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POSITION PAPER

EAACI position statement on asthma exacerbations and severe asthma

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Abstract

Asthma exacerbations and severe asthma are linked with high morbidity, significant mortality and high treatment costs. Recurrent asthma exacerbations cause a decline in lung function and, in childhood, are linked to development of persistent asthma. This position paper, from the European Academy of Allergy and Clinical Immunology, highlights the shortcomings of current treatment guidelines for patients suffering from frequent asthma exacerbations and those with difficult-to-treat asthma and severe treatment-resistant asthma. It reviews current evidence that supports a call for increased awareness of (i) the seriousness of asthma exacerbations and (ii) the need for novel treatment strategies in specific forms of severe treatment-resistant asthma. There is strong evidence linking asthma exacerbations with viral airway infection and underlying deficiencies in innate immunity and evidence of a synergism between viral infection and allergic mechanisms in increasing risk of exacerbations. Nonadherence to prescribed medication has been identified as a common clinical problem amongst adults and children with difficult-to-control asthma. Appropriate diagnosis, assessment of adherence and other potentially modifiable factors (such as passive or active smoking, ongoing allergen exposure, psychosocial factors) have to be a priority in clinical assessment of all patients with difficult-to-control asthma. Further studies with improved designs and new diagnostic tools are needed to properly characterize (i) the pathophysiology

and risk of asthma exacerbations, and (ii) the clinical and pathophysiological heterogeneity of severe asthma.

At a recent summit organized by the European Academy of Allergy and Clinical Immunology (EAACI), a group of experts discussed current issues of concern and unmet needs in regard to the treatment of asthma. Most attendees presented evidence that the current guideline-driven treatment strategies fail in two vital aspects of asthma. There was a general consensus that the needs of patients with severe asthma or frequent asthma exacerbations are not being adequately covered by the current treatment guidelines and are of major health and socio-economic concern. Such patients suffer from significantly reduced quality of life and incur disproportionately higher costs on health service resources. This report summarizes the current data that indicate the need for a more rational approach to the treatment of asthma and one that takes into account the emerging evidence for pathophysiological heterogeneity of the disease, including its more severe forms.

Asthma exacerbations

A significant outstanding problem in the clinical management of asthma is the failure to prevent and/or efficiently treat asthma exacerbations, which are associated with significant morbidity, risk of death and high treatment cost (1–3). Generally, an asthma exacerbation is considered to be an increase in a patient's asthma symptoms with increasingly impaired lung function that require increased medication, an unscheduled visit to a physician or hospitalization. A single asthma exacerbation requiring extra medication and possibly emergency treatment and hospitalization can increase the annual treatment costs by more than threefold (3). Recurrent asthma exacerbations lead to a progressive decline in lung function (4), and the risk of an exacerbation doubles in children who have had one or more in the previous year (5). A rare but distinct phenotype of asthma exacerbation is characterized by the development of sudden severe asthma symptoms in an otherwise mild or asymptomatic asthmatic subject, which may be triggered by an allergen, drug (e.g. aspirin), food, air pollutant, occupational agent, virus infection or, in many cases, an unknown (or unidentified) trigger (6). It has been proposed that within the group of patients with recurrent exacerbations, detailed phenotyping in terms of clinical symptoms, lung function, inflammatory and other biomarkers is warranted (7, 8). There is a significant unmet need for identifying and characterizing the factors that increase the risk of asthma exacerbations and the therapeutic and preventive options that reduce these risks.

Severe asthma

Patients with severe asthma have high morbidity and mortality, often require hospitalization and are expensive to treat. They have diverse clinical profiles, which probably reflect diverse disease mechanisms, and, for many of them, standard treatment is not sufficiently effective (9–11). Severe asthma comprises a highly heterogeneous group of patients, which is defined in various ways in the published literature and in the national and international guidelines. A consensus is emerging that patients should be considered to have a 'difficult-to-control asthma' if they have persistent symptoms and recurrent exacerbations despite being prescribed therapy at the highest steps of the guidelines' pharmacological management (12). However, it is worth emphasizing that the guidelines also make clear that 'difficult-to-control asthma' is multifactorial, and issues such as incorrect diagnosis, comorbid conditions, nonadherence to prescribed medication, psychosocial morbidity and a number of other factors discussed later in this manuscript are major causes of 'difficult' asthma (12). Patients should be considered to have severe asthma that is resistant to currently available therapies only following a detailed analysis and appropriate management of all these background problems that are amenable to intervention. A recently published consensus statement on severe asthma broadened the concept of 'difficult asthma' to reflect the situation in less developed countries, where access to medications and appropriate care is a major issue, by defining three different patient groups including un(der)treated symptomatic patients, patients with low treatment adherence or unconventional therapies, and those remaining symptomatic despite high doses of anti-asthmatic therapies (13, 14).

Nonadherence to prescribed medication has been identified in a number of studies in the developed countries as the most common clinical problem amongst adults (15) and children (16) with asthma, including those with difficult-to-control asthma (15, 17). Appropriate assessment of adherence (18) and other potentially modifiable factors (such as passive or active smoking, ongoing allergen exposure, psychosocial factors, etc.) (19) has to be a priority in clinical assessment of all patients with difficult-to-control asthma, before any decision about increasing the treatment is made (including possible prescription of an expensive biological therapy) (17).

The clinical diversity and the underlying pathophysiology of severe treatment-resistant asthma need to be characterized, so that rational therapeutic targets can be identified and relevant biomarkers validated (20). In addition, there is a need for controller as well as noninterventional studies in this patient population.

Asthma exacerbations

Asthma exacerbations in childhood

Although inhaled corticosteroids may protect against asthma exacerbations due to allergen exposure, they are reported to be relatively ineffective in children with virus infection-induced wheezing (21). This suggests the existence of different types of childhood asthma with different underlying pathophysiologies (22, 23). Recent joint modelling of longitudinal observations on wheezing from parental reports and

medical records identified a novel phenotype of persistent troublesome wheeze with high rates of severe asthma exacerbations and healthcare utilization (24). Despite having phenotypic markers commonly considered to be indicators of good therapeutic response (atopy and eczema), these children had relatively poor response to currently available anti-inflammatory treatments (24).

An atopy-related phenotype of children with high risk of asthma exacerbations has recently been identified by Bayesian inference in two birth cohort studies in which multiple skin and IgE tests were collected throughout childhood (25, 26). The analysis revealed several different atopic vulnerabilities, only one of which had a much higher risk of asthma exacerbations (25, 26). However, this group of children with a significant risk of asthma exacerbations was identified only using longitudinal data, and cross-sectional biomarkers allowing their identification in clinical practice are still lacking.

Asthma exacerbations in adults

Several attempts have been made to identify predictors of asthma exacerbations. Several comorbidities associated with recurrent asthma exacerbations have been identified in adult patients (27), including severe nasal sinus disease, gastro-oesophageal reflux disease, recurrent respiratory infections, psychological dysfunction and obstructive sleep apnoea. Psychological dysfunction (28) and treatment nonadherence are separate psychosocial factors that may significantly contribute to the risk of asthma exacerbations. A significant number of patients with high rates of asthma exacerbations, and increased airway eosinophilia, were found to have a low perception of their lung dysfunction (29). Asthma exacerbations are frequent in asthma patients with poor treatment adherence, and poor adherence remains one of the major challenges in the treatment of severe asthma (15, 18).

The basis of asthma treatment guidelines is the use of clinical symptoms or impaired lung function to guide treatment of airway inflammation. However, there is a strong rationale for using direct measurement of airway inflammation as an additional means to guide treatment in severe asthma. Green et al. (30) reported that titrating treatment to sputum eosinophil counts was more successful in reducing asthma exacerbations than treatment in accordance with guidelines. This was confirmed in a larger, multicentre study (31), which also reported that the frequency and severity of eosinophilic exacerbations were reduced without increasing the dose of inhaled corticosteroids (ICS) (the severity but not the frequency of noneosinophilic exacerbations was also reduced). The treatment strategy of these authors was to (i) treat patients with sputum eosinophil counts of >2% with the minimal ICS dose required to reduce sputum eosinophil counts to normal and (ii) consider other treatment options in patients with normal sputum eosinophil counts, such as treatment of airway obstruction with long-acting beta-agonists (LABAs) or a leukotriene receptor antagonist, or treatment of neutrophilic inflammation with antibiotics. Of interest, a treatment approach aimed at specifically reducing airway eosinophils using a monoclonal antibody directed against interleukin (IL)-5 reduced the risk of asthma exacerbations in patients with severe asthma and persisting airway eosinophilia (32, 33). However, it is of note that even after using this targeted approach, approximately 50% of severe exacerbations remained unaffected by the treatment.

Attempts to identify clinical biomarkers for predicting the risk of asthma exacerbation have so far failed. However, some small studies have identified possible candidate biomarkers. For example, Gelb et al. (34) evaluated the use of spirometry and exhaled nitric oxide (F_ENO) in predicting the risk of asthma exacerbations in 44 stable, mild-to-severe patients with asthma over 18 months. Those patients with a baseline FEV_1 < 76% of predicted plus an F_ENO >28 ppb had a probability of an asthma exacerbation in 18 months of 85%, while those with FEV_1 > 76% of predicted plus a F_ENO <28 ppb had zero probability of an asthma exacerbation in the same period. The F_ENO parameter may be a robust measure of the degree of eosinophil airway inflammation (35, 36).

Asthma exacerbations and infection

Numerous epidemiological studies indicate that asthma exacerbations are associated with upper respiratory viral infections, mostly with rhinoviruses, and to a lesser degree with respiratory syncytial virus or coronavirus, with frequency estimates of 85% and 60% for childhood and adult asthma, respectively (37, 38). This was confirmed by the GA^2LEN-DARE systematic review (39) that reviewed data from 98 published epidemiological studies. The data for childhood asthma are more extensive than that for adult asthma and reveal the absence of geographical influence.

The same review indicated that high rates of respiratory bacterial infections are also associated with asthma exacerbations, but the data are inconsistent. However, Bisgaard et al. (40) provided evidence that bacterial infection and viral infection were independently associated with wheezing episodes in infants (<3 years old), with odds ratios of 2.9 and 2.8, respectively.

Although confirmatory studies need to be performed, current data strongly suggest that respiratory infections are the major cause of asthma exacerbations. Case–control studies have revealed a synergism between viral infection and allergen exposure in increasing the risk of asthma exacerbation requiring hospitalization in children (41) and in adults (42).

Airway infection and impaired innate immunity

Atopic asthmatic patients have more severe and prolonged lower respiratory tract symptoms during rhinovirus infections than nonatopic healthy controls (43). This may be explained by impaired innate and acquired immunity of the airways in asthma, as indicated from the studies of experimental and clinical viral infection (37, 44). Such impairments in airway immunity correlate with the *in vivo* severity of the infections and with the viral load (45, 46). Consequently, specific and nonspecific antiviral strategies may have great potential as therapeutic and preventative strategies for asthma exacerbations, a hypothesis that is supported by preliminary clinical studies (37). Patients with asthma also have deficient interleu-

kin-12 and type III interferon responses to bacterial stimuli, suggesting that inadequate host defence mechanisms and mechanisms specific to the infectious agents are the underlying factors for increased susceptibility (45, 46). Rhinovirus and enterovirus infections are more likely to cause an asthma exacerbation than most other viruses in patients of any age, with the exception of RSV in infants (39), while virus load and virus co-infection rates correlate with symptom severity (47).

Case–control studies indicate that asthma subjects are at greater risk of invasive pneumococcal infections than patients without asthma, with reported ORs ranging from 2.5 to 12.0 (48–50). For example, the population-based case–control study by Klemets and colleagues (49) assessed the risk of invasive pneumococcal (*Streptococcus pneumoniae*) infection (IPI) amongst adult patients with asthma. Using a national population-based laboratory surveillance, 1,282 cases of IPI were selected in patients aged 18–49 years (thus largely excluding COPD patients) along with 10 noninfected controls per IPI case, matched for age, sex and health district. Asthma cases were categorized as high (≥1 hospitalization within the previous 12 months) and low risk (with prescription drug entitlement and no hospitalization within the previous 12 months). Overall, 7.1% of cases had asthma (6.0 and 2.4% with high- and low-risk asthma, respectively) *vs* 2.5% of controls (1.0 and 1.1% with high- and low-risk asthma, respectively), indicating that adults of working age with asthma are at substantially increased risk of IPI.

Impaired immune responses may be associated with exacerbations in asthmatic children with reduced lung function, but not in those with normal lung function (51). Specifically, at the time of an asthma exacerbation, a lower expression of Th1 response genes was observed in children with reduced lung function than in children with normal lung function. Other studies have shown that genetic factors such as vitamin D (52) or particulate matter (PM_{10}) (53) can modify the effect of environmental exposure on exacerbation frequency. The advent of genomewide association studies in populations with severe asthma (54) and asthma exacerbations (55) may aid in better prediction of exacerbation phenotypes and the subclassification of patients into subphenotypes that may reflect the differing aetiopathogenesis and response to treatment and so allowing better targeting of treatment.

Severe asthma

Attempts to characterize severe asthma in childhood

In childhood asthma, guidelines that outline stepwise treatment escalation with increased disease severity or impaired symptom control fail to adequately deal with nonresponders (56–58). In particular, the stepwise treatment appears not always to be appropriate for children younger than 4 years, particularly those with mainly virus-driven asthma, who often do not respond to inhaled corticosteroids (57).

Severe asthma in children is complex, with the asthma phenotype changing during development and requiring continual reassessment (56, 58, 59). This makes cross-sectional analyses of childhood asthma less useful, as any apparent phenotypic stability within a population will obscure the significant individual instability of disease expression. One of the characteristics of severe treatment-resistant asthma in childhood is the large size of skin test wheal to inhalant and food allergens (60). Furthermore, in this patient group, the results of skin tests and IgE measurements for individual allergens are not always concordant; as a consequence, both tests should be carried out and quantified (61). Similar quantitative relationship between skin tests (and sIgE levels) has also been reported in relation to severity of airway hyper-reactivity in adults (62).

Rhinovirus infection in infants induces wheeze and, in a longitudinal study, was shown to be significantly associated with the development of childhood asthma (63). In another 11-year prospective study, teenage asthma was strongly associated with infant wheezing requiring hospitalization (64). This study identified eczema and allergen-specific IgE as early asthma-predictive factors and the risk of developing teenage asthma to be increased fivefold after respiratory syncytial virus-induced wheezing in infants and >10-fold after rhinovirus-induced wheezing. Rhinoviruses are frequently found in the lower airways in infants with recurrent respiratory symptoms, with the majority of these rhinovirus-infected infants exhibiting increased airway resistance (65). In infants with wheezing requiring hospitalization, sole rhinovirus infection, but not sole infection with any other common airway viruses, was associated with atopy (66). A recent study has demonstrated that a cardinal feature of bronchial epithelial cells from children with severe treatment-resistant asthma is impaired interferon-β and IFN-λ induction by rhinovirus (67). Although this patient group was highly atopic, no relationship was observed between atopy, allergy or Th2-mediated inflammation with impaired interferon (67).

A longitudinal study of an unselected birth cohort, which monitored lung function from the age of 3–26 years (68), reported that persistent wheezing, starting early in life, was associated with a decline in lung function in adult life and increased risk of exacerbations. A decline in lung function has also been associated with severe asthma exacerbations in adult asthma (4). A German birth cohort of more than 900 children showed that the risk of development of persistent asthma at age 13 years was significantly increased by early allergen sensitization in combination with exposure to high levels of perennial allergens early in life (69). In a recent study, predictors of subsequent troublesome symptoms amongst 3-year-old children with wheezing were large skin test responses to allergens and history of previous exacerbations and eczema (24).

Attempts to characterize severe asthma in adults

Attempts to identify phenotypes of adult asthma include the use of unsupervised cluster analyses (70, 71) aiming to group patients who share key features of asthma and airway inflammatory disease. Haldar and colleagues (70) grouped patients according to clinical symptoms and evidence of airway inflammation (based on sputum eosinophil count) and

found that symptom-led treatment of airway inflammation was appropriate in patients with mild and moderate asthma, but failed in more severe forms. They identified two discordant groups of patients who were refractory to standard treatment approaches and represented about 25% of all patients. One discordant group of patients were characterized as an obese, symptom-predominant, noneosinophilic phenotype, while the other group had few asthma symptoms, but a high degree of airway inflammation. Using symptom-driven asthma treatment in these two discordant groups would lead to overtreatment of the former and undertreatment of the latter group.

One difficulty with attempts to use clustering techniques to define disease mechanisms is defining cause and effect. In other words, 'are the pathophysiological features a consequence or an underlying cause of the disease?' A further confounding factor is the influence of treatment or lack of it (nonadherence). Defining groups of patients with chronic diseases according to different personality traits (72) has identified personality traits that govern treatment adherence.

There was a significant overlap between the phenotypes identified by Haldar et al. (70) and those identified by Moore et al. (71). Other similar initiatives included the EU-sponsored Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) consortium that has published a consensus-based systematic algorithm approach to differentiate between 'problematic', 'difficult' and 'severe refractory' asthma in the evaluation of patients with chronic severe asthma symptoms for use in clinical research and specialized care (73). The published PRACTAL consensus report on 'endotypes' (74) attempts to assign patients with asthma to groups sharing specific pathophysiological features, with the aim of identifying a basis for rational treatment of heterogeneous groups. Patients with severe asthma are found in each of these groups. Three recognizable clinical phenotypes of severe asthma emerge from these various analytical studies (see Table 1): (i) a severe atopic form, (ii) severe 'intrinsic' asthma (the most malignant severe asthma phenotype (75)) and (iii) severe asthma with obesity. However, it has to be emphasized that distinct pathophysiological mechanisms underpinning these different clinical phenotypes of severe asthma have not as yet been identified.

One potential problem of the cross-sectional approach to unbiased clustering is that the analysis does not include the important dimension of time, which may be essential to take into account potentially crucial longitudinal changes. Furthermore, while unsupervised learning may be a useful tool to generate new hypotheses, using these techniques to find an association with predefined outcomes such as severe asthma can be misleading if asthma severity is derived using the same variables that are used for clustering.

There is mounting evidence to demonstrate a close association between sensitisation to fungi and asthma severity (76), and the term 'severe asthma with fungal sensitization' (SAFS) has been proposed for patients with persistent severe asthma and fungal sensitization (77). Proof-of-concept pilot studies have suggested an improvement in asthma after antifungal treatment in this patient group (78).

Table 1 Four distinct clinical phenotypes of severe asthma and their characteristics

Type of severe asthma	Predominant clinical features
Severe atopic form	High serum IgE levels Detectable allergen-specific IgEs Frequently presenting with fungal sensitivity (predominantly to *Aspergillus*).
Severe 'intrinsic' asthma	High eosinophil counts in bronchoalveolar lavage fluid Nasal polyps Sinusitis Air trapping
Severe asthma with obesity	Several comorbidities Sleep apnoea Gastro-oeosophageal reflux disease Low eosinophil counts
Sudden asthma attacks	Recurrent in otherwise mild asthmatics More frequent in women Triggered by allergens, drugs, food, chemicals Often unrecognized cause

Treatment approaches to severe asthma and prevention of asthma exacerbations

Several studies have shown that the standard guideline treatment of persistent asthma with ICS provides a variable response, with 25–35% of asthmatic subjects showing little improvement in FEV_1 and/or bronchial hyper-responsiveness (9–11). In the Gaining Optimal Asthma Control ('GOAL') study (79), Bateman and colleagues used 1 year of increasing doses of combined ICS and LABA treatment in patients with persistent asthma and reported that about 30% of patients, with varying degrees of disease severity, did not achieve 'well-controlled asthma'. Asthma exacerbation risk may be further reduced using the same medication (i.e. an inhaled combination of a rapid-acting beta-2 agonist and corticosteroid (80)) as a controller and as a reliever of the disease. The PRICE trial (81) aimed to identify predictors of short-term (6 weeks) response to ICS. Although several baseline biomarkers and asthma symptoms correlated with short-term improvements, only greater bronchodilator (short-acting β2-agonist) reversibility showed a strong ($P < 0.001$) correlation. Differentiating between responders (>5% FEV_1 improvement) and nonresponders (<5% FEV_1 improvement) revealed that asthma control in responders was maintained only with continued ICS, while, in nonresponders, no improvement was observed with or without ICS. Interestingly, tiotropium, a long-acting antimuscarinic agent, still approved only for COPD, has been recently shown to further improve lung function in patients with severe uncontrolled asthma (82).

Of the four clinical phenotypes of severe asthma described in Table 1, the severe atopic form partially responds to standard treatment. Table 2 indicates possible treatment approaches in the two groups of patients with

severe asthma, which were described by Haldar et al. (70), that are less responsive to standard treatment. These treatment options for patients with severe asthma who remain symptomatic despite adhering to standard medical care include novel anti-inflammatory drugs that have been shown in preliminary studies to be effective in treating airway inflammation in asthma and so warrant further investigation (32, 83–86), and other novel approaches such as bronchial thermoplasty (87). It is important to note that, for a more effective use of these novel treatment options, a better understanding of the pathophysiology and of the inflammatory mechanisms of the severe asthma subtypes are required in order that studies can delineate specific response patterns. As previously noted, antifungal treatments may be of benefit in patients with severe asthma with fungal sensitization (78, 88), but large studies are needed to support these initial findings.

Current treatment of asthma exacerbations is inadequate, and new approaches to treatment are needed. These may include interferon-based treatments, treatments that aim to boost deficient antiviral immune responses and/or specific antiviral treatments. There may be patients with severe asthma who could benefit from treatments that target neutrophilic inflammation without further suppressing anti-infective immunity. Another question that needs to be addressed is the possible benefit in asthma exacerbations of antibacterial treatments that are widely used (89), despite not being recommended in guidelines.

The advances in molecular biology and immunology are being used to develop novel biological drugs for asthma treatment. These include therapeutic antibodies, soluble receptors, cytokines, small molecules and combinations thereof that target different effector molecules that influence the underlying immune and inflammatory processes. Some biological drugs are currently in clinical trials in asthma (90). However, there are major difficulties in developing novel drugs to treat asthma. These include (i) the complexity of the disease (in terms of the different disease phenotypes and the underlying molecular mechanisms), (ii) the limited number of biomarkers that have been identified for disease classification, (iii) the effectiveness of the current standard treatment approaches (combined inhaled steroid and beta-adrenergic agonist is not only effective but cheap) makes any comparative improvement difficult to identify in multicentre clinical trials, (iv) low patient adherence, which is characteristic of treatments of chronic disease, and (v) preclinical animal models may be poorly predictive of clinical efficacy (90).

Importantly, future clinical trials will need to identify the patient groups that respond to novel treatment to provide evidence for the stratified, personalized approach to asthma management.

Table 2 Possible treatment approaches in treatment-resistant severe asthma

Type of severe asthma	Possible treatment approaches
Severe asthma with obesity	Focus on comorbidities Reduction in body weight Cessation of smoking Direct treatment of airway smooth muscle Treating impaired airway defences Targeting neutrophil-driven inflammation of the lower airways Treatment of rhinosinusitis
Severe 'intrinsic' asthma	Focus on nasal polyps Reducing air trapping using ICS Novel anti-inflammatory drugs shown to be effective in airway inflammation Omalizimab (86) (an anti-IgE monoclonal antibody for treatment of eosiniphilic inflammation) is effective in improving asthma control, reducing asthma exacerbations (84) and reducing seasonal peaks in exacerbations (especially in patients with increased (>2%) F_ENO) (83). Mepolizamab (anti-interleukin-5 monoclonal antibody) reduces asthma exacerbations and airway inflammation in patients selected for eosinophilic airway inflammation (32, 33).
Sudden asthma attacks	Focus on education of the patient to avoid trigger Focus on education of the patient to treat attacks High dose inhaled rapid-acting bronchodilators High dose oral steroids Intramuscular adrenaline if required Magnesium sulphate Prompt referral to the emergency room

Severe asthma in primary care

In primary care, recognition of the clinical heterogeneity of asthma and the existence of different forms of severe asthma is obscured by a number of general deficiencies, including limited available time and clinical resources and lack of capacity and clinical capability. Nonguideline treatment of asthma is high, and provision of treatment to patients with asthma varies greatly, for example, in the use of ICS across European countries (91). The influence of comorbidities and of asthma exacerbations on asthma symptoms, in both children and adults, are not sufficiently recognized (92, 93). Most patients with asthma in primary care have been found to have uncontrolled disease (94). Furthermore, it is becoming increasingly clear that many patients diagnosed as asthmatic, even after full evaluation at tertiary centres, do not have asthma, but various other diagnoses (95, 96), which indicate a fundamental need to establish improved diagnosis as a basis of appropriate management (97). The resources needed to review patients frequently until disease control is achieved vary between healthcare systems. The Finnish National Asthma programme (98), predicated on a systematic approach to disease management and underpinned by educational and skills training in primary care, demonstrates that investment in the structure of the health system that delivers asthma care reduces morbidity significantly and at a lower overall cost.

Other issues

The above discussion aims to highlight the prominent issues and the attempts to acquire a better understanding of asthma exacerbations and severe asthma. However, there are several additional clinical and pathophysiological issues of importance for improving our understanding of asthma as a complex disease. These have not been highlighted here partly because there is no scientific consensus of their exact relevance. However, two examples are briefly reviewed here.

Airway remodelling is associated with poor clinical outcomes amongst asthmatic patients, but the pathophysiological relevance of, and the effect of treatment on, airway remodelling is unclear (99). Airway remodelling is a feature of adult asthma and is found to a similar extent, and quite early, in children with difficult-to-treat asthma (100). Using epithelial reticular basement membrane thickening as a marker for airway remodelling, no association between airway remodelling and age, symptom duration, lung function and concurrent eosinophilic airway inflammation was found (100), albeit in a small number of patients. Inflammatory and structural changes typical of asthma, such as airway eosinophilia and angiogenesis, have been observed not only in children with asthma but also in atopic children without asthma, raising the possibility that some of these pathological lesions may be associated with atopy even in the absence of asthmatic symptoms. Reticular membrane thickening and the eosinophilic inflammation characteristic of asthma in older children and adults are not present in the wheezing infants with reversible airflow obstruction, even in the presence of atopy (101, 102). It was proposed that this lack of RBM thickening in wheezy infants was due to the apparent paucity of eosinophilic inflammation (102), which may have a role in driving allergic airway remodelling (103).

Based on the data from many population studies, it is generally considered that the environment has an important influence on the development of asthma and other allergic diseases. However, the proposed mechanisms, particularly the role of atopy, that underlie the effects of environment on asthma aetiology need to be revised in the light of recent findings (104), such as the evident increase in prevalence of severe asthma in developing countries and its parallel decline in several developed countries (105). The interaction of environment and asthma disease mechanisms is complex, and genetic variants that are protective in one environment may be associated with increased risk in another environment (106).

Position statement

- Although clinical guidelines improve patient treatment by bringing treatments to groups of patients who best benefit from them, they fail many patients who fall outside of the 'mean' clinical characteristics on which clinical guidelines are based.
  - Standard treatment with inhaled corticosteroids and LABAs is insufficiently effective in many patients with severe asthma.
  - Young children, particularly those with virus-driven asthma, are often poorly managed with currently available medications.
  - In asthma, there is a need to focus more on the individual patient, particularly those with severe asthma.
  - There is a need to recognize asthma as a heterogeneous disease and to properly identify the different disease mechanisms involved in patients with severe asthma. Only in this way, we will begin to understand what is 'driving' severe asthma and identify novel therapeutic targets.
  - In childhood asthma, expression of atopy varies over time and in different characteristic ways that suggest differences in underlying pathophysiological mechanisms in relation to exacerbation-prone asthma phenotype.
  - In adult asthma, several forms of severe asthma have become recognized, and different treatment approaches to these forms of severe asthma are proposed.
- There is a need for a consensus definition of asthma exacerbation that could usefully guide treatment. We need to better understand the mechanisms of asthma exacerbation, develop novel treatments for exacerbations and carry out studies of existing and new treatments to better guide their use.
  - As in COPD, asthma diagnosis and treatment decisions should include consideration of future risk of exacerbations.
  - Current data strongly link impaired innate immune responses and consequent increased risk of infection with increased risk of asthma exacerbations. This provides a sound basis for the development of novel treatments.
  - There is general concern that patients with asthma are not being sufficiently alerted to the risk of asthma exacerbations and that another term be considered other than 'asthma exacerbation' when describing these events to patients (such as 'lung attack' or 'asthma attack' to equate the seriousness of such an event with a heart attack).

Improving diagnosis and stratification

- Development of diagnostic procedures accessible within primary care to ensure correct diagnosis.
- An acceptance of the need for iterative review to gain control of the disease; patients, in whom asthma fails to become controlled, need further evaluation to confirm that asthma is the correct diagnosis and what further evaluations are required.
- Improved tools for 'scoring' the asthma patient in terms of disease severity, and future risk needs to be developed for use in primary care (97, 107).
  - Future studies should aim to establish whether serum IgE, F_ENO and induced sputum eosinophil counts are valuable biomarkers of the severity of asthmatic airway inflammation.
  - New biomarkers are needed to predict the severity of asthma, the risk of exacerbation and the response to treatments.

- There is a need for a more objective definition of childhood asthma, with broader use of lung function tests, especially in preschoolers, and so obtain more uniform criteria for diagnosis before initiating treatment to control the disease.
- In both childhood and adult asthma, expression of atopy varies over time and in different characteristic ways that reveal differences in underlying pathophysiological mechanisms, including a severe asthma-prone phenotype.

Future clinical trials

- Observational longitudinal studies should be performed in a standardized way with patient and biological data sampling (using an asthma register) to allow a better characterization of the epidemiology, current healthcare utilization, risk factors (including genetic susceptibility) and comorbidities that are linked to exacerbations and severity.
- The future task is to devise studies that differentiate between patient phenotypes, use robust clinically relevant biomarkers, include longitudinal outcomes (such as time to exacerbation and increase in airway remodelling) and identify relevant environmental factors, including the influence of current and prior medication. To facilitate the identification of new asthma endotypes, such studies should contribute to a repository (or biobank) of biological samples from the asthma population.
- For characterization of the heterogeneity of severe asthma, more and improved clinical studies are needed to improve the evidence base.
  - Randomized, controlled trials in asthma include highly selected patients, who are, almost exclusively, 'healthy asthmatics' with $ß_2$-agonist reversibility.
  - Cohort studies may complement clinical trials.
  - There are still insufficient longitudinal data in adult asthma, and cohort studies in this age group need to be established.

The asthmatic patient in primary care

- Improving primary care of the asthmatic patient is in need of urgent attention and requires radical changes.
  - The ideal approach to dealing with the asthmatic patient in primary care is to (i) characterize the patient, (ii) confirm diagnosis, (iii) confirm whether a new or existing patient gains control by the iterative application of a structured review (108) and consider reducing treatment when control is achieved, while undertaking appropriate monitoring, (iv) maintain control by teaching the patient about asthma and developing the patient's self-management skills (109) according to the model developed by Glasziou (110), (v) attempt to understand the patient's perspective; this may be the key to improving patient compliance (111), (vi) consider the risk of exacerbations (which is separate from controlling everyday symptoms) and factors that may increase the risk of exacerbations (93) and (vii) realize that nonsymptomatic patients are also at risk of exacerbations.
- The complexity of the multifactorial nature of asthma and the resource limitations in primary care needs to be better characterized in order to address the wide variability of care delivered in this environment (98).
- Support mechanisms that enable readily accessible means for patient self-management and self-education, having already met with varying degrees of success (112–115), need to be further developed.
- Primary clinicians have themselves recognized the research agenda that is needed to direct improvement in asthma care (97).
- Whether seen in primary care or secondary care, patients with uncontrolled asthma either (i) have treatment-resistant disease, (ii) are not fully compliant with treatment, (iii) are unable to appreciate deterioration in their disease, (iv) have a physician who is underestimating the degree of disease control, is undertreating or not recognizing the effect of comorbidities, or (v) do not have asthma.

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Conflicts of interest

A. Custovic serves as a consultant for Circassia. He received speaker fees from Glaxo Smith Kline, Thermo Fisher Scientific, Airsonet, Novartis, MSD and ALK. He received research grants from the UK Medical Research Council, Moulton Charitable foundation National Institute of Health Research.

In the past five years S. L. Johnston has had research grants from Astra Zeneca, Centocor, GlaxoSmithKline, MedImmune, Sanofi-Pasteur and Synairgen. S. L. Johnston holds share options in Synairgen. S. L. Johnston does some consultancy work for AstraZeneca, Centocor, GlaxoSmithKline, MedImmune, Sanofi-Pasteur and Synairgen.

In the last five years, I. D. Pavord has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Inglehiem, Aerocrine and GSK. He has received honoraria for attending advisory panels with Almirall, Astra Zeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey and Napp. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca and Napp.

M. Gaga received research grants from Novartis, BI, Cephalon, Teva and GSK.

L. M. Fabbri has received consultancy fees from: Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MSD, Nycomed, Pearl Therapeutics, Sterna, Peer Voice Europe, OM Pharma Sa, Kyorin Pharmaceutical, Boston Scientific and Bayer. Readings, advisory board or reimbursement of expenses: AstraZeneca, Novartis, Sigma-Tau, Roche, Deutsches Zentrum für Luft und Raumfahrt, German Aerospace Center, Mundipharma Int., Genetech Inc., Elevation Pharmaceutical, Ferrer Group, Nycomed, Dynamicon and Laboratori Guidotti.

E. Bel has received consultancy fees from Novartis, GSK and Sanofi-Regeneron, and fees for speaking from GSK.

P. Le Souëf has received speaker fees from Glaxo Smith Kline and AstraZeneca and has received research funding from AstraZeneca and Pharmanet AG. He has received research grants from the National Health and Medical Research Council of Australia and the Australian Research Council.

J. Lötvall has over the last five years been a consultant and/or given lectures for GSK, AstraZeneca, Aerovant, Novartis, UCB, Oriel and Merck, for which he has received honoraria. He has also received research grants and participated in clinical trials for Novartis, GSK, AstraZeneca and Actelion under the full organization of the University of Gothenburg.

P. Demoly is a consultant and a speaker for Stallergenes, ALK, Circassia and Chiesi and is a speaker for Merck, AstraZeneca, Menarini and GlaxoSmithKline.

C. Akdis serves in the scientific advisory boards of Novartis, Actellion, Circassia, Allergopharma and Stallergenes. He received research grants from Novartis, Swiss National Science Foundation, Swiss-Polish Research Grant.

D. Ryan has been supported to attend conferences, provide consultancy services to or lectured on behalf of AZ, Novartis, Chiesi, Mundipharma, MSD and Aerocrine.

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F. D. Martinez served as a consultant to MedImmune in 2010. He received speaker fees from Merck in 2011 and from Abbott in 2011 and 2012. He receives grant funds from the National Institutes of Health.

P. O'Byrne serves in the scientific advisory boards of Abbott, AstraZeneca, Asmacure, Boehringer Ingelheim, GlaxoSmithKline and Medimmune Merck. He received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline and Nycomed, and also he received grants from AIM, Amgen, AstraZeneca, Genentech, GlaxoSmithKline, Novartis and ONO.

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References

1. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000;**161**:1720–1745.
2. Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B, Silverman S. Risk factors and costs associated with an asthma attack. *Thorax* 2000;**55**:19–24.
3. Lane S, Molina J, Plusa T. An international observational prospective study to determine the cost of asthma exacerbations (COAX). *Respir Med* 2006;**100**:434–450.
4. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009;**179**:19–24.
5. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc* 2009;**6**:272–277.
6. Romagnoli M, Caramori G, Braccioni F, Ravenna F, Barreiro E, Siafakas NM et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. *Clin Exp Allergy* 2007;**37**:552–557.
7. Loymans RJ, Ter Riet G, Sterk PJ. Definitions of asthma exacerbations. *Curr Opin Allergy Clin Immunol* 2011;**11**:181–186.
8. Anon. Global Initiative for Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. [html] 2010 [cited 2011; Available from: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosismanagement.
9. Kerrebijn KF, van Essen-Zandvliet EE, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol* 1987;**79**:653–659.
10. Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Pineiro A, Wei LX et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med* 1999;**130**:487–495.
11. Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM et al. Significant variability in response to inhaled

corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;**109**:410–418.
12. Anon. British guideline on the management of asthma: a national clinical guideline. Edinburgh & London, 2008. June, 2009 (Revision).
13. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010;**126**:926–938.
14. Bush A, Zar HJ. WHO universal definition of severe asthma. *Curr Opin Allergy Clin Immunol* 2011;**11**:115–121.
15. Murphy AC, Proeschal A, Brightling CE, Wardlaw AJ, Pavord I, Bradding P et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax* 2012;**67**:751–753.
16. Nikander K, Turpeinen M, Pelkonen AS, Bengtsson T, Selroos O, Haahtela T. True adherence with the Turbuhaler in young children with asthma. *Arch Dis Child* 2011;**96**:168–173.
17. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009;**180**:817–822.
18. Heaney LG, Horne R. Non-adherence in difficult asthma: time to take it seriously. *Thorax* 2012;**67**:268–270.
19. Bracken M, Fleming L, Hall P, Van Stiphout N, Bossley C, Biggart E et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. *Arch Dis Child* 2009;**94**:780–784.
20. Agache I, Akdis C, Jutel M, Virchow JC. Untangling asthma phenotypes and endotypes. *Allergy* 2012;**67**:835–846.
21. Doull IJ, Lampe FC, Smith S, Schreiber J, Freezer NJ, Holgate ST. Effect of inhaled corticosteroids on episodes of wheezing associated with viral infection in school age children: randomised double blind placebo controlled trial. *BMJ* 1997;**315**:858–862.
22. Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gern J, Lemanske R et al. International consensus on (ICON) pediatric asthma. *Allergy* 2012;**67**:976–997.
23. Custovic A, Lazic N, Simpson A. Pediatric asthma and development of atopy. *Curr Opin Allergy Clin Immunol* 2013;**13**:173–180.
24. Belgrave DCM, Simpson A, Semic-Jusufagic A, Murray CS, Buchan I, Pickles A et al. Joint modeling of parentally-reported and physician-confirmed wheeze identifies children with persistent troublesome wheezing. *J Allergy Clin Immunol* 2013;**132**:575–583.
25. Lazic N, Roberts G, Custovic A, Belgrave D, Bishop CM, Winn J et al. Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts. *Allergy* 2013;**68**:764–770.
26. Simpson A, Tan VY, Winn J, Svensen M, Bishop CM, Heckerman DE et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010;**181**:1200–1206.
27. ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005;**26**:812–818.
28. Calam R, Gregg L, Simpson A, Simpson B, Woodcock A, Custovic A. Behavior problems antecede the development of wheeze in childhood: a birth cohort study. *Am J Respir Crit Care Med* 2005;**171**:323–327.
29. Veen JC, Smits HH, Ravensberg AJ, Hiemstra PS, Sterk PJ, Bel EH. Impaired perception of dyspnea in patients with severe asthma. Relation to sputum eosinophils. *Am J Respir Crit Care Med* 1998;**158**:1134–1141.
30. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;**360**:1715–1721.
31. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemiere C, Pizzichini E et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;**27**:483–494.
32. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;**360**:973–984.
33. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;**360**:985–993.
34. Gelb AF, Flynn Taylor C, Shinar CM, Gutierrez C, Zamel N. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. *Chest* 2006;**129**:1492–1499.
35. Gibson PG. Using fractional exhaled nitric oxide to guide asthma therapy: design and methodological issues for AStma TReatment ALgorithm studies. *Clin Exp Allergy* 2009;**39**:478–490.
36. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;**184**:602–615.
37. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol* 2010;**125**:1178–1187; quiz 1188–1179.
38. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ* 1995;**310**:1225–1229.
39. Papadopoulos NG, Christodoulou I, Rohde G, Agache I, Almqvist C, Bruno A et al. Viruses and bacteria in acute asthma exacerbations–a GA(2) LEN-DARE systematic review. *Allergy* 2011;**66**:458–468.
40. Bisgaard H, Hermansen MN, Bonnelykke K, Stokholm J, Baty F, Skytt NL et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. *BMJ* 2010;**341**:c4978.
41. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;**61**:376–382.
42. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002;**324**:763.
43. Corne JM, Marshall C, Smith S, Schreiber J, Sanderson G, Holgate ST et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002;**359**:831–834.
44. Laza-Stanca V, Message SD, Edwards MR, Parker HL, Zdrenghea MT, Kebadze T et al. The role of IL-15 deficiency in the pathogenesis of virus-induced asthma exacerbations. *PLoS Pathog* 2011;**7**:e1002114.
45. Message SD, Laza-Stanca V, Mallia P, Parker HL, Zhu J, Kebadze T et al. Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc Natl Acad Sci USA* 2008;**105**:13562–13567.
46. Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PA, Bartlett NW et al. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006;**12**:1023–1026.
47. Jartti T, Lehtinen P, Vanto T, Hartiala J, Vuorinen T, Makela MJ et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J* 2006;**25**:482–488.

48. Pilishvili T, Zell ER, Farley MM, Schaffner W, Lynfield R, Nyquist AC et al. Risk factors for invasive pneumococcal disease in children in the era of conjugate vaccine use. *Pediatrics* 2010;**126**:e9–e17.
49. Klemets P, Lyytikainen O, Ruutu P, Ollgren J, Kaijalainen T, Leinonen M et al. Risk of invasive pneumococcal infections among working age adults with asthma. *Thorax* 2010;**65**:698–702.
50. Talbot TR, Hartert TV, Mitchel E, Halasa NB, Arbogast PG, Poehling KA et al. Asthma as a risk factor for invasive pneumococcal disease. *N Engl J Med* 2005;**352**:2082–2090.
51. Bosco A, Ehteshami S, Stern DA, Martinez FD. Decreased activation of inflammatory networks during acute asthma exacerbations is associated with chronic airflow obstruction. *Mucosal Immunol* 2010;**3**: 399–409.
52. Du R, Litonjua AA, Tantisira KG, Lasky-Su J, Sunyaev SR, Klanderman BJ et al. Genome-wide association study reveals class I MHC-restricted T cell-associated molecule gene (CRTAM) variants interact with vitamin D levels to affect asthma exacerbations. *J Allergy Clin Immunol* 2012;**129**:368–373.
53. Canova C, Dunster C, Kelly FJ, Minelli C, Shah PL, Caneja C et al. PM10-induced hospital admissions for asthma and chronic obstructive pulmonary disease: the modifying effect of individual characteristics. *Epidemiology* 2012;**23**:607–615.
54. Wan YI, Shrine NR, Soler Artigas M, Wain LV, Blakey JD, Moffatt MF et al. Genome-wide association study to identify genetic determinants of severe asthma. *Thorax* 2012;**67**:762–768.
55. Xu M, Tantisira KG, Wu A, Litonjua AA, Chu JH, Himes BE et al. Genome Wide Association Study to predict severe asthma exacerbations in children using random forests classifiers. *BMC Med Genet* 2011;**12**:90.
56. Bush A, Saglani S. Management of severe asthma in children. *Lancet* 2010;**376**:814–825.
57. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;**32**:1096–1110.
58. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;**63**:5–34.
59. Schultz A, Devadason SG, Savenije OE, Sly PD, Le Souef PN, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010;**99**:56–60.
60. Sharples J, Gupta A, Fleming L, Bossley CJ, Bracken-King M, Hall P et al. Long-term effectiveness of a staged assessment for paediatric problematic severe asthma. *Eur Respir J* 2012;**40**:264–267.
61. Frith J, Fleming L, Bossley C, Ullmann N, Bush A. The complexities of defining atopy in severe childhood asthma. *Clin Exp Allergy* 2011;**41**:948–953.
62. Marinho S, Simpson A, Marsden P, Smith JA, Custovic A. Quantification of atopy, lung function and airway hypersensitivity in adults. *Clin Transl Allergy* 2011;**1**:16.
63. Kotaniemi-Syrjanen A, Vainionpaa R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy–the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;**111**:66–71.
64. Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi MO. Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. *Pediatr Pulmonol* 2005;**40**:316–323.
65. Malmstrom K, Pitkaranta A, Carpen O, Pelkonen A, Malmberg LP, Turpeinen M et al. Human rhinovirus in bronchial epithelium of infants with recurrent respiratory symptoms. *J Allergy Clin Immunol* 2006;**118**:591–596.
66. Jartti T, Kuusipalo H, Vuorinen T, Soderlund-Venermo M, Allander T, Waris M et al. Allergic sensitization is associated with rhinovirus-, but not other virus-, induced wheezing in children. *Pediatr Allergy Immunol* 2010;**21**:1008–1014.
67. Edwards MR, Regamey N, Vareille M, Kieninger E, Gupta A, Shoemark A et al. Impaired innate interferon induction in severe therapy resistant atopic asthmatic children. *Mucosal Immunol* 2013;**6**:797–806.
68. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;**349**:1414–1422.
69. Illi S, von Mutius E, Lau S, Niggemann B, Gruber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;**368**:763–770.
70. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;**178**:218–224.
71. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;**181**:315–323.
72. Axelsson M, Brink E, Lundgren J, Lotvall J. The influence of personality traits on reported adherence to medication in individuals with chronic disease: an epidemiological study in West Sweden. *PLoS ONE* 2011;**6**:e18241.
73. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2011;**66**:910–917.
74. Lotvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;**127**:355–360.
75. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;**160**:1001–1008.
76. Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A et al. Fungi and allergic lower respiratory tract diseases. *J Allergy Clin Immunol* 2012;**129**:280–291; quiz 292–283.
77. Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* 2006;**27**:615–626.
78. Denning DW, O'Driscoll BR, Powell G, Chew F, Atherton GT, Vyas A et al. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: The Fungal Asthma Sensitization Trial (FAST) study. *Am J Respir Crit Care Med* 2009;**179**:11–18.
79. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;**170**:836–844.
80. Bateman ED, Harrison TW, Quirce S, Reddel HK, Buhl R, Humbert M et al. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. *Respir Res* 2011;**12**:38.
81. Martin RJ, Szefler SJ, King TS, Kraft M, Boushey HA, Chinchilli VM et al. The Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial. *J Allergy Clin Immunol* 2007;**119**:73–80.
82. Kerstjens HA, Disse B, Schroder-Babo W, Bantje TA, Gahlemann M, Sigmund R et al. Tiotropium improves lung function in

patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011;**128**:308–314.
83. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;**364**:1005–1015.
84. Pavord ID, Bush A. Anti-IgE for asthma in inner-city children. *N Engl J Med* 2011;**364**: 2556–2557; author reply 2557–2558.
85. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;**368**:2455–2466.
86. Lommatzsch M, Korn S, Buhl R, Virchow JC. Against all odds: anti-IgE for intrinsic asthma? *Thorax* 2013, doi: 10.1136/thoraxjnl-2013-203738.
87. Wahidi MM, Kraft M. Bronchial thermoplasty for severe asthma. *Am J Respir Crit Care Med* 2012;**185**:709–714.
88. Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. *J Asthma* 2012;**49**:423–433.
89. Bafadhel M, Clark TW, Reid C, Medina MJ, Batham S, Barer MR et al. Procalcitonin and C-reactive protein in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. *Chest* 2011;**139**:1410–1418.
90. Akdis CA. Therapies for allergic inflammation: refining strategies to induce tolerance. *Nat Med* 2012;**18**:736–749.
91. Lagerlov P, Veninga CC, Muskova M, Hummers-Pradier E, Stalsby Lundborg C, Andrew M et al. Asthma management in five European countries: doctors' knowledge, attitudes and prescribing behaviour. Drug Education Project (DEP) group. *Eur Respir J* 2000;**15**:25–29.
92. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J* 2009;**33**:897–906.
93. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Respir J* 2009;**18**:300–305.
94. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**:802–807.
95. Starren ES, Roberts NJ, Tahir M, O'Byrne L, Haffenden R, Patel IS et al. A centralised respiratory diagnostic service for primary care: a 4-year audit. *Prim Care Respir J* 2012;**21**:180–186.
96. Heaney LG, Robinson DS. Severe asthma treatment: need for characterising patients. *Lancet* 2005;**365**:974–976.
97. Pinnock H, Ostrem A, Rodriguez MR, Ryan D, Stallberg B, Thomas M et al. Prioritising the respiratory research needs of primary care: the International Primary Care Respiratory Group (IPCRG) e-Delphi exercise. *Prim Care Respir J* 2012;**21**:19–27.
98. Haahtela T, Tuomisto LE, Pietinalho A, Klaukka T, Erhola M, Kaila M et al. A 10 year asthma programme in Finland: major change for the better. *Thorax* 2006;**61**:663–670.
99. Bergeron C, Tulic MK, Hamid Q. Airway remodelling in asthma: from benchside to clinical practice. *Can Respir J* 2010;**17**:e85–e93.
100. Payne DN, Rogers AV, Adelroth E, Bandi V, Guntupalli KK, Bush A et al. Early thickening of the reticular basement membrane in children with difficult asthma. *Am J Respir Crit Care Med* 2003;**167**:78–82.
101. Saglani S, Molyneux C, Gong H, Rogers A, Malmstrom K, Pelkonen A et al. Ultrastructure of the reticular basement membrane in asthmatic adults, children and infants. *Eur Respir J* 2006;**28**:505–512.
102. Saglani S, Malmstrom K, Pelkonen AS, Malmberg LP, Lindahl H, Kajosaari M et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005;**171**:722–727.
103. Humbles AA, Lloyd CM, McMillan SJ, Friend DS, Xanthou G, McKenna EE et al. A critical role for eosinophils in allergic airways remodeling. *Science* 2004;**305**:1776–1779.
104. Asher MI. Urbanisation, asthma and allergies. *Thorax* 2011;**66**:1025–1026.
105. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tuberc Lung Dis* 2005;**9**:10–16.
106. Vartiainen E, Petays T, Haahtela T, Jousilahti P, Pekkanen J. Allergic diseases, skin prick test responses, and IgE levels in North Karelia, Finland, and the Republic of Karelia, Russia. *J Allergy Clin Immunol* 2002;**109**:643–648.
107. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;**100**:616–621.
108. Pinnock H, Fletcher M, Holmes S, Keeley D, Leyshon J, Price D et al. Setting the standard for routine asthma consultations: a discussion of the aims, process and outcomes of reviewing people with asthma in primary care. *Prim Care Respir J* 2010;**19**:75–83.
109. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2003;(1):CD001117.
110. Glasziou P, Irwig L, Mant D. Monitoring in chronic disease: a rational approach. *BMJ* 2005;**330**:644–648.
111. Horne R, Price D, Cleland J, Costa R, Covey D, Gruffydd-Jones K et al. Can asthma control be improved by understanding the patient's perspective? *BMC Pulm Med* 2007;**7**:8.
112. Ostojic V, Cvoriscec B, Ostojic SB, Reznikoff D, Stipic-Markovic A, Tudjman Z. Improving asthma control through telemedicine: a study of short-message service. *Telemed J E Health* 2005;**11**:28–35.
113. van der Meer V, Bakker MJ, van den Hout WB, Rabe KF, Sterk PJ, Kievit J et al. Internet-based self-management plus education compared with usual care in asthma: a randomized trial. *Ann Intern Med* 2009;**151**:110–120.
114. Jan RL, Wang JY, Huang MC, Tseng SM, Su HJ, Liu LF. An internet-based interactive telemonitoring system for improving childhood asthma outcomes in Taiwan. *Telemed J E Health* 2007;**13**:257–268.
115. Ryan D, Price D, Musgrave SD, Malhotra S, Lee AJ, Ayansina D et al. Clinical and cost effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial. *BMJ* 2012;**344**:e1756.