

Review article

Difficult asthma

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Asthma is a chronic inflammatory disorder of the airways that is increasing in prevalence, which can pose significant morbidity and mortality. Most patients with asthma are easily diagnosed, responding to standard treatment with a short-acting inhaled β_2 -agonists for symptom control, and to long-term therapy including inhaled glucocorticosteroids (GCS) to control airway inflammation. Some patients who fail to respond to this therapy require further investigation to establish reasons for the lack of response (1). The introduction of national and international guidelines for the management of asthma has made it possible to achieve a definition of “difficult-to-treat” or “therapy-resistant” asthma as poorly controlled asthma in terms of chronic symptoms, episodic exacerbations, persistent, variable airways obstruction, continued requirement for short-acting β_2 -agonists, despite the use of high doses of inhaled glucocorticosteroids, i.e. daily doses of 2000 μg of beclomethasone, or 1600 μg of budesonide or 1000 μg of fluticasone in adults (2). Response to therapy is included in this concept. Some patients may also require pulsed or continuous doses of oral GCS to maintain reasonable control of asthma.

There are several factors that may contribute to a poor response to conventional therapy. It is important to assess these patients carefully to identify whether there are any correctable factors that may contribute to their poor control.

Diagnosis of difficult asthma

Diagnosis of asthma

It is essential to be as certain as possible of a primary diagnosis of asthma. This diagnosis is based on a clinical

history and physiological evidence of variable and reversible airway obstruction (3), and on the exclusion of possible alternative diagnoses that may mimic asthma (4).

In the elderly, the principles of the diagnosis are similar to those in other age groups, but asthma in older age is commonly underdiagnosed and undertreated (5). The prevalence of asthma over the age of 60 years has been estimated to be 5–7% (6). Only a very small minority will develop the disease *de novo* after this age. In older individuals, increased bronchial responsiveness is an even less specific marker for asthma, as it is also found in chronic obstructive pulmonary disease (COPD), left ventricular dysfunction, and even in healthy elderly individuals (7). In a longitudinal survey study of respiratory disease, Burrows et al. (8) showed that among asthmatic patients newly diagnosed over the age of 60, two-thirds had respiratory symptoms, and one-third had obstructive defects in lung function for a mean period of 8.5 years prior to the diagnosis. The reasons for this delay in diagnosis are unexplained but several factors may contribute including changes in perception of disease with increasing age (9). Elderly asthmatics are also prone to more frequent and longer hospital stays (10), and it is thought that they have a greater risk of asthma death (11, 12). Nevertheless, it appears that asthma deaths in the elderly are probably due to other causes, such as cardiac disease or COPD, and not pure asthma (13). Thus asthma in the elderly is a relatively common problem, with difficulties in both diagnosis and management.

Exclusion of other diagnoses

In some patients, an incorrect diagnosis of asthma results in an apparent failure to respond to conventional

therapy. Several diseases may cause wheezing, including left ventricular failure, COPD or vocal cord dysfunction. COPD is characterized by poorly reversible or irreversible airflow limitation, whereas asthma is characterized by reversible airflow limitation. Considering these definitions, the differential diagnosis is quite simple in most cases. However the distinction from late onset asthma may be difficult particularly in cigarette smokers (14, 15). In this category of patients, a trial of oral GCS is indicated for 14 days. An increase in forced expiratory volume in one second (FEV₁) or peak expiratory flow (PEF) of more than 15% indicates that there may be an asthmatic component in the patient's condition. A negative response may indicate COPD, or rarely GCS-resistant asthma.

Vocal cord dysfunction is a term used to indicate the presence of upper laryngeal airway obstruction caused by adduction of the anterior two-thirds of the vocal cords (16). This abnormality may be identified in people with or without asthma. In a series of such patients, 32% had coexistent asthma, which complicate the diagnosis (17). Some of these patients may be treated with large doses of antiasthma therapy, including oral GCS (18). The wheezing in these patients is never present during sleep and often worsens during examination of the chest (19). Management of vocal cord dysfunction is difficult. Reassurance, psychiatric assessment, and speech therapy may be useful (20).

Asthma control

It is important to establish that the asthmatic patient has been given an adequate dose of inhaled GCS. Indeed, undertreatment may lead to a patient with continuing symptoms being mislabeled as suffering from difficult asthma (21). Asthma control is usually assessed by evaluation of the patients' perceptions of their symptoms of wheeze (22), shortness of breath, cough, nocturnal awakenings and need to use short-acting β_2 -agonists medication. Additional elements are important in defining control: the number of acute exacerbation requiring oral/systemic GCS, the monitoring of peak flow (PEF) and FEV₁, and the measures of quality of life and functional status (23). The observation of the asthmatic over a period of several weeks or months will allow both diagnosis of asthma and assessment of its severity and control with therapy.

Exacerbating factors

A number of medical factors can contribute to poor control of asthma.

Gastroesophageal reflux

Gastroesophageal reflux (GER) is common in patients with asthma, with an estimated prevalence of 34–80%

(24, 25), vs. 5–10% in the general population (26). This large variation in GER prevalence reflects substantial differences in the standards applied for establishing the diagnosis of both asthma and GER and the frequency of silent GER (27). Twenty-five percent of asthmatic subjects with proven GER do not have the typical GER symptoms of heartburn and acid regurgitation (28). In some patients reflux may exacerbate respiratory symptoms, and enhance the bronchoconstriction resulting from natural stimuli. It is particularly important to consider GER in patients who appear not to respond to standard therapy (29). A carefully monitored trial of antireflux therapy, in addition to optimal asthma therapy, may be the best way to assess the contribution of GER. If GER is suspected, measures should be taken to reduce GER and a trial of therapy with proton-pump inhibitors should be undertaken (30). Both medical therapy (31) and surgical treatment (32) of GER have been reported to reduce the asthma symptoms. Patients in whom reflux is suspected but who do not respond to antireflux therapy should be referred for further investigations such as 24-h esophageal pH monitoring and endoscopy.

Upper airway diseases

Rhinitis implies inflammation of the paranasal sinuses. Persistent rhinitis is defined as signs and symptoms of inflammation of the sinuses persisting for more than 12 weeks per year (33, 34). An association between chronic rhinitis and asthma has been reported in 20–70% of adult asthmatic people. History of an upper respiratory tract infection preceding the worsening of asthma should raise the suspicion of rhinitis (35). Nasal endoscopy provides excellent visualization of the entire nasal cavity and sinus ostial area that helps in diagnosing rhinitis (36). Coronal CT scan is presently considered the best imaging mode for patients suspected of having chronic rhinitis (37). Appropriate and effective treatment of coexisting rhinitis by nasal GCS improves airway hyperresponsiveness and may result in improvement of asthma (38).

Nasal polyposis (NP) is commonly found in association with lower tract respiratory disorders, such as asthma and bronchial hyperresponsiveness. NP is a frequent rhinitis that is responsible for persistent nasal obstruction and anosmia. NP is characterized by protrusion of bilateral benign edematous polyps from the meatus into the nasal cavities. The events initiating the formation of nasal polyps remain poorly understood, although eosinophils seem to play a central role in their pathogenesis (39). NP may predispose to poor asthma control. Treatment of NP consists of medical and/or surgical treatment. Topical glucocorticosteroid therapy has a well established role in the management of NP, since it has proven efficacy on symptoms and size of polyps and may help prevent the recurrence of NP after surgery (40). Surgical management

of NP aims to restore normal nasal function, including nasal ventilation and sinus drainage, when topical GCS alone are insufficient. The impact of medicosurgical treatment of NP on the evolution of associated asthma and asymptomatic bronchial hyperresponsiveness is still controversial. Some studies have indicated that polypectomy and sinus surgery may induce worsening of asthma severity (41).

Treatment of upper respiratory tract symptoms is an integral part of asthma management. Intranasal GCS are recommended for the treatment of chronic rhinitis in patients with persistent asthma. Intranasal GCS reduce nasal inflammation, obstruction and discharge, and have been shown to reduce lower airway hyperresponsiveness and asthma symptoms (35).

Poor adherence and psychosocial factors

Noncompliance or poor adherence to medical advice is a significant problem and may account in part for the failure to improve morbidity in the treatment of patients with asthma (21). Reported levels of compliance to treatment with inhaled GCS therapy has ranged from as low as 30% in adolescents to 55% in adults. The degree of adherence to prescribed therapy in asthmatic patients remains difficult to estimate. Poor compliance with inhaled GCS may result from a lack of immediate beneficial effects on asthma symptoms and an unwarranted fear of side effects, an inappropriate and complex drug regimen, and lack of family support. Many patients with poorly controlled asthma who are admitted to hospital show rapid improvement when the previously prescribed medication is given under supervised conditions. However, more studies are needed to determine the factors that contribute to poor compliance. Adolescent patients are particularly poor at complying with regular therapy. Physician-patient partnership is required and must recognize the patient's own goals and personal circumstances.

Psychosocial factors are present in fatal, near-fatal asthma, and severe asthma (42). Medications prescribed for psychosocial problems, depression, conflict, and psychiatric illness in people with asthma are associated with higher risk of asthma death (43). Psychological factors are most likely to be present in patients who appear to have severe chronic asthma or difficult-to-control asthma. Identification of these patients should result in involvement of a mental health professional because of the high associated psychiatric morbidity (44). Some people are "exaggerated perceivers" and have more symptoms than can be predicted by physiological measures (45). This group of patients is at risk of being overtreated. By contrast, patients with a high level of denial will delay seeking treatment and probably not accept that they have a significant problem that requires regular treatment. The identification of psychological factors can be facilitated by questionnaires to assess

denial and bother. However, there are no obvious personality traits in those that comply poorly.

Allergen and occupational exposure

Other factors may include exposure to allergens, indoor and outdoor air pollution, and endotoxin. The most common domestic allergens are house-dust mites, cockroaches, cat dander, and other domestic pets. All may contribute to difficult asthma. Severe exacerbations of asthma leading to respiratory arrest have been attributed to airborne mould spores like *Alternaria* (46). Sensitization and seasonal exposure to *Alternaria* has been proposed as a risk factor for sudden death from asthma. The degree of exposure of the people with severe brittle asthma to relevant aeroallergens in their home is not known, but this may be relevant to some rapid episodes of deterioration (47).

Many people exposed to chemical sensitizers at work (48). It is therefore critical to consider an occupational history, particularly when asthma improves during weekends and on holidays (49). It is important to make the diagnosis of occupational asthma early, as exposure to the causative agent for more than 6 months can be associated with the persistence of asthma, even when avoidance is complete.

Exposure to cigarette smoke clearly decreases the efficacy of specific asthma therapy, emphasizing the relevance of smoking cessation in asthmatics. Pedersen et al. (50) have evaluated the long-term effects of inhaled GCS on symptoms of asthma, FEV₁, bronchial hyperresponsiveness, and blood markers of eosinophilic inflammation. One major conclusion of this study is the negative effect of smoking on asthma care with a trend to GCS resistance in asthmatic smokers.

Patterns of difficulty in asthma

Brittle asthma

Brittle asthma refers to unstable asthma that is unpredictable, and often no consistent trigger factors can be identified. The term brittle asthma should be applied to two different asthma phenotypes, each characterized by the presence of recurrent severe attacks (51). Type 1 is persistent, with chaotic variability in PEF diurnal variation > 40% for more than 50% of the time despite medical therapy. Type 2 is sporadic; sudden falls in PEF on a background of normal or near normal lung function and well-controlled asthma. Brittle asthma is rare. Little is known about the incidence or prevalence of brittle asthma. In type 1 brittle asthma, there are usually no identifiable trigger factors that are related to the falls in PEF. Many of the patients have psychological problems and there may be problems with adherence to therapy (52). However, this cannot be regarded as the only reason for the underlying difficult

asthma (53, 54). Brittle asthma is not due to poor compliance. In type 2 brittle asthma, there may be rapid and unexpected falls in PEF with severe exacerbations that may require ventilation (55). There is some evidence that patients with type 2 brittle asthma have a high incidence of food allergy and reported food allergy is a risk factor in death and near death from asthma (56). In patients who have had near-fatal asthma attacks, a reduced perception of worsening airway function can be identified, and this might be a relevant factor in both type 1 and type 2 brittle asthma. Such patients may not be aware of the severity of the attacks and therefore delay taking appropriate preventive or reliever therapy.

Worsening of asthma may occur premenstrually in some women (57). The characteristic pattern is an increase in asthma symptoms and a fall in PEF 2–5 days before the menses. Although premenstrual exacerbation may be mild and may respond to an increased dose of inhaled GCS, it can be particularly severe, and may appear to be GCS-resistant (58). The mechanisms of premenstrual symptoms are uncertain.

Glucocorticosteroid resistant and dependent asthma

GCS are the mainstay of treatment for bronchial asthma and inhaled GCS are the preferred treatment of persistent asthma. There has been recognition of a group of asthma patients who do not appear to benefit from GCS therapy, i.e. the so-called GCS resistant asthmatics. True GCS resistant asthma is very uncommon and may occur in only one asthmatic in 1000 or 10 000 (59). It is important to establish firmly the diagnosis with a formal trial of oral GCS (30–40 mg daily in a single morning dose for 2 weeks). This trial should be preceded by a 2-week period of monitoring, ideally with placebo tablets. GCS resistance is diagnosed if the increase in FEV₁ is < 15% above baseline values (60). GCS-resistant asthma is associated with impaired responsiveness of monocytes and T lymphocytes *in vitro* and *in vivo* to the suppressive effects of GCS. In fact, GCS responsiveness is probably a continuous spectrum with individuals who demonstrate GCS resistance falling at one end of an unimodal distribution.

GCS-dependent asthma is defined as asthma that can only be controlled with oral GCS. By definition, it is severe, different from GCS resistant asthma by the fact that there is a positive response to GCS therapy. Lowering the maintenance dose of GCS results in worsening asthma control (61). This suggests that these patients are relatively resistant to the anti-inflammatory effects of GCS and may be part of a continuum, as described above. The mechanisms of relative GCS resistance are not yet known, as these patients are difficult to investigate with invasive techniques (62). Studies with biopsies, bronchoalveolar lavage and induced sputum have shown that inflammation persists, despite high doses

of GCS and there is an increase in neutrophils in the airways of these patients (63, 64).

Airway remodelling or irreversible obstruction

Although asthma is a reversible disease, progressive obstruction is seen in some patients. This irreversible narrowing of the airways only appears to occur in some patients and usually in those with most severe disease, but there is no way of predicting which person will show the greatest decline (65). The nature of airway obstruction in these patients is not yet known, but it is presumed to be due to structural changes in the airways, such as fibrosis and thickening of airway smooth muscle as a consequence of chronic airway inflammation (66). Structural changes are presumed to be irreversible using currently available therapies, and this emphasizes the need for early and effective control of the inflammatory process (67). There is increasing evidence that the early use of inhaled GCS may prevent irreversible changes in the airway function, but more controlled studies are needed.

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is an immunologically mediated response to inhaled *Aspergillus* spores in *Aspergillus*-sensitive patients. The diagnosis is based on a combination of clinical, serological and radiological criteria. Major criteria are asthma, episodic pulmonary infiltrates, central bronchiectasis, eosinophils in sputum and blood, elevated total serum IgE concentration, immediate reaction to *Aspergillus* antigen on skin testing, and precipitating antibodies against *Aspergillus* antigens. ABPA is a rare diagnosis. Oral GCS remain the mainstay of the treatment. The efficacy of oral GCS in the acute phase or in exacerbations is well known. The long-term benefits of oral GCS therapy are unclear. Stevens et al. (68) conducted a randomized, double-blind trial showing a beneficial effect of oral itraconazole in the treatment of ABPA. The optimal duration of itraconazole therapy has not been defined (69).

Churg–Strauss syndrome

Churg–Strauss syndrome is an eosinophil-associated small vessel granulomatous vasculitis, characterized by late-onset asthma, upper airway disease, eosinophilia, and clinical manifestations of systemic vasculitis. Extra-pulmonary manifestations include weight loss, myalgia, arthralgia, skin signs, mononeuritis multiplex, gastrointestinal tract involvement, and cardiomyopathy (70). In 1990 the American college of Rheumatology promulgated specific diagnostic criteria for the syndrome. For the diagnosis of Churg–Strauss syndrome to be made the patient must present with at least four of the following six features: 1) moderate to severe asthma; 2) peripheral

blood eosinophilia (>10%); 3) mononeuropathy or polyneuropathy; 4) nonfixed pulmonary infiltrates; 5) paranasal sinus abnormalities; and 6) a biopsy specimen containing a blood vessel with extravascular eosinophils. Churg–Strauss syndrome has recently received much attention because of several reports that the syndrome may present clinically in difficult asthma when oral GCS are replaced by other asthma therapies, including leukotriene receptor antagonists or inhaled GCS (70, 71). Physicians should be alert to the early symptoms of Churg–Strauss syndrome and be especially cautious if patients with difficult asthma are being treated with long-term oral GCS.

Management and treatment

Attention to the exacerbating factors may improve the control of difficult asthma to a considerable extent.

Allergen avoidance

Reversal of bronchial hyperresponsiveness, with a reduction in oral GCS requirement during prolonged hospitalization in an environment with low level of house-dust mites, has been reported in mild-to-moderately severe asthma patients. Assessment of allergen exposure would probably require a home visit and measurement of the levels of the common home allergens, with specific measures being taken to reduce exposure. The role of certain allergens, in causing difficult asthma needs further evaluation.

Psychosocial factors

Retrospective analysis of patients who have died of asthma indicates that psychosocial factors may have contributed to poor asthma control and therefore to death caused by asthma. An association between psychiatric disturbances and asthma morbidity has been reported in near-fatal asthma attacks. In particular, the importance of denial has been identified as a barrier to the use of appropriate treatment. Patients with the highest levels of compliance had significantly fewer exacerbations than those with a confirmed record of poor compliance (72). Identifying the presence of noncompliance will allow the clinician to develop an appropriate educational and self-management plan for the individual patient (73). In difficult-to-control asthma, support from a mental health professional may improve asthma control.

Patient education plays a pivotal role in the integration of the therapeutic process. Education programs can be very useful for the patient with difficult asthma (74). These patients are helped to integrate specific knowledge, attitudes, and practical skills to optimally cope with asthma. In addition, smoking cessation programs should be proposed to all asthma patients who smoke.

Specific therapy

Glucocorticosteroids

By definition, difficult asthmatics will be receiving high doses of inhaled GCS, often together with oral GCS. One of the gray areas is whether further increases in dose will bring further benefit. Studies of dose–response relationships of inhaled GCS indicate there is a progressively diminishing response above 800 µg/day of budesonide or 400 µg/day fluticasone propionate (75, 76). Individuals may, however, respond to higher doses. Oral GCS should be added in patients with chronic uncontrolled symptoms, or frequent exacerbations despite high doses of inhaled GCS.

Long-acting β -adrenergic agonists

Complementary action of long-acting β_2 -agonists with medium or high doses of inhaled GCS has been reported in moderately severe asthma in terms of both improvement in lung function and prevention of asthma exacerbation (77, 78). Such benefits have been shown to persist for up than one year. Therefore, the addition of long-acting β_2 -agonists in difficult asthma is a reasonable step (79).

Leukotriene inhibitors

Leukotriene inhibitors, particularly leukotriene receptor antagonists, have been added in patients already taking inhaled GCS, with consistent improvements in lung function (80). An inhaled corticosteroid-sparing effect of one leukotriene receptor antagonist has been demonstrated in moderate to severe asthma (81), but these results are controversial (82). Further studies are needed in difficult-to-treat asthma.

Immunosuppressants and antimetabolites

The use of methotrexate and cyclosporine A has been examined in oral glucocorticosteroid-dependent asthmatics in double-blind placebo-controlled studies and a significant oral glucocorticosteroid-sparing effect have been found (83, 84). However, these medications are potentially toxic and cannot be generally recommended at present due to their unfavorable risk–benefit ratio.

Areas for research

Definition of clinical phenotype

A major problem in attempting to understand difficult asthma lies in the difficulty in recruiting large cohorts of appropriate patients for specific studies. A definition for difficult or therapy-resistant asthma based on practical and theoretical considerations should lay the foundations for a large database.

Assessing new therapies

Studies examining the efficacy of potential new agents should be targeted towards more clearly defined specific types of difficult asthma. It is of major importance to attempt to perform studies on as uniform a population as possible of patients with difficult asthma. Many

potential mechanisms have been identified that may form the basis of treatments for asthma. Such potential mechanisms include exploitation of antieosinophil strategies (such as anti-IL-5 antibodies), antichemokine receptors (CCR-3 antagonists), and antiadhesion molecules; other possibilities include anti-IgE therapy (85, 86).

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