Eur Respir J 1999; 13: 1198–1208
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European Respiratory Journal
ISSN 0903-1936

ERS TASK FORCE

Difficult/therapy-resistant asthma

The need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies

ERS Task Force on Difficult/Therapy-Resistant Asthma

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CONTENTS

A Task Force supported by the European Respiratory Society was set up in 1997 in order to address the major issues relevant to difficult/therapy-resistant asthma. Although the group of patients involved is small in comparison to the high numbers of patients with asthma, these patients consume a significant proportion of medical resources in terms of both time and money [1]. The major issues facing the Task Force were how to define "difficult asthma", how the patient with difficult asthma should be evaluated, the pathophysiological mechanisms underlying difficult asthma and the treatments available. The Task Force also concerned itself with defining the areas of research necessary to bring about a greater understanding of the causes of difficult asthma and novel treatments. The document resulting from this Task Force represents a consensus of different opinions, which will form the basis for further research.

Formulating the definition

A large number of terms are used by clinicians when referring to asthmatic patients who have "difficult to treat" disease: difficult acute, difficult chronic, chronic severe, acute severe, therapy-resistant, difficult to control, corticosteroid-resistant or corticosteroid-dependent, symptomatic, life-threatening, and fatal. An encompassing inclusive rather than exclusive definition was sought and the use of the term "difficult/therapy-resistant asthma" was adopted to include all such cases of asthma of all age groups. Since wheezing disorders in preschool children are poorly characterized, this report specifically excludes children below the age of 5 yrs. Response to therapy is included in this concept and will have research implications. It was accepted that the definition needed to be inclusive, although losing some precision, but it was also recognized that its

This position document of the European Respiratory Society was officially adopted by the ERS Executive Committee.

This report was compiled following the submission of manuscripts from the Task Force membership and a meeting held at the National Heart & Lung Institute in London, UK in January 1998. The full manuscripts will be published in the *European Respiratory Review.*

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use was dependent to some extent on the objective of individual research. For example, a definition for epidemiological purposes may not be entirely similar to one used for determining the mucosal pathology of the condition. One further difficulty is the need to assess patients over a period of time, generally 6–12 months, rather than immediately on presentation, before they can be labelled as having difficult/therapy-resistant asthma.

Diagnosis of asthma

It is essential to be as certain as possible of a primary diagnosis of asthma. This diagnosis very much rests on a clinical history and physiological evidence of variable and reversible airways obstruction and on the exclusion of possible alternative diagnoses that may mimic asthma (see below). Often, on presentation to the specialist, it may not be possible to obtain contemporary evidence of these features if the patient is already established on anti-asthma therapy, which it is not usually possible to discontinue. At this stage, the bronchodilatory response to β-agonist therapy may be small and the response to high-dose corticosteroid therapy blunted (*e.g.* "steroid-resistant" or "steroid-insensitive" asthma). Supportive evidence may only be available from previous records of variable and reversible airflow obstruction. Both from the clinical and the research viewpoint, certainty in the diagnosis of asthma is essential, but it may not be achieved immediately in many patients because of the nonspecificity of symptoms and the lack of diagnostic markers.

Exclusion of other diagnoses

Many conditions can induce wheezing associated with airways obstruction and a patient with a presumed diagnosis of asthma but not apparently responding to asthma medication should be investigated for other possible alternative or associated diagnoses (table 1). Asthma may be mistaken for many superficially similar conditions and this leads to many patients being prescribed inhaled steroid therapy. Although cough and the presence of eosinophils in sputum may be considered a variant of asthma, cough alone in the absence of evidence of intermittent bronchial obstruction is unlikely to be caused by asthma. Allergic bronchopulmonary aspergillosis and pulmonary eosinophilic syndromes (*e.g.* pulmonary eosinophilia or Churg–Strauss syndrome) may be considered unique diseases with some of the clinical features of asthma and are often difficult to treat; these are probably best considered outside the definition of difficult/therapy-resistant asthma. Vocal cord dysfunction characterized by adduction of the vocal cords can masquerade as and may coexist with asthma [2], which could make asthma appear more severe than it really is. Other respiratory conditions such as chronic bronchitis or bronchiectasis may also coexist with asthma, but the effect of these on asthma severity or control is not known.

Asthma control

Asthma control is usually assessed by evaluation of the patient′s perceptions of their symptoms of wheeze, shortness of breath, cough, and nocturnal awakenings and need to use reliever short-acting β-agonist medication. This control can be difficult to assess in the absence of antiasthma therapy nowadays because, by the time of presentation to the specialist, most patients have been started on some form of therapy. Patients vary in their perception of airflow limitation and poor perceivers may be particularly prone to severe attacks [3, 4]. Two patterns of symptoms are important in defining control. The number of acute exacerbations requiring oral/systemic corticosteroid therapy is one marker of asthma control; however, the term "exacerbation" requires refinement and classification. The extent of chronic symptomatology is the other means of recognizing poor control. Monitoring of peak expiratory flow (PEF) may be used to document airway obstruction and its diurnal variability. Such measurements, often recorded by the patient at home, are effort-dependent and require total cooperation.

Within the definition of asthma control lies the concept of asthma severity, which may be considered as the amount of airways obstruction or of symptoms or the need for β-agonist reliever therapy. PEF and forced expiratory volume in one second (FEV_1) have been used to grade the severity of asthma, with values <60% of predicted graded as severe, those 60–80% pred as moderately severe and those >80% as mild [5]. There have been no studies comparing this classification with other asthma outcome measures but such measurements of airways obstruction may be useful for asthmatics with "fixed" airways obstruction. The presence of persistent airways obstruction does not necessarily reflect loss of control.

Asthma-specific measures of quality of life and functional status are another dimension of outcome and a measure of the impact of the disease on patients in their environments [6]. Finally, the value of using asthma biomarkers to assess the amount of airways inflammation and the relationship of this to asthma control is under

Table 1. – Diagnoses that may masquerade as difficult/therapy-resistant asthma

In children
Obliterative bronchiolitis
Vocal cord dysfunction
Bronchomalacia
Inhaled foreign bodies
Cystic fibrosis
Recent aspiration (particularly in handicapped children)
Developmental abnormalities of the upper airway
Immunoglobulin deficiencies
Primary ciliary dyskinesia
In adults
Cystic fibrosis
Bronchiectasis
Inhaled foreign body
Tracheobronchomalacia
Recurrent aspiration
Chronic obstructive pulmonary disease
Congestive cardiac failure
Tumours in or impinging on central airways
Obstructive bronchiolitis
Vocal cord dysfunction
Bronchial amyloidosis
As part of the asthmatic diathesis
Allergic bronchopulmonary aspergillosis
Pulmonary eosinophilic syndromes (*e.g.* Churg–Strauss)

evaluation. Increasingly, the amount of inhaled anti-inflammatory therapy needed for control of asthma, rather than the quantification of symptoms or of lung function [7], which require a period of follow-up in order to observe response and optimally titrate symptoms with treatment, is being used to define asthma severity. The observation of the asthmatic over a period of 6–12 months, therefore, will allow both diagnosis of asthma and assessment of its severity and control with therapy. This is applied in the Task Force′s proposed definition of difficult asthma (see below).

Factors contributing to loss of asthma control

It is important to distinguish between the factors that either predispose to or cause asthma and those factors which, in a patient already suffering from asthma, contribute to loss of control and difficult/therapy-resistant asthma. The difficulty in making this distinction is that some of these factors may be common to both causation and worsening. This is an important concept in the light of ongoing studies examining both genetic susceptibility to and environmental factors in asthma. However, the difficult/therapy-resistant asthmatic patient may have a distinct genotype.

A number of medical factors may contribute to poor control in asthma (table 2). Gastro-oesophageal reflux is commonly noted in asthmatics, with a reported incidence of up to 60% in children with moderate-to-severe asthma [8, 9]. Although a precise mechanistic link between gastro-oesophageal reflux and a decline in asthma control is not established, varying degrees of improvement in asthma have been observed when concomitant gastro-oesophageal reflux has been treated [10, 11]. Sinusitis/rhinitis and asthma are frequently coexisting problems [12], and significant improvement in asthma control may be obtained with targeted treatment for sinusitis/rhinitis [13]. Viral and sometimes bacterial infection of the sinuses have been implicated as exacerbating factors in asthma, but their importance in initiating difficult asthma needs to be assessed.

Psychosocial factors, which may be linked with or compounded by poor patient compliance and lack of appropriate medical care [14] have also been implicated in retrospective analyses of asthma deaths. High scores of psychiatric morbidity have been correlated with severe asthma and in the families of children who die.

Other factors may include exposure to allergens, indoor and outdoor air pollution, endotoxin and viral respiratory tract infections [15, 18]. There is some evidence for the involvement of chlamydial infections [19]. Retrospective analyses of asthma deaths or near-asthma deaths indicate the following relative risk factors: female sex, young age (<25 yrs old), exposure to high levels of allergen (*e.g.* soya bean or *Alternaria*), psychosocial disturbances, being in an ethnic minority group, concomitant smoking, having had a previous life-threatening episode, and discontinuity of physician care [20–23]. In the case of most of these associations, it is not known whether these are direct or indirect effects, but they do provide areas where therapeutic possibilities can be investigated. At the more mechanistic and research level, potential risk factors that may contribute to difficult/therapy-resistant asthma may involve: 1) the development of specific inflammatory changes in airways; 2) chronic structural changes; 3) certain genetic polymorphisms, perhaps related to airway inflammation; and 4) specific environmental factors including exposure to pollutants and allergens.

Table 2. – Factors that may contribute to loss of control in asthma

Poor compliance/adherence to therapy
Psychosocial and emotional factors
Inadequate medical facilities
Poor access to medical facilities
Inadequate treatment
Exposure to allergens
Viral respiratory tract infections
Indoor/outdoor pollution
Gastro-oesophageal reflux
Sinorhinitis
Genetic factors

Asthma therapy

On presentation to the specialist, patients with difficult asthma will have been established on asthma therapy for a period of time, usually inhaled corticosteroid therapy. The dosage of inhaled corticosteroid therapy required above which one may consider asthma to be difficult to manage is arbitrary, reflecting the balance between diminishing therapeutic returns and increasing risks of unwanted effects. In adults, a total daily dosage in excess of 2,000 μg beclomethasone, 1,600 μg budesonide, 1,000 μg fluticasone or equivalent doses of other inhaled corticosteroids and, in children, a dose of beclomethasone or budesonide >800 $\mu g \cdot day^{-1}$ or 400 $\mu g \cdot day^{-1}$ of fluticasone would appear to be a reasonable threshold for the definition of difficult asthma. These doses are likely to be on the relatively "flat" portion of the corticosteroid dose–response relationship, above which the potential for further therapeutic effect diminishes and the likelihood of systemic side-effects is significant [24]. Often, the patient with difficult asthma is taking doses of inhaled corticosteroid therapy higher than these and/or oral corticosteroid therapy. From a practical standpoint, patients whose asthma is not controlled on high-dose inhaled corticosteroid therapy can be considered to have difficult/therapy-resistant asthma. From a clinical standpoint, the initial aim is to determine whether or not there are immediately remediable or avoidable factors contributing to this lack of response.

Patient compliance and supervision

Since response to therapy is part of the definition of difficult/therapy-resistant asthma, the question of patient adherence to treatment must be considered. Compliance to inhaled corticosteroid therapy in asthma has been reported to be 30–70% [25, 26]. How much this contributes to poor asthma control is not known. This remains an area where more definite answers are needed. Adequacy of anti-asthma treatment (particularly with preventive or anti-inflammatory therapy) relevant to the degree of severity of asthma is also of importance. The use of electronic monitors on inhalers should ideally form part of the assessment of the patient with difficult asthma, not only for regular therapy but also for as needed therapy, such as inhaled short-acting β_2-agonists.

Definition of difficult/therapy-resistant asthma

Difficult/therapy-resistant asthma is that which is poorly controlled in terms of chronic symptoms, episodic exacerbations, persistent and variable airways obstruction and a continued requirement for short-acting β_2-agonists despite delivery of a reasonable dose of inhaled corticosteroids (as defined above). Patients may require courses of oral corticosteroids or a regular dose of oral corticosteroids to maintain reasonable control of the disease. Rarely, control of asthma may be totally uninfluenced by corticosteroid therapy. Diagnosis on the basis of this definition can be established by means of follow-up of and care for the patient by a respiratory specialist for a period of $\geq$6 months during which time asthma management is carried out according to published asthma guidelines [27–29] and issues such as compliance with treatment, identification of exacerbating factors and exclusion of other diagnoses are dealt with (table 1). The diagnosis should thus be confirmed, features of the difficulty in asthma determined, treatment optimized and its effects observed, and adherence to treatment and delivery of care optimized. Ideally, this would be achieved by evaluation of the patient at the initial visit and again 6–12 months later.

Patterns of difficulty in asthma

Some distinct "patterns" in the patient with difficult asthma have been described, usually characterized by the temporral sequence of exacerbations and symptoms, the chronicity and rapidity of onset of the symptoms and the response to treatment [30]. Such descriptions have been obtained for the most part from personal observations in small groups of patients and must be verified in larger cohorts. It is important to confirm such different patterns, particularly in patients already established on inhaled corticosteroid therapy. Descriptive patterns of airway obstruction can be classified, generally supported by recordings of PEF measurements, as follows. 1) Patients who experience a fatal or near-fatal episode of asthma that is associated with hypercapnia or necessitates mechanical ventilation. These episodes may recur despite "adequate" treatment; therefore, such patients are at risk of death caused by asthma. Within this group are those that have recurrent episodes of severe asthma necessitating frequent intermittent systemic corticosteroids. 2) Patients experiencing recurrent episodes of severe airway narrowing that appear rapidly over minutes-to-hours, occurring at any time of day, with no obvious triggers and often labelled "brittle asthma" when the onset is particularly rapid [31]. These patients have either normal lung function between episodes that cannot be prevented by corticosteroid therapy or a persistent background of wide variability in airways obstruction. Some patients with nocturnal or morning asthma symptoms show severe morning dips in PEF with marked diurnal flow variability, sometimes accompanied by a large bronchodilator response. 3) Patients with a persistent pattern of airway obstruction, with or without episodes of sudden deterioration, and requiring oral corticosteroid treatment, to which they show an incomplete response. The terms "corticosteroid-dependence" or "a partial corticosteroid resistance" are often used. This pattern seems to be rare in children. The term "fixed" obstruction is also used occasionally; although this term implies a more irreversible state, some patients still retain a bronchodilator response to β_2-agonists. However, it should be noted that these categories are not mutually exclusive.

It is not known whether any of these clinical phenotypes differ in terms of their airway pathology. In addition to these patterns, other subgroups of patients in whom asthma may be difficult to treat include those with aspirin-induced asthma (triad of symptoms: usually of late-onset, not associated with atopy, rhinosinusitis and nasal polyps, and exhibiting sensitivity to aspirin and/or nonsteroidal anti-inflammatory drugs), premenstrual worsening of asthma and adult-onset asthma, usually with a nonatopic background. Other clinical patterns may emerge on examination of larger cohorts.

Evaluation and pathophysiology of difficult/therapy-resistant asthma

A protocol for evaluating difficult/therapy-resistant asthma is necessary in order to address and attempt to validate issues raised in the proposed definition, to provide data that can be compared between centres and to standardize patient categories for research purposes, including therapeutic trials. A proposed list of techniques for the investigation of difficult/therapy-resistant asthma is proposed in table 3. A discussion of some of the aspects of this investigation with regard to understanding the pathophysiology and cause of difficult/therapy-resistant asthma follows.

Table 3. – Investigation of difficult/therapy-resistant asthma

Assessment of severity
Symptom score chart and use of β_2-agonist reliever therapy
Spirometric measurement of lung volumes and gas transfer
Bronchial responsiveness to methacholine/histamine
Diurnal variation in peak expiratory flow
Quality of life assessment
Determination of pharmacological responsiveness
Assessment of compliance to therapy and inhaler technique
Bronchodilator response to β_2-adrenergic agonists
Response to prednisolone (corticosteroid-responsiveness)
Radiology
Chest radiograph
Barium swallow
Computed tomography of sinuses
High-resolution computed tomography of the lungs
Blood tests
Full blood count, including eosinophil count
Serum IgG, IgA, IgM and IgG subclasses
Serum total IgE
Specific IgE to selected allergens
Thyroid function tests
Other tests
Biomarkers of inflammation (exhaled nitric oxide, eosinophils in induced sputum)
Sweat test and genetic assessment of CFTR mutations (if indicated)
24-h oesophageal pH monitoring
Examination of nasopharyngeal airways
Tests of ciliary function
Skin prick test to common aeroallergens
Fibreoptic bronchoscopy with bronchial biopsy and bronchoalveolar lavage
Psychological assessment

Ig immunoglobulin; CFTR: cystic fibrosis transmembrane conductance regulator.

Lung mechanics and airway responsiveness

Lung mechanics and airway responsiveness are major determinants of the clinical severity and expression of difficult/therapy-resistant asthma, although these appear to be of minor importance in the evaluation of patients. One of the pathophysiological features of severe asthma is excessive airway narrowing, as can be demonstrated by the loss of maximal plateau responses following high doses of bronchoconstrictor stimuli [32]. This unlimited airway narrowing may be related to an increased amount of airway smooth muscle [33, 34], exudative swelling of the airway wall [35, 36] and airway–parenchymal interactions [37]. A notable feature of severe asthma is the loss of bronchodilatation on deep inspiration, which may be associated with airways inflammation [38] and excessive narrowing during bronchoconstriction [39]. The loss of deep breath-induced bronchodilatation may contribute to the increased perception of breathlessness in patients with asthma [40]. Loss of mechanical load may also affect the behaviour of airway smooth muscle by favouring the development of force-maintenance [41]. These observations may form the basis of the rapidity of development of severe airway narrowing in certain patients and also the chronic shortness of breath observed in some patients with difficult asthma. It is not known whether the difficult/therapy-resistant asthma patient demonstrates more pronounced abnormalities of airway smooth muscle mass and contractility or of loss of airway–parenchymal interdependence.

Computed tomography of the airways and lungs

Computed tomography has been used to assess potential structural changes in the medium-sized airways. One early study demonstrated that the severity of asthma, as defined by a clinical score, was related to the degree of airway thickening and dilatation [42], whereas another related it to the degree of air-trapping, measured on inspiratory and expiratory scans [43]. The pathological correlates of these changes on computed tomographic scanning have not been determined. Whether these airway wall changes are a reflection of thickening of the muscle or submucosa or oedema are not known. The usefulness of this technique in assessing difficult/therapy-resistant asthma remains undefined. One advantage of performing these scans is the exclusion of other pathologies such as bronchiectasis, emphysema, obliterative bronchiolitis and extrinsic allergic alveolitis. Its value in assessing airway wall remodelling is unclear and the significance of radiological evidence of airway wall thickening and dilatation in a patient with asthma remains speculative in the absence of pathological correlation.

Airway inflammation

Since so few studies have evaluated airways inflammation in difficult asthma, the value of this remains undetermined for both clinical and research purposes. It seems likely that routine evaluation of the bronchial inflammatory infiltrate at the cellular and molecular level may provide clues as to the likely clinical course of the disease and response to therapy. The use of fibreoptic bronchoscopy to obtain mucosal biopsies for histological examination is likely to be safe, although the risks and benefits of this investigation in the patient with difficult asthma have not been widely assessed [44]. There is already suggestion that difficult/therapy-resistant asthma may be subclassified histologically. The presence of eosinophils and activated T-cells despite anti-inflammatory therapy may indicate "resistance" to the effects of treatment. A recent investigation of patients with difficult asthma on oral corticosteroid therapy did not reveal significant submucosal eosinophilia but rather an increase in neutrophil numbers [45]. Some patients with difficult to treat asthma have persistently elevated levels of exhaled nitric oxide despite being on high-dose oral corticosteroid therapy [46]. Use of biomarkers of inflammation obtained by means of noninvasive techniques will be useful in understanding the pathophysiology and also in the management of these patients.

Since inflammatory abnormalities may not only be confined to the proximal airways, the value of examining transbronchial lung biopsies to assess the distal airways and lung parenchyma needs to be ascertained. There are, however, potential dangers in this procedure. It may exclude other bronchiolar diagnoses. In a small study of patients with difficult asthma undergoing steroid therapy, no complications were reported following transbronchial lung biopsy showing a neutrophilic rather than an eosinophilic infiltrate, similar to changes observed in more proximal bronchial biopsies [45]. In nocturnal asthma, there is a more pronounced eosinophilic inflammation in the distal airways sampled by transbronchial lung biopsies [47]. Use of video-assisted thoracoscopic surgery for obtaining peripheral lung tissue from patients with difficult asthma should be debated: it may be associated with lesser risk. However, no consensus can yet be arrived at concerning its potential utility. Examination of peripheral lung tissues could advance understanding of the pathological process and perhaps help in the staging of the chronicity of the process, but it should be debated as to whether such information will benefit patients in terms of their future management.

Pathology

In patients with mild asthma, patchy loss of the surface epithelium, thickening of the reticular basement membrane and increased cellular infiltrate in the bronchial mucosa, consisting mainly of eosinophils, often mast cells and T-lymphocytes, are observed in bronchial biopsy sections. The severity of asthma, as measured by the expression of symptoms and degree of airflow limitation, has been associated with the presence of activated eosinophils and expression of certain cytokines in the mucosa (*e.g.* interleukin (IL)-5, granulocyte-macrophage colony-stimulating factor) in several studies [48–50]. In more severe asthmatics on chronic oral steroid therapy, marked neutrophilia in bronchoalveolar lavage fluid and endo- and transbronchial biopsies has been observed, whereas moderately severe asthmatics not on oral steroids demonstrated eosinophilia [45]. Neutrophilic inflammation has also been reported during acute exacerbations of asthma, and in cases of fatal asthma attacks of sudden onset [51].

Immunohistochemical studies of fatal asthma as compared to mild nonfatal asthma have not provided any clear indications as to possible contributing factors to the severe obstruction. Some studies have indicated that the eosinophilic inflammatory response is worse in the proximal airways, with a redistribution of T-lymphocytes away from the airway epithelium, and others emphasize the even distribution of inflammation in both small and large airways [52, 53]. Submucosal vascular congestion may also be an important feature. It is not entirely clear whether or not the cellular components of airway inflammation are distinct in difficult asthma. If there are distinct clinical phenotypes of difficult asthma, it behoves us to characterize these subgroups thoroughly before embarking on studies of the airway mucosal pathology.

Airway wall remodelling

A proportion of patients with asthma experience a relentless decline in lung function [54, 55], which may be partially corticosteroid-resistant. What underlies this decline in lung function is unclear but it may reflect chronic progressive airway wall "remodelling". This has been defined as structural changes, with the appearance of subepithelial fibrosis and collagen deposition and an increase in the number of submucosal blood vessels and of airway smooth muscle mass [56]. The pathogenesis of this process of remodelling as well as its physiological significance remains to be elucidated, but may involve the expression of growth factors and pro-inflammatory cytokines influencing the deposition and breakdown of the collagen matrix and increasing airway smooth muscle mass and the number of submucosal blood vessels. These changes may not be reversible with corticosteroid therapy. Obtention of lung tissue would be useful in grading this process and defining potential therapeutic avenues.

Glucocorticoid responsiveness

The proposed definition of difficult/therapy-resistant asthma rests very much on the therapeutic response of asthmatic patients to inhaled or oral corticosteroid therapy. To some extent, difficult asthma may be viewed as a spectrum of disease that responds suboptimally to inhaled or oral corticosteroids, thus necessitating high doses of these treatments at the risk of side-effects. Much work has focused on "steroid-resistant" asthma, defined for research purposes as asthma in which airways obstruction improves after β-agonist bronchodilator inhalation but not following a course of oral prednisolone, usually taken at a dose of 40 $mg \cdot day^{-1}$ for 2 weeks [57]. A failure of patients to demonstrate an improvement in morning PEFs or FEV_1 by >15% has been used. However, resistance to corticosteroids is relative because beneficial responses can be obtained if the doses are increased to even higher levels [58].

The typical inflammatory infiltrate of eosinophils observed in the airways submucosa in the steroid-resistant asthmatic is similar to that in the steroid-sensitive patient. However, corticosteroid treatment does not cause a reduction in the number of eosinophils or suppression of expression of IL-4 and IL-5 messenger ribonucleic acid in the airways submucosa of steroid-resistant asthmatics [59]. Corticosteroids also do not inhibit *ex vivo* proliferation of the peripheral blood T-cells of steroid-resistant asthmatics [60]. A reduction in the number of glucocorticoid receptors available for binding to deoxyribonucleic acid in steroid-resistant asthmatics may be attributed to increased activation of the transcription factor, activating protein-1 [61]. The mechanisms underlying corticosteroid-resistant asthma may shed light on those underlying difficult asthma [62]. Circulating mononuclear cells in patients with spontaneously deteriorating asthma show a decreased binding affinity of their corticosteroid receptors, which is reversed on treatment with oral corticosteroids. A decreased binding affinity is also observed in patients taking long-term oral corticosteroids, but this is unlikely to be secondary to the effect of long-term treatment with oral corticosteroids. However, what is needed is a study of the mechanism of action or inaction of corticosteroids in the airways of patients with difficult asthma. Corticosteroid receptors are expressed at a particularly high level in the airway epithelial cells of nonasthmatics and mild asthmatics [63], and these cells may reflect the responsiveness of the airways to corticosteroid therapy as the epithelium is exposed to the highest concentrations of topical corticosteroids. Further research should determine the factors which modulate corticosteroid-responsiveness in difficult asthma and ways of restoring responsiveness.

Management and treatment

Many of the aspects of diagnosis and optimization of treatment have already been addressed. Attention to these factors may improve the control of difficult asthma to a considerable extent [64]. Two areas that deserve particular investigation relate to the role of allergen exposure and psychosocial factors.

Allergen avoidance

Reversal of bronchial hyperresponsiveness, with a reduction in oral steroid requirement during prolonged hospitalization in an environment with a low level of house dust mites, has been reported in mild-to-moderately-severe asthmatics [65]. Sensitization and seasonal exposure to *Alternaria* has been proposed as a risk factor for sudden death caused by asthma [66]. The degree of exposure of patients with severe brittle asthma to relevant aeroallergens in their homes is not known, but may be relevant to the rapid onset of episodes of deterioration in these patients. It is not clear whether or not residence at high altitude in an atmosphere devoid of allergens improves symptoms in patients with difficult asthma. 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/therapy-resistant asthma needs further evaluation, and there are no studies at present that indicate that effective allergen avoidance reduces the likelihood of asthma exacerbations or alters the natural history of the disease.

Psychosocial factors

Retrospective analysis of patients who have died of asthma indicates that psychosocial factors may have contributed to poor control of asthma and, therefore, to death caused by asthma. These have included social isolation, marital problems, alcoholism, anxiety and depression [14, 67]. An association between psychiatric disturbances and asthma morbidity has been reported in near-fatal asthma attacks. In particular, the importance of denial as a barrier to the use of appropriate self-management plans has been emphasized. 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.

Poor control of asthma can result from poor compliance to therapy [68]. Patients with the highest levels of compliance had significantly fewer exacerbations than those with a confirmed record of poor compliance [69]. Reported levels of compliance to treatment with inhaled corticosteroid therapy have ranged from as low as 30% in adolescents to 55% in adults [25]. In another study, although mean compliance with inhaled therapy was 60–70%, treatment was only taken as prescribed on 30–40% of days [26]. The degree of adherence to prescribed therapy in difficult asthma is difficult to estimate but this should always be attempted. Finally, the reasons behind the tendency to poor adherence to therapy need to be established. These may be related to psychosocial factors, the relationship between carer and patient, poor patient education and comprehension, too complicated antiasthma regimens and fear of unwanted effects.

Patient education has been advocated as a pivotal part of the integrated therapeutic process [70]. Educational programmes can be useful for the patient with difficult asthma. Through education, these patients are helped to integrate specific knowledge, attitudes and practical skills into appropriate behaviour to optimally cope with asthma. Detailed descriptions of the potentials and limits of educational methods are required.

Specific therapy

Corticosteroids. By definition, the difficult asthmatic will be receiving high doses of inhaled corticosteroid therapy, often together with oral corticosteroids. One of the grey areas is whether further increases in dose will bring further benefit. Studies of dose–response relationships of inhaled corticosteroids indicate that, in terms of symptoms and PEFs, there is a progressively diminishing response above 800 $\mu g \cdot day^{-1}$ of budesonide or 400 $\mu g \cdot day^{-1}$ fluticasone propionate [71–72]. Individual patients, however, may respond to higher doses. The precise side-effect profile of higher doses of inhaled steroids is not known. lt would therefore be advisable to perform a trial of higher doses of inhaled steroids in difficult asthmatics for a limited period. The introduction of potent topical corticosteroids has been beneficial in reducing the need for oral corticosteroid therapy in some severe therapy-resistant asthmatics. The search for even more potent topical corticosteroids continues despite their potential for increased systemic side-effects and the apparent limited therapeutic gains at higher doses of inhaled corticosteroids. Recently, hydrofluoroalkane aerosols with a finer particle size and a greater degree of distal penetration have been introduced, with the potential for improved therapeutic effects, as reported for beclomethasone dipropionate [73]. This needs close evaluation. The use of topical corticosteroids delivered from a nebulizer has been advocated but more data demonstrating efficacy are required.

Oral corticosteroids may be added under various clinical situations. 1) Patients with chronic uncontrolled symptoms and exacerbations may be started on a trial of prednisolone followed by a step-down strategy to find the minimum effective dose. 2) Patients with intermittent frequent exacerbations of asthma despite maintenance high-dose inhaled corticosteroid therapy when frequent short courses of oral corticosteroid therapy for these exacerbations are needed. 3) Patients already on a maintenance dose of oral corticosteroids needing higher doses to maintain control or treat exacerbations of asthma [58, 74].

Short-acting β-adrenergic agonists. Short-acting (SA) inhaled β_2-adrenergic agonists are used for the immediate relief of asthma symptoms. Their use in asthma is one measure of the severity of the disease. Excessive reliance on these agents is not advisable because of the following controversial issues. 1) Regular use of high-dose SA β_2-agonists may cause a partial loss of effectiveness, which in turn may lead to the use of even higher doses. 2) High doses of SA β_2-agonists may be detrimental to the control of asthma, perhaps by interfering with corticosteroid action [75]. What constitutes an optimal and "safe" level of SA β_2-agonist has not yet been determined. Preventing excessive use of SA β_2-agonists (*i.e.* >24 puffs salbutamol$\cdot day^{-1}$) nevertheless appears to be a reasonable step to take. Studies of β_2-adrenoreceptor polymorphisms may be helpful in determining which patients will be relatively unresponsive to SA β_2-agonist therapy or show severe tolerance to the effects of these drugs. One study showed an arginine^{16} to glycine^{16} mutation to be associated with a greater degree of bronchodilator desensitization compared to the wild-type β_2-receptor [76] but this needs confirmation. The use of SA β_2-agonists delivered at high doses from a nebulizer should be reserved for the treatment of exacerbations. On occasion, continuous subcutaneous administration of terbutaline may be helpful in controlling attacks of brittle asthma [77]. How a beneficial effect is achieved from a subcutaneous infusion of terbutaline is unclear. Patients with type 2 brittle asthma should be given a syringe preloaded with adrenalin to be self-administered in extreme situations.

Long-acting β-adrenergic agonists. Complementary action of long-acting β_2-agonists with medium or high doses of inhaled corticosteroid therapy has been reported in moderately severe asthma in terms of both improvement in lung function and prevention of asthma exacerbations [78, 79]. Such benefits have been shown to persist for up to 1 yr. Therefore, the addition of long-acting β_2-agonists to corticosteroid therapy in difficult asthma is a reasonable step. This may also help to reduce any excessive use of SA β_2-agonists. There are no reports to suggest that such an addition worsens asthma control or accelerates decline in lung function.

Theophylline. Theophylline, in addition to its bronchodilator properties, has immunomodulatory properties in asthma [80, 81]. Its potential value in difficult asthma is unclear. Addition of slow-release theophylline to moderate doses of inhaled corticosteroids in moderately severe asthma provided similar or better control of asthma compared to high-dose inhaled corticosteroid therapy [82]. Beneficial effects of theophylline have been reported in five cases of severe difficult asthma already established on high-dose inhaled and oral corticosteroids [83].

Leukotriene inhibitors. Leukotriene inhibitors, particularly leukotriene receptor antagonists, have been added in patients already taking inhaled corticosteroids, with or without oral corticosteroid therapy, with consequent improvement in lung function and reduction in SA β_2-agonist use [84, 85]. An inhaled steroid-sparing effect of one leukotriene receptor antagonist has been demonstrated in moderate-to-severe asthma [86], whereas other preliminary studies show equivocal effects. Leukotriene inhibitors have been shown to be of particular benefit in patients with aspirin-induced asthma [87]. Corticosteroids do not reduce leukotriene biosynthesis as measured by urinary leukotriene E_4 excretion, and, therefore, the combination of leukotriene inhibitors with corticosteroids may provide additional benefit for some patients with difficult asthma already taking high-dose inhaled or oral corticosteroid therapy. This requires further study. Such data indicate that, in certain patients with difficult asthma, the severity of the asthma may result from increasing sulphidopeptide leukotriene metabolism.

Immunosuppressants and antimetabolites. The use of methotrexate, gold salts and cyclosporin A has been examined in oral corticosteroid-dependent asthmatics in double-blind placebo-controlled studies and significant oral corticosteroid-sparing effects have been found [88–91]. On average, a halving of the dose of corticosteroids has been reported after 4–5 months of continuous therapy. These medications are potentially toxic and should be instituted in specialized centres. Other treatments that have been reported include intravenous immunoglobulins (particularly in children), lignocaine aerosols, dapsone, colchicine and hydroxychloroquine, but these trials have been open and small [92, 93]. These agents cannot be generally recommended at present.

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/therapy-resistant asthma based on practical and theoretical considerations should lay the foundation for a large database. Records of such patients undergoing a standardized protocol of investigations and possibly of management should be kept in regional centres throughout Europe. It would be most important for such patients to be clinically categorized as fully as possible, particularly with the identification of patients who may not turn out to have asthma, or whose "difficulty" may be due to lack of compliance or "psychosocial" factors. There is already a European group (the European Network For Understanding Mechanisms of Severe Asthma), funded partly by a European Union collaborative grant gathering such data. Large populations that have been characterized clinically and in terms of their responses to corticosteroids and of airway inflammatory response are needed to study the epidemiology and risk factors, economic impact and natural history of difficult asthma. A cohort of patients with nondifficult asthma, preferably well-controlled on inhaled therapy, should serve as a comparative group.

Factors associated with difficult/therapy-resistant asthma

Which factors are associated with the development of difficult/therapy-resistant asthma? Are there well-defined clinical subgroups of difficult asthma, and are they sufficiently different to invoke different pathophysiological mechanisms? Tools and measures for the assessment of severity should be validated and developed; some effort needs to be expended in examining clinical outcome measures, the use of lung function parameters, the quantification of severity of acute episodes ("exacerbations") and the use of the amount and kind of therapies needed to control asthma symptoms or attacks. Studies of genetic polymorphisms would be possible with such large cohorts of patients with difficult asthma.

Specific areas for investigation

Other important areas for investigation in well-defined groups include the following. 1) Assessment of the inflammatory response using induced sputum and bronchial biopsies, and evaluation of the sampling of distal airway changes using transbronchial biopsies and, possibly, video-assisted thoracoscopic surgery. The value of biomarkers of asthma obtained by means of noninvasive methods needs to be determined, but they are more likely to be useful in following the course of disease activity. 2) Studying corticosteroid-responsiveness as a basis for the definition of difficult asthma relies on the poor response of symptoms to a threshold dose of corticosteroid therapy. What are the factors that determine corticosteroid responsiveness in severe asthma and what can be done to reverse the lack of corticosteroid responsiveness? In order to classify difficult asthma into varying degrees of corticosteroid responsiveness, means of measuring this response either by clinical and physiological methods or by assaying the numbers of circulating cells such as mononuclear cells are needed. These responses need to be correlated with those in airway cells. 3) Specific focus on the particular group of "brittle" asthma, in which severe life-threatening attacks are not prevented by corticosteroid therapy. The rapidity of onset of these attacks is typical and may invoke specific mechanisms such as rapid activation of mast cells through either allergic or neural mechanisms leading to bronchoconstriction. In such patients, the experience or the continued apprehension of such attacks may form the basis of important psychosocial disturbances that have been described previously.

Assessing new therapies

Studies examining the efficacy of potential new agents should be targeted towards more defined specific types of difficult asthma and the availability of large numbers of patients would increase the reliability of these observations. It is of major importance to attempt to perform studies on as uniform a population of patients with difficult asthma as possible. Many potential mechanisms have been identified as forming the basis of possible treatments for asthma, but are usually reserved for patients with mild-to-moderate asthma. Although there may not be any rationale for exploiting similar mechanisms as the basis of treatment of difficult/therapy-resistant asthma, it is the latter group that desperately need new effective drugs and other approaches for improved asthma control. Potential mechanisms include exploitation of suppression of CD4+ T-cells using cytotoxic anti-CD4+ T-cell antibodies, anti-eosinophil strategies such as anti-IL-5 antibodies, antichemokine receptors (antagonists) and anti-adhesion molecule approaches (anti-very late activation antigen-4 or anti-intercellular adhesion molecule-1 antibodies). A recent study of an anti-CD4+ T-cell antibody showed beneficial effects in a group of corticosteroid-dependent asthmatic patients [94]. Other approaches include the administration of anti-inflammatory cytokines such as IL-10, or the use of cytokines that could suppress the activation of T-helper type-2 lymphocytes and increase the number of T-helper type-1 lymphocytes such as IL-12, or interferon-γ or anti-immunoglobulin E therapy. Other mechanisms may be identified in studies of the difficult/therapy-resistant asthma patient. Different subgroups of difficult asthma may need different treatments to obtain different outcome measures such as: 1) prevention of severe life-threatening attacks as in brittle asthma; 2) inhibition of inflammatory processes usually characterized by persistent eosinophil activation despite systemic steroid therapy; 3) prevention of decline in lung function, perhaps by preventing aspects of the "remodelling" process; 4) restoration of corticosteroid-responsiveness; and 5) addressing novel inflammatory processes that may come to light through further investigation of the disease.

Europe-wide research group

This Task Force sees the need to organize a Europe-wide research group to formulate and initiate the creation of a database of difficult/therapy-resistant asthmatics since even heavily-populated European countries may not possess sufficient patients to answer the research questions posed. The outcome of such desperately needed research may shed light on not only difficult/therapy-resistant asthma but also asthma in general.

Acknowledgements. The authors would like to thank R. Stirling for acting as rapporteur.

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