multidisciplinary asthma clinic by a team including a respiratory physician, physiotherapist, asthma nurse specialist and psychologist. Pharmacological and non-pharmacological interventions are important in chronic severe asthma (Figure 1).

Address poor adherence and check inhaler technique

Attempts to improve adherence to maintenance therapy (Figure 1) should be made before escalating treatment in patients with difficult asthma. Assessment of inhaler technique is part of routine clinical review.