

Review article

Severe asthma: definition and mechanisms

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The severe asthmatic is easily recognized, but creating an all-encompassing definition of asthma severity has been difficult. Attempts at such definition must acknowledge the impacts of the disease in terms of symptom burden and functional impairment, of which the three key contributors are symptom frequency, impairment of lung function, and treatment requirement for control of asthma symptoms (1). More recently, quality-of-life measures and markers of socio-economic burden, together with noninvasive inflammatory markers, have emerged as additional potential parameters for inclusion. However, the selection, quantitation, method, and timing of application of severity measures remains arbitrary, and there is also a lack of consistency between severity measures established for national and international asthma management guidelines (2–6).

The aim of asthma treatment must also be formalized in order to establish realizable and definable outcomes for physicians and patients, so that the physician may clearly define treatment intention. The goals of asthma treatment may be simply stated as the control of asthma symptoms and lung function, with the prevention or minimization of symptoms and exacerbations, and the normalization or maximization of lung function. Surveys of asthma treatment would suggest that these goals are achievable in 80% of asthmatics when treated appropriately.

Thus, asthma severity has been considered as the

degree to which symptoms and lung function are perturbed and/or the amount of treatment required to control the disease.

Definition and assessment

The WHO/NHLBI initiative, Global Initiative for Asthma (GINA) (6), defines severe asthma as a condition in which any of the following are manifest: symptoms prior to treatment are continuous, and punctuated by frequent exacerbations or frequent nighttime symptoms; impairment of lung function is demonstrated by FEV₁ of <60% predicted, or peak expiratory flow variability of >30%; or there is limitation of daily physical activities by asthma symptoms. Importantly, this assessment applies to clinical features before treatment is commenced. The British Thoracic Society classifies the severity of asthma by response to the institution of treatment; therefore, an element of treatment of responsiveness is incorporated in the assessment. Treatment requirement defines asthma severity such that mild intermittent asthma may be controlled by rescue β -agonists alone, while moderate to severe asthma may be controlled by moderate to high-dose inhaled or oral corticosteroids. However, the use of medication as a marker of severity remains somewhat arbitrary, as dose selection is dependent on a physician observer, and both assessment strategy

and frequency may vary within and between observers. It is noted that most classifications of asthma severity have not been validated in relation to classification thresholds, reproducibility, or measurement reliability.

With increasing asthma severity, control is less readily achieved despite appropriate treatment, and symptoms and exacerbations, and impairment of lung function remain evident. Thus, the inclusion of asthma control by therapy within a definition of asthma severity is of key importance (7).

Achieving control, however, entails assurance of compliance, the management of factors which exacerbate asthma (e.g., sinusitis and gastro-oesophageal reflux), and appropriate exclusion of other diagnoses. Furthermore, the severity of asthma in any individual may not be fixed and may vary with treatment, intercurrent infection or illness, environmental exposure, and disease chronicity. For example, an asthmatic patient may suffer from chronic symptoms upon which are superimposed exacerbations of asthma.

The concept of assessing asthma over a protracted period has several advantages. The proposal of Redier et al. (8) reviews disease features over the preceding year as reflective of disease *severity*, while assessment over the preceding month is more reflective of disease *activity* or control. Thus, the overall severity may be seen as a cumulative assessment of disease activity over a protracted period, thereby providing adequate time for the identification and avoidance of specific and nonspecific irritants, control of exacerbating factors, and institution and modification of an appropriate treatment regimen.

An important component of severe asthma involves "difficult-to-treat", "therapy-resistant", or refractory asthma in which poor control is evidenced by chronic symptoms, episodic exacerbations, and persistent and variable airflow obstruction despite the use of high-dose inhaled corticosteroids and often concomitant oral corticosteroids. The clinical evaluation of such severe asthmatics is described in Fig. 1.

Prevalence and impact of severe asthma

Asthma currently affects 100 million people worldwide, with a rising prevalence particularly among the young in the Western world (9). The social, medical, and economic impacts of asthma are also rising, and the costs attributable to this disease are now measured globally in billions of dollars (10, 11). Accurate figures on the prevalence of severe asthma are not available, mainly because of the lack of precise figures for the prevalence of asthma itself, and partly because of a lack of a uniform definition.

However, there are pointers to the increasing burden of asthma worldwide, not only from the point of view of increasing disease prevalence, but also from increased health resource consumption and, in a few countries, increasing asthma deaths. In an English asthma community survey ($n=3373$), just 4.6% of subjects had treatment consistent with severe asthma (BTS guidelines steps 4–5), while 8.5% of asthmatics received no treatment at all (12). In a French survey of 4362 asthmatics, 16–17% had continuous daily and frequent nocturnal symptoms, 9% had FEV₁ of <60% predicted, and 5.1% were treated with over 2000 µg/day inhaled and/or oral corticosteroids (13). Patients with the most severe asthma consume more medicines, and use more hospital facilities and medical manpower, and there are also indirect socio-economic costs attributable to loss of productivity and impairment of social function. It is estimated that 80% of asthma expenditure is consumed by only the 20% of the asthmatic population who experience more severe disease (10, 12, 14, 15).

Diagnosis of asthma

The diagnosis of asthma rests on clinical history and physiological evidence of variable and reversible airways obstruction. Symptoms of cough, wheeze, shortness of breath, chest tightness, and sputum production are suggestive of asthma and characteristic when nocturnal worsening or diurnal variation is evident. Allied to this clinical picture, evidence of at least partial reversibility of airway obstruction confirms the diagnosis of asthma. Such evidence may be derived from spontaneous reversibility of airflow obstruction demonstrated by peak flow diary monitoring, bronchodilator response to an inhaled β -agonist such as salbutamol, or an improvement of airways obstruction with a course of oral prednisolone (e.g., 40 mg per day for 2 weeks). Demonstration of bronchial hyperresponsiveness to histamine or methacholine challenge may also be used to support a clinical diagnosis.

In the initial presentation of untreated asthma, the physiological changes required to support the diagnosis of asthma are generally readily elicited. However, in long-standing disease, the effects of treatment, chronic inflammation, and remodelling may influence airway physiology. Combined steroid and β -agonist treatment serves to reverse airway obstruction, and reduces diurnal variability and bronchial hyperresponsiveness (16). Thus, in controlled, or partially controlled severe asthma, there may be no clear evidence of reversible airflow obstruction unless treatment is withdrawn. Irreversible or fixed airflow obstruction is well recognized in chronic asthma (17–20), and frequently

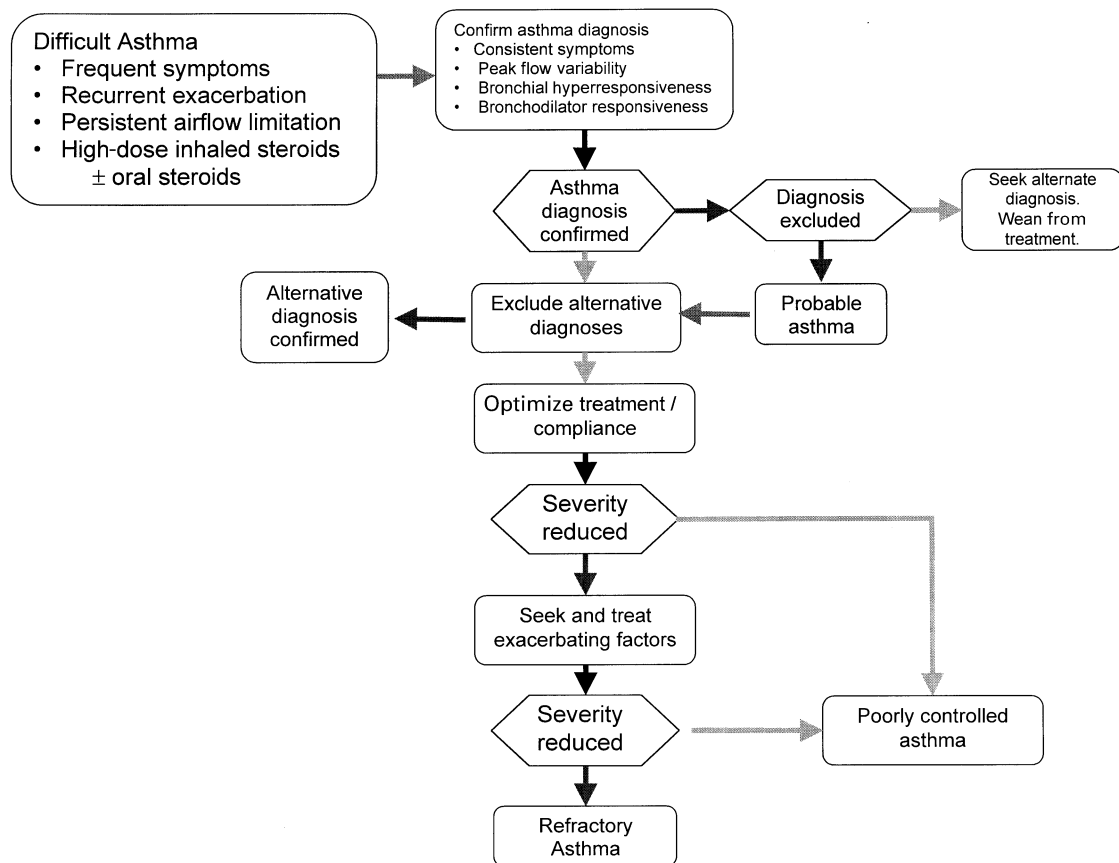


Figure 1. Approach to evaluation of difficult asthma.

these patients present with a diagnostic problem, particularly when there is significant smoking history. Although the determinants of such fixed airflow obstruction are not determined yet, a number of risk factors have been associated with both airflow obstruction and reversibility of such obstruction (Table 1) (21).

Measurement of bronchial responsiveness may provide valuable evidence in support of a diagnosis of asthma, but in severe asthma, this is frequently impractical, as provocative challenge in the presence of marked airflow obstruction is potentially dangerous and may be clinically inappropriate. Historical evidence of reversible airflow obstruction may be available; if not, the diagnosis must rest on a high

index of clinical suspicion and exclusion of alternative diagnoses. Occasionally, bronchial biopsy provides further findings such as the presence of submucosal eosinophils or thickening of the subepithelial basement membrane, both of which are supportive of an asthma diagnosis, if not pathognomonic.

Difficult asthma: differential diagnosis

Asthma is not infrequently complicated by the concomitant presence of other pulmonary disorders such as chronic obstructive pulmonary disease (COPD), bronchiectasis, obliterative bronchiolitis, pulmonary embolism, and granulomatous or fibrotic lung processes, each of which may worsen symptomatology and lung function and may or may not be

Table 1. Factors adversely affecting airflow obstruction and reversibility

Female sex
Environmental tobacco smoke exposure in childhood
Personal tobacco smoking in adolescence and adulthood
Age of onset of symptoms
Severity of childhood asthma
Duration of asthma
Severity of lung function abnormality in childhood
Bronchodilator reversibility
Degree of airway hyperresponsiveness
Delay in initiating anti-inflammatory therapy

Table 2. Difficult asthma: differential diagnosis

Chronic obstructive pulmonary disease
Congestive cardiac failure
Laryngeal dyskinesia
Vocal cord dysfunction
Mechanical obstruction – tumour
Pulmonary embolism
Bronchiectasis
Obliterative bronchiolitis

Table 3. Clinical factors contributing to asthma severity

Environment	Inhalant allergens Occupational exposure Irritants	HDM, moulds, pollen, animal dander Sensitizers, indoor or unvented fires Pollution, cigarette smoke
Medications	β -blockers Aspirin NSAIDS	
Host factors	Rhinitis Nasal polyposis Sinusitis Gastro-oesophageal reflux Respiratory tract infection	Aspirin sensitivity Influenza vaccination

HDM: house-dust mite; NSAIDS: nonsteroidal anti-inflammatory drugs.

recognized distinctly from asthma. In addition, interaction between cigarette smoking and asthma may be present. Before a diagnosis of difficult asthma is reached, other disorders that can masquerade as asthma need to be discounted or excluded as necessary (Table 2). Vocal cord dysfunction presenting as laryngeal or upper airway wheeze may masquerade as asthma or accompany severe asthma as an expression of stress or anxiety (22). Localized obstruction of the large airways by an intraluminal tumor or by extrinsic compression may also mimic asthma. Asthma is sometimes incorrectly diagnosed in patients with COPD, although these two conditions may coexist, particularly in an asthmatic patient who has been a long-standing smoker. Other conditions include congestive cardiac failure, particularly with nocturnal dyspnoeic episodes (23).

Treatment: adequacy and adherence

It is important to establish that the asthmatic has been provided with and indeed taken an appropriate dose of inhaled or oral corticosteroid therapy. Undertreatment is consistently recognized in fatal and near fatal asthma and is frequently the most important contributor to poor asthma control (24). Patients with the highest levels of adherence to treatment have significantly fewer exacerbations than those with a confirmed record of poor compliance (25). Reported levels of compliance to treatment with inhaled corticosteroid therapy has ranged from as low as 30% in adolescents to 55% in adults (26), with similarly poor compliance with oral corticosteroids demonstrated in some studies (27).

The degree of adherence to prescribed therapy in a particular asthmatic patient remains difficult to estimate, but this should always be attempted by pill counts, prescription counts, and direct questioning. The best objective measures entail using a computerized monitor attached to the inhaler, but these are not yet clinically available. In the case of

theophylline and prednisolone treatment, compliance may be estimated by measurement of serum drug levels.

Contributing factors

Comorbid conditions are capable of contributing to and thereby worsening asthma symptoms, including gastro-oesophageal reflux (28, 29), sinusitis (30), allergic rhinitis (31, 32), nasal polyposis, and post nasal drip (31, 32) (Table 3). In general, the contribution of these factors to asthma severity has been difficult to establish objectively, and their consequent impact on asthma severity remains quantitatively unknown.

Gastro-oesophageal reflux

Gastro-oesophageal reflux is commonly noted in asthmatics, with a reported incidence of up to 60% in children with moderate-to-severe asthma (33, 34). It has been implicated as a cause of asthma exacerbations and increasing asthma symptoms, by mechanisms involving the vagally mediated oesophagobronchial reflex or microaspiration into the upper airways. Studies of the effects of spontaneous reflux or distal acid perfusion of the oesophagus have revealed only small responses in terms of pulmonary function changes (35, 36), but it is not known whether the effects of oesophageal reflux would be amplified in patients with difficult asthma. A precise mechanistic link between gastro-oesophageal reflux and a decline in asthma control is not established, and little beneficial effect to varying degrees of improvement in asthma have been observed when concomitant gastro-oesophageal reflux has been treated (37–41). It would make sense to treat any concomitant gastro-oesophageal reflux in patients with difficult severe asthma, but larger trials are needed to establish the value of this treatment in the difficult asthma patient.

Sinusitis/rhinitis

The coexistence of rhinosinusitis with asthma suggests that there is a relationship between nasal and sinus disease, and the airways. Several mechanisms have been proposed by which disease of the sinuses could exacerbate asthma. These include rhinobronchial reflexes, enhancement of systemic airway inflammatory responses, or direct deposition of inflammatory mediators and cytokines from the upper airways into the lower airways. Significant improvement in asthma control may be obtained with targeted treatment for sinusitis/rhinitis (42) in children and adults with severe or refractory asthma (43).

Allergen exposure

Asthma symptoms, lung function, and treatment requirement deteriorate on exposure to specific and nonspecific environmental agents and improve after cessation of exposure (44). Specific allergen triggers include common perennial allergens such as house-dust mite (HDM), mould, cat, dog, cockroach, and latex, seasonal allergens such as grass and tree pollens, and industrial exposure to occupational agents such as isocyanates and laboratory animals.

First, in the case of specific allergens, mechanisms leading to asthma deterioration are suggested by studies of seasonal and occupational allergen exposure. Djukanovic et al. (45) have shown increases in activated (IL-2R⁺) T cells and IL-4⁺ T cells in grass-pollen-allergic asthmatics during the grass-pollen season compared to prior to the pollen season. Similarly, inhalational challenge with toluene diisocyanate (TDI) in TDI-sensitized asthmatics caused elevation of IL-5 immunoreactive cells and further increased IL-4 immunoreactivity (46). Second, the glucocorticoid receptor (GCR)-binding affinity (K_d) of blood mononuclear cells is significantly reduced in ragweed-allergic asthmatics during the ragweed pollen season compared with affinity before and after the ragweed season (47, 48). Using IL-2 and IL-4 blocking antibodies, these investigators were able to demonstrate the dependence of this effect on the combination of IL-2 and IL-4. These allergen-induced reductions in GCR-binding affinity also reduced peripheral blood mononuclear cell sensitivity to the inhibitory effects of steroids on allergen-induced T-cell proliferation. Therefore, proinflammatory T_{H2} cytokine synthesis is augmented by seasonal and occupational specific allergen exposure, leading to a reduction in glucocorticoid sensitivity.

Exposure to nonspecific irritants

Nonspecific indoor environmental agents include indoor air pollutants from gas stoves, fireplaces, and environmental tobacco smoke (49), and all of these agents may worsen asthma symptoms. The

bacterial lipopolysaccharide endotoxin is frequently found associated with various indoor pollutants including house dust. Endotoxin levels are more closely related to asthma symptom scores than levels of HDM allergen, and endotoxin exposure thus appears to be an important determinant of severity (50, 51). Endotoxin promotes eosinophil and neutrophil recruitment, activates alveolar macrophages, and induces the release of proinflammatory cytokines and nitric oxide (NO) (52). Inhalation of endotoxin induces bronchial hyperresponsiveness in asthmatics (53). A polymorphism of the gene encoding CD14, the endotoxin receptor, is found in linkage disequilibrium with a genomic region controlling serum IgE levels (52, 54). Overall, endotoxin may act as a cofactor in worsening airway inflammation and symptom severity.

Drugs

Aspirin and nonsteroidal anti-inflammatory drugs may cause exacerbation of asthma in aspirin-sensitive asthmatics, but the condition of aspirin-sensitive asthma may also present with particularly severe asthma, even in the absence of ingestion of such drugs. The inflammatory process may in part result from environmentally encountered salicylates, as found in fruits, vegetables, and other drink additives and foodstuffs (55, 56). Aspirin-sensitive asthma usually presents as nonatopic late-onset asthma in the presence of rhinosinusitis and nasal polyps. There is increased production of cysteinyl-leukotrienes particularly after ingestion of aspirin. Overexpression of leukotriene (LT)_{C4} synthase enzyme has been shown in bronchial biopsies, particularly in eosinophils, when compared to patients with non-aspirin-sensitive asthma (57). Aspirin-sensitive asthma is more frequently associated with a genetic polymorphism, in the promoter sequence of LTC₄ synthase, that leads to increased enzyme expression (58). Aspirin-induced asthmatic attacks are blocked by leukotriene inhibitors, and aspirin-induced asthma is also improved by these agents, although the clinical response may be variable (59–61).

β-Blockers may also precipitate acute deterioration, and catastrophic events have been described after the administration both systemic and seemingly innocuous topical ophthalmic preparations (62). Selective β₁-receptor blockers are not necessarily devoid of this adverse effect; indeed, all β-adrenergic receptor blockers should be avoided in asthmatic patients.

Respiratory tract infections

Viral infections of the upper respiratory tract have been recognized as important precipitants of acute severe exacerbations of asthma (63, 64), and a variety of potential mechanisms are apparent. In animal

Table 4. Risk factors for asthma death

Older age	Frequent symptoms
Smoking	Regular (high-dose) rescue medication use
Atopy	High health-care resource utilization
Impaired lung function	Three or more different asthma medications
Moderate to high reversibility	Previous intubation
Severe asthma	Previous emergency department visit
	Regularly missed appointments with hospital and/or general practitioner
Poor compliance	Poor knowledge about medications
	Suboptimal self-management
Stress	Domestic/financial/employment
Psychological disturbance	Denial/depression
Substance abuse	

models of viral upper respiratory tract infection employing the respiratory syncytial virus (RSV), a downregulation of CD8⁺ antiviral activity has been observed, associated with increased CD8⁺ dependent IL-4 and IL-5 synthesis, resulting in augmented airway eosinophilia on rechallenge (65).

Virally mediated mechanisms have also been implicated in airway obstruction in children (66). In a study of children after viral respiratory infection, a cohort showing suboptimal response to anti-inflammatory and bronchodilator treatment also showed persistence and replication of adenovirus in the airways, a feature which was not seen in those responding appropriately to drug treatment.

In vitro studies using rhinovirus and respiratory syncytial virus have shown virus-mediated upregulation of the expression of proinflammatory mediators such as 5-lipoxygenase, ET-1, NO, leukotrienes, and the chemoattractant cytokine IL-8 from airway epithelium (67–69).

Preventive measures are available by vaccination against influenza and streptococcus, and these measures have provided some protective effect, particularly for the elderly with impaired lung function in COPD (70). However, this has not yet been clearly demonstrated in asthma.

Mycoplasma pneumoniae has been recovered from the airways of patients with chronic stable asthma, and this pathogen has been proposed as a contributory factor in asthma severity (71). In children, persistent infection with *Chlamydiae pneumoniae* has been associated with more frequent exacerbations of asthma (72). In patients with severe corticosteroid-dependent asthma, treatment of *Chlamydiae* with macrolide antibiotics such as clarithromycin or azithromycin may lead to an improvement in asthma (73). The role of these infections in asthma severity needs further investigation.

Psychosocial factors

In a retrospective analysis of asthma deaths, psychosocial factors present in severe, near-fatal, and fatal asthma have been linked with or compounded by poor patient compliance and lack of appropriate medical care (74). High scores of psychiatric morbidity have been correlated with severe asthma and in the families of children who have died of asthma. Although there is no clear causal relationship between psychosocial factors and asthma severity, many factors such as denial, panic, fear, depression, low socio-economic class, minority status, alcoholism, marital problems, and avoidance coping have been linked to poor asthma outcomes (74, 75). An association between psychiatric disturbances and asthma morbidity has been reported in near-fatal asthma attacks; in particular, the importance of denial has been emphasized as a barrier to the use of appropriate self-management plans. It is often difficult to clarify how psychosocial factors and pathophysiological determinants of the disease interrelate in determining the severity of asthma. However, patients commonly cite emotional factors or stress as an exacerbating factor.

Patterns of difficult-to-treat asthma

A number of terms are used by clinicians to describe “difficult-to-treat” asthma such as “chronic severe”, “acute severe”, “therapy-resistant”, “difficult-to-control”, “refractory”, “corticosteroid-resistant or -dependent”, “near-fatal”, and “fatal asthma”, illustrating the heterogeneity of the clinical presentation of difficult asthma. These classifications attempt to characterize the temporal sequence of exacerbations and of symptoms, the chronicity and rapidity of onset of symptoms, and the response to treatment. Other subcategories of severe asthma relate to other clinical features of asthma.

Brittle asthma

“Brittle asthma” was a term first used to describe patients with asthma who had a wide and chaotic variation in peak expiratory flow (PEF) despite high doses of inhaled steroids (76), distinct from the controlled patterns of PEF variation seen in patients with uncontrolled asthma. It was implied that these patients had a more life-threatening disease from the rapidity of onset of the severe bronchoconstriction. Two types of brittle asthma have been proposed: type 1, with persistent and chaotic variability in peak flow despite considerable medical therapy, and type 2, with sporadic sudden falls in PEF rate on a background of normal or near-normal lung function and well-controlled asthma (77). Type 1 brittle asthma often fails to respond to inhaled β_2 -agonists administered

by nebulizer or long-acting β_2 -agonists. Many of these patients have psychological problems (78). The attacks of type 2 brittle asthma appear not to be controlled or prevented by steroids, and often do not respond sufficiently to inhaled β_2 -agonists. Patients with type 2 brittle asthma have a high incidence of food allergy, which appears to be a risk factor in death and near-death from asthma (79). Since the attacks are unpredictable, they are difficult to prevent. In addition, there may be impaired perception of airway narrowing and a reduced ventilatory response to hypoxia in patients with sudden onset near-fatal attacks of asthma (80, 81), leading to reduced awareness of the severity of attacks and subsequent delay in taking appropriate therapy.

Chronic difficult asthma

This term is often used for patients affected by chronic symptoms interfering with sleep, exercise tolerance, and the ability to go to work or attend school or classes. There may be frequent exacerbations of these symptoms, which persist despite the use of maximal asthma therapy. Such patients have evidence of airflow limitation, and may or may not demonstrate significant variability. They may already be on chronic oral corticosteroid therapy. Higher doses of corticosteroids may lead to further improvement of airflow obstruction, and the patients may experience worsening of asthma when corticosteroids are reduced or discontinued. Therefore, the term "corticosteroid-dependent" asthma is often used for these patients. Rarely, some patients show no airway response to prednisolone (40 mg/day) administered for 2 weeks, despite a bronchodilator response to inhaled β_2 -agonists (82), and, according to this definition, their disorder is labelled as corticosteroid-resistant asthma (83). However, it is possible that they may respond to higher doses of corticosteroids. Some patients may have developed asthma in later years rather than in childhood, and some may not demonstrate evidence of atopy as measured by skin prick tests to common aeroallergens ("intrinsic" asthma).

Fatal asthma

Difficult asthma also includes the disorder of patients who have an increased risk of severe attacks or of dying from asthma. Patients with brittle asthma are particularly at risk, but asthma deaths are not confined only to this group (84) (Table 4). The characteristics of the fatality-prone asthmatic have been described from retrospective analyses of case-control studies of asthma deaths, and include respiratory failure needing intubation, respiratory acidosis associated with an attack of asthma not requiring intubation, two or more hospitalizations for

asthma despite the chronic use of oral corticosteroid therapy, and two episodes of acute pneumomediastinum or pneumothorax associated with an attack of asthma (85, 86). The risk of asthma deaths is also greater in patients with previous attacks that occurred suddenly or were associated with hypoxic seizures, hypercapnia, very low peak flows, and the use of medication from three or more classes of therapy for asthma (87).

Premenstrual worsening of asthma

A proportion of females with severe asthma describe cyclic deterioration of symptoms and PEF occurring 3–10 days before the onset of the menses, and improving with the onset of menstrual flow (88). This cycle of deterioration occurs during the late luteal phase when circulating progesterone and oestrogen levels fall to their nadir. The prevalence of menstrual asthma among ovulating asthmatic female patients has been reported to be as high as one-third of female patients in a hospital asthma clinic (89, 90). Augmented doses of corticosteroids in the premenstrual phase are occasionally, but not always, effective in controlling these recurrent exacerbations (91, 92). The use of the intramuscular synthetic progestin, medroxyprogesterone acetate, has been reported to control premenstrual exacerbations in three patients (91), but this compound also displays potent corticosteroid activity. Gonadotrophin-releasing hormone agonist analogues may be used to suppress the menstrual cycle by creating a "pseudomenopause", but the long-term risks of osteoporosis and atherosclerotic cardiovascular disease mean that this decision should be taken only on expert advice.

Intrinsic and extrinsic asthma

Intrinsic ("nonallergic") and extrinsic ("allergic") asthma represent further subdivisions. In intrinsic asthma, despite rigorous attempts to identify allergen precipitants, no such trigger factors have been found, and skin prick tests to a variety of common allergens are negative. These subjects are heavily overrepresented in higher levels of asthma severity and adult onset asthma. Investigation of the inflammatory processes in intrinsic asthma reveals low or normal levels of IgE while the expression patterns of cytokines may differ. Increased levels of GM-CSF (93) and IL-10 (94) have been reported, and elevated levels of IL-5 unaccompanied by elevation of IL-4 levels (95–97) are described in some, but not all, studies. T-cell activation and airway eosinophil infiltration along with bronchial hyperresponsiveness and reversible airflow obstruction are evident in both intrinsic and extrinsic asthma, leading some investigators to claim that these two states share the same disease processes (98).

Atopy and serum IgE

Total IgE is related to the prevalence of asthma, and to airway hyperresponsiveness with a dose-dependent relationship (99–102). A link between total IgE levels and features of asthma severity has also been suggested. The rate of decline of lung function in asthma patients compared to nonasthmatics is increased (103–105). In cross-sectional studies, total serum IgE has been associated with lower levels of FEV₁, if it is not predictive of decline in lung function (106–109). Furthermore, a monoclonal antibody to IgE that markedly suppresses circulating IgE levels leads to concomitant reduction in symptom score and oral corticosteroid treatment requirement (110).

We performed a prospective survey of 133 subjects with physician-diagnosed severe difficult-to-treat asthma (paper in preparation). We sought to describe the distribution of total and specific IgE within this group and to determine any association with a composite measure of asthma severity. We found significant correlations between specific IgE for HDM, cat, and dog with a composite measure of severity and with symptom severity subscores. Asthma severity scores were also correlated with elevated HDM-specific IgE, but not with total IgE levels. Elevation of IgE has also been noted in nonatopic asthmatics; indeed, it has been inversely associated with large airway obstruction as a marker of severity (111).

Pathophysiology of severe asthma

There are likely to be many potential mechanisms underlying increased asthma severity, and different mechanisms may be operative in different groups of patients. Overall, it is not clear whether severe asthma results from a greater intensity of one or more mechanisms, or from mechanisms that may be different from mild or moderately severe asthma. Indeed, there is debate as to whether or not severe asthma is the same disease as mild-moderate asthma expressed at a higher intensity, or is indeed different and potentially differentiated by distinct inflammatory processes involving varied cytokine expression profiles and/or effector cells (e.g., neutrophils). Airway remodelling or possibly altered distribution of asthmatic inflammation may also contribute to the altered pathophysiology of severe asthma.

Patterns of airway inflammation

Histopathologic analysis of the airway mucosa in severe asthma reveals increased numbers of activated eosinophils and of CD4⁺ T cells expressing cytokines such as IL-5 and GM-CSF in the mucosa (112–114). Increased numbers of activated T cells and eosinophils are also noted in the bronchoalveolar fluid from severe asth-

matics (115). However, in severe asthmatics on chronic oral steroid therapy, marked neutrophilia in bronchoalveolar lavage fluid and in endo- and transbronchial biopsies has been observed, while moderately severe asthmatics not on oral steroids demonstrated eosinophilia (116). Patients in whom there were increased airway mucosal eosinophils in severe asthma also had increased mast cells, subepithelial fibrosis, and an increased number of cells expressing the fibrogenic cytokine, TGFβ (117). Analysis of induced sputum shows the presence of eosinophils, with greater release of the eosinophil product, eosinophil cationic protein (ECP), in the more difficult, therapy-resistant asthmatics, together with increased numbers of neutrophils, and increased IL-8 levels in the sputum supernatant (4). Neutrophilic inflammation has also been reported during acute exacerbations of asthma, and in cases of fatal asthma attacks of sudden onset (118). However, the contribution of the neutrophil to severe asthma remains somewhat circumstantial. In addition, some patients with difficult severe asthma have excessive NO levels in their exhaled breath despite high-dose glucocorticoid therapy, suggesting either parallel inflammatory mechanisms or relative steroid unresponsiveness in this group (119).

Studies in patients with nocturnal asthma have revealed differences in the inflammatory components during the night from those during the day. These patients provide an interesting model of changes in severity within a 24-h study, and the concomitant inflammatory components can be studied. Increased airway eosinophils, superoxide levels, and histamine levels in bronchoalveolar lavage fluid have been seen at 4 am in subjects with nocturnal asthma, when compared to 4 pm (120, 121). Significant inflammation is present in both proximal airways and alveolar tissues in subjects with asthma, but it is the alveolar tissue inflammation that increases significantly during the night, as compared to the proximal airways of patients in whom there is no significant diurnal change in PEF (122). A significant elevation of LTB₄, cysteinyl leukotrienes, and thromboxane in bronchoalveolar lavage fluid has been reported (123). Therefore, patients with severe asthma appear to demonstrate more severe eosinophilic inflammation, with greater degree of mediator expression and subepithelial fibrosis; the presence of increased neutrophils may indicate that there is a different inflammatory process in the airways of patients with severe asthma. However, patients with severe asthma are already established on oral steroid therapy, and the potential contribution of corticosteroid therapy to the neutrophilia is not known.

Intensity of cytokine expression

Intuitively, high levels of expression of inflammatory mediators with a potential to induce many of the

pathologic features of asthma are a likely explanation for increased intensity of asthma. This proposition would suggest that severe asthma is merely the result of a more intense expression of asthma. There is some evidence to support this concept in relation to soluble cytokines such as IL-5 (124), IL-11 (125), and TGF β (117); chemokines such as eotaxin (126, 127); and inflammatory cells such as activated T cells (128, 129) and eosinophils (112). Inflammatory markers also show consistent change: levels of exhaled NO (119), serum ECP (130), induced sputum ECP (131), and urinary LTE₄ (132) have all shown quantitative relationships with asthma severity. Importantly, the institution of anti-inflammatory therapy also leads to a reduction of these inflammatory cytokines, cells, and markers, reinforcing their possible mechanistic relationship with asthma severity (133–135). The explanation for upregulation of expression of these factors is still unclear. Genetic polymorphism is likely to account for a proportion, but the role of unidentified post-transcriptional factors relating to protein stability and protein receptor interactions has yet to be fully determined.

Genetic polymorphisms and gene expression

Various asthma candidate genes have been suggested and identified, and, increasingly, genes associated with asthma severity are being described. Aberrant regulation of gene expression due to genetic polymorphisms may influence asthma severity by augmenting pro-inflammatory mediator expression or by reducing expression of anti-inflammatory mediators.

IL-4 induces differentiation of the naive T cell to the T_{H2} phenotype, IgE isotype switching, and a series of related immunomodulatory functions in relation to the T_{H2} phenotype. Polymorphisms of both the IL-4 and IL-4 receptor have been demonstrated to be positively associated with asthma severity (136–139). These studies observed no relationship between haplotype and IgE levels, suggesting that IL-4-induced T_{H2} differentiation, not isotype switching, may explain this relationship (139).

Conversely, reduced expression of anti-inflammatory mediators may augment asthma severity. Such anti-inflammatory properties have been ascribed to IL-10, IL-1R α , and glutathione S-transferase in airway disease, and an association between asthma severity and these polymorphisms has been recognized for each of these genes (140–142).

Treatment response is also at least in part genetically determined. Homozygous Gly-16 polymorphisms of the β_2 -adrenoceptor have been associated with agonist-mediated desensitization of receptor responses (143) and are positively linked with severe asthma and exacerbation frequency (144–146). In the leukotriene metabolic pathway,

5-lipoxygenase polymorphisms have been identified and may contribute to asthma severity in specific individuals by influencing the response to leukotriene pathway blocking agents (147, 148). Other polymorphisms, including the genes for IL-9, TGF β , LTC₄-synthase, and 5-lipoxygenase-activating protein (FLAP), have been associated with asthma (149–152), if not directly related to asthma severity, and such an impact remains to be determined. Such genetic variability may partly explain the phenotypic heterogeneity manifest in severe asthma.

Glucocorticoid responsiveness

The proposed definition of difficult, therapy-resistant asthma rests on the therapeutic response of asthmatic patients to inhaled or oral corticosteroid therapy. Difficult asthma may be viewed as a disease that responds suboptimally to inhaled or oral corticosteroids, thus necessitating high doses of these treatments at the risk of side-effects. Much of the work has focused on “steroid-resistant” asthma, but the response to corticosteroids is relative to the doses of corticosteroids used (153). In the “steroid-resistant” asthmatic, the inflammatory infiltrate of eosinophils in the airway submucosa is similar to that of the steroid-sensitive patient; in addition, there is similar expression of the T_{H2} cytokines IL-4 and IL-5 (154). However, corticosteroid treatment does not cause a reduction in eosinophils, or suppression of the expression of IL-4 and IL-5 mRNA in the airways submucosa of steroid-resistant asthmatics (154). Levels of IL-12 mRNA do not change with corticosteroid therapy in steroid-resistant asthma, although they were increased in corticosteroid-sensitive asthmatics. Corticosteroids also do not inhibit the *ex vivo* proliferation of peripheral blood T cells of steroid-resistant asthmatics (155). A reduction in the number of GCRs available for binding to DNA in steroid-resistant asthmatics may be attributed to an increased activation of the transcription factor, activating-protein-1 (AP-1) (155). The mechanisms underlying steroid-resistant asthma may shed light on those underlying difficult asthma (156). The circulating mononuclear cells of patients with deteriorating asthma on exposure to allergen show a decreased binding affinity of corticosteroid receptors, which recovers on treatment with oral corticosteroids (48). A decreased binding affinity of circulating mononuclear cells is also observed in severe patients on long-term oral corticosteroids, but this is not secondary to the effect of long-term treatment with oral corticosteroids. Drugs that may reverse the partial lack of response of corticosteroids in severe asthma may be beneficial. There are few data on the state of the corticosteroid receptors in the airways and on their properties. Corticosteroid receptors are

particularly well expressed in the airway epithelial cells of nonasthmatics and mild asthmatics (157), and these cells may well reflect the responsiveness of the airways to corticosteroid therapy, as the epithelium is exposed to the highest concentrations of topical corticosteroids.

In a similar vein, it is apparent that asthma-related cytokines may influence the mRNA structure affecting intron-exon splice variants. Alternative splicing involving exon 9 of the GCR gene gives rise to two homologous messenger ribonucleic acids (mRNAs) and protein isoforms, termed GCR- α and GCR- β . GCR- β is elevated under the influence of IL-2 and IL-4, and inhibits GR- α -mediated transactivation of target genes (158, 159). An association between elevated GCR- β expression and relative steroid resistance *in vitro*, and also clinically, with steroid resistance, and near-fatal and fatal asthma *in vivo*, has been reported (159–161).

Airway wall remodelling

Airway wall remodelling comprises a complex series of structural changes including thickening of the airway smooth muscle due to hypertrophy and hyperplasia, myofibroblast activation with increase in subepithelial basement membrane collagen deposition, angiogenesis and increase in submucosal blood vessels, and an increase in the numbers of goblet cells in the airway epithelium (162–164). The importance of remodelling is highlighted by the observations of prominent bronchial hyperresponsiveness and symptomatology in the absence of airway inflammatory cells, and the association of these factors with remodelling (165).

Increase in the smooth-muscle mass and thickening of the subepithelial basement membrane layers are controlled by a complex interaction between mesenchymal growth factors such as TGF β , EGF (166, 167), IGF, and their receptors (168), and the balance between degradative enzymes, such as the matrix metalloproteinase (MMP-9), and the tissue inhibitor of metalloproteinase (TIMP-1) (169, 170). Tissue remodeling, as demonstrated by collagen deposition and expansion of the smooth-muscle mass, may be promoted by an imbalance in this system. Tissue remodeling may also involve an increase in neural innervation, and the neurotrophin, nerve growth factor (NGF), has been implicated in the upregulation of the neuropeptides, substance P and calcitonin gene-related peptide, in the primary sensory neurons innervating the inflamed tissues (171).

Several studies have demonstrated important relationships between aspects of airway remodelling and asthma severity (172–174). Thickening of subepithelial basement layers due to fibrosis is apparent in asthma and appears to increase with greater asthma severity

(175). Inverse associations between subepithelial basement membrane thickening and FEV₁ and PEF variability have also been described (176). The role of subepithelial fibrosis in progressive and fixed airflow obstruction is not defined. Importantly, however, fibrosis has been observed in the airways of asthmatic children (177) and in newly diagnosed adult asthmatics (174). Some studies suggest that antiasthma treatment with inhaled corticosteroids may have the potential to control or reverse these abnormalities (178–180).

Thus, both structural and functional changes in the airway wall may potentially increase asthma severity. Further investigation may shed light on the natural history and importance of structural and functional airway changes in chronic severe asthma.

Differences between mild-moderate and severe asthma: a different disease?

Patients with chronic severe asthma demonstrate phenotypic heterogeneity, with subgroups including brittle asthma, aspirin-sensitive, steroid-dependent, steroid-resistant, menstrual, and asthma with fixed airflow obstruction (181). A possible explanation for this observation is that severe asthma may represent one or several distinct disease processes with common yet indistinguishable symptomatology. Several studies have now demonstrated the presence in severe and fatal asthma of neutrophils, which are not demonstrated in mild-moderate asthma (4, 116, 118).

Further clinical problems contributing to worsening asthma are the early (missed diagnosis) or late failure (incorrect diagnosis) to diagnose asthma or to identify correctly the levels of severity of asthma. Each of these problems may lead to failure to prescribe appropriate corticosteroid and β -agonist therapy or to prescription of insufficient amounts of these drugs.

Conclusion

In 1695, Floyer observed, “Since the cure of the asthma is observed by all physicians, who have attempted eradicating that chronic distemper, to be very difficult and frequently unsuccessful; I may thence infer, that either the true nature of that disease is not thoroughly understood by them, or they have not yet found out the medicines by which the cure may be effected.” Then, as now, many questions remained unanswered, particularly in the pathophysiology and pathogenesis of chronic severe asthma.

By definition, patients with chronic severe asthma do not respond satisfactorily to currently available drugs, and, in this category of patients, new effective treatments are needed. It is therefore important that the pathophysiologic mechanisms are identified, in

parallel with characterization of the severe asthma phenotype. Research in chronic severe asthma would be enhanced if large cohorts of such patients could be studied systematically. A systematic investigative/management protocol for patients with chronic severe asthma should be instituted to ascertain the diagnosis and to characterize the asthma phenotype with particular attention to the determination of patterns of responsiveness to corticosteroids. This would be best done in a few research asthma centres, so that sizeable cohorts of patients with severe asthma can be followed. This would enable the

recruitment of a critical mass of severe asthmatics for studies relating to genetic polymorphisms, pathophysiologic mechanisms, or investigations of new agents.

Although the definition of asthma severity remains somewhat arbitrary, the importance of assessing severity is crucial for application of an asthma management plan. In that way, management plans may be tailored to the individual and allow flexibility for changes in asthma severity and degree of disease control. Similarly, improved definition of severe asthma phenotypes will enable further study of specific mechanisms of pathophysiology in severe asthma.

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