



## Asthma

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Asthma is a heterogeneous group of conditions that result in recurrent, reversible bronchial obstruction. Although the disease can start at any age, the first symptoms occur during childhood in most cases. Asthma has a strong genetic component, and genome-wide association studies have identified variations in several genes that slightly increase the risk of disease. Asthma is often associated with increased susceptibility to infection with rhinoviruses and with changes in the composition of microbial communities colonising the airways, but whether these changes are a cause or consequence of the disease is unknown. **There is currently no proven prevention strategy; however, the finding that exposure to microbial products in early life, particularly in farming environments, seems to be protective against asthma offers hope that surrogates of such exposure could be used to prevent the disease.** Genetic and immunological studies point to defective responses of lung resident cells, especially those associated with the mucosal epithelium, as crucial elements in the pathogenesis of asthma. Inhaled corticosteroids continue to be the mainstay for the treatment of mild and moderate asthma, but limited adherence to daily inhaled medication is a major obstacle to the success of such therapy. Severe asthma that is refractory to usual treatment continues to be a challenge, but new biological therapies, such as humanised antibodies against IgE, interleukin 5, and interleukin 13, offer hope to improve the quality of life and long-term prognosis of severe asthmatics with specific molecular phenotypes.

### Introduction

Asthma is characterised by recurrent episodes of airway obstruction, which reverse either spontaneously or after use of medication, and is usually associated with bronchial hyper-responsiveness and evidence of chronic airway inflammation. More elaborate definitions have been proposed and there is no clear consensus on how to define asthma; fortunately, most cases are mild and are not difficult to diagnose and treat by family doctors. However, at the more severe end of the asthma spectrum, comorbidities overlap with chronic obstructive pulmonary disease (COPD), and refractoriness to available therapy make asthma troublesome and costly for health-care systems.

A previous Seminar on asthma was published in *The Lancet* more than a decade ago.<sup>1</sup> Here, we mainly review information emerging thereafter. During this period, there have been **substantial advances in our understanding of the genetics, pathogenesis, and natural course of the disease**, offering great hope for the development of new, targeted therapies, particularly for severe asthma. For now, the main therapeutic method continues to be the so-called adrenal substance recommended for treatment of asthma by Solis-Cohen<sup>2</sup> in 1900, when he noted “It has...served to cut short a paroxysm... [and] been useful in averting the recurrence

of paroxysms and in finally bringing about a state of freedom from fear of their recurrence.” As much can be said today for the available corticosteroids and beta-adrenergic agonists, which are close relatives of the natural products contained in the Burroughs & Wellcome’s tablets (to be taken as 5 grains once daily, then twice, then three times daily) mentioned by Solis-Cohen.<sup>2</sup>

### Epidemiology

Surveys based on questionnaire data, in which the disease is usually defined as current episodes of wheezing or a physician’s diagnosis, show that asthma affects 5–16% of people worldwide.<sup>3</sup> Rates vary widely in different countries,<sup>4</sup> reflecting differences in prevalence and in diagnostic standards. Prevalence increased markedly worldwide during the second half of the 20th century,<sup>5</sup> but seems to have plateaued thereafter, particularly in countries with the highest asthma rates, such as the UK.<sup>6</sup> An exception is the USA, where asthma prevalence increased from 7·3% to 8·4% between 2001 and 2010,<sup>3</sup> and continues to mainly affect children, African-Americans, and the poor; 11·2% of people with incomes lower than the poverty level had asthma, compared with 8·7% for those with incomes up to twice the poverty level, and 7·3% for those with higher incomes. **Asthma-related hospitalisations and emergency room visits remained stable in the USA from 2001–10, and mortality decreased slightly.**<sup>3</sup> **There have been large increases in asthma expenditures in the USA, which were calculated at US\$18 billion per year for adults alone in 2003–05.**<sup>7</sup> **Moreover, the costs of asthma medication as a proportion of total costs have substantially increased;** in 1985, 57% of asthma expenditures were for emergency room visits and hospitalisations,<sup>8</sup> whereas drug treatment now accounts for up to 75% of asthma costs.<sup>9</sup>

### Search strategy and selection criteria

Since roughly 51 000 articles have been published on asthma since 2002, when the last *Lancet* Seminar on the disease was published, we did a non-systematic review of articles published in English and collected by the authors. We searched PubMed, using the term “asthma”, from January, 2002, to March, 2013. We gave priority to randomised controlled trials when available, to larger studies, and to articles published in high-quality journals.

## Natural history

Knowledge of factors associated with the inception and progression of asthma has advanced substantially in the past few years, thanks to the availability of findings from birth cohorts focused on these issues. In most cases, the first symptoms of asthma occur during the preschool years,<sup>10</sup> and even among patients who develop chronic symptoms as young adults, higher rates of episodic wheezing and bronchial hyper-responsiveness are detected in early life.<sup>11</sup> Clinical expression patterns are established very early during the course of the disease; symptom severity and lung function deficits track with age.<sup>12</sup> **The strongest predictor of continued and increasingly severe symptoms is chronic airflow limitation—ie, the presence of persistent bronchial obstruction not readily reversible with bronchodilators.**<sup>13,14</sup> Only a small proportion of patients with asthma have airflow limitation, and three distinct phases have been noted for the development of airflow limitation, as follows (figure 1): a prenatal phase, resulting in reduced lung function shortly after birth;<sup>15–18</sup> a preschool phase (birth to age 5–7 years), resulting in delays in accelerated lung-function growth;<sup>17,19</sup> and a third phase, probably lasting a lifetime, during which further losses occur at a slower rate.<sup>20,21</sup> Although postnatally acquired airflow limitation is more likely to be seen in patients with recurrent, severe exacerbations,<sup>22</sup> declines in lung function are not steeper in asthmatic individuals who smoke than in non-asthmatic smokers.<sup>21</sup> Impaired lung function is associated with occupational asthma and exposure to air pollution,<sup>23,24</sup> but it is unclear whether this exposure leads to irreversible airflow limitation.<sup>25,26</sup>

Many children have mild, transient, or sporadic episodes of airway obstruction that do not lead into chronic asthma, and several subphenotypes of childhood wheeze have been identified.<sup>27,28</sup> In wealthy societies, allergic sensitisation to many aeroallergens during preschool years is strongly associated with subsequent severe asthma and deficits in lung-function growth.<sup>29</sup> **Chronic asthma can also be highly prevalent in poorer countries,**<sup>30</sup> but the association with allergy markers is much less conspicuous or absent.<sup>31</sup> Whether these findings point to the presence of different asthma pathogenic mechanisms in different communities, or support the notion that atopy is often consequence and not the cause of the disease is still unclear.

## Genetics

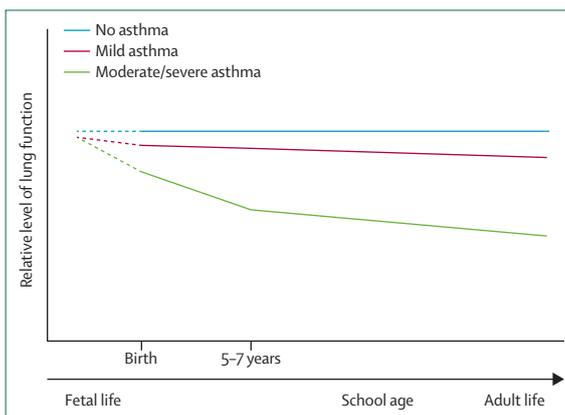
Chips containing hundreds of thousands of common genetic variants have become widely available and have been used in genome-wide association studies (GWAS) to search for associations among thousands of asthma cases and controls (figure 2).<sup>32–37</sup> These studies have reported evidence for the presence of asthma-related loci at or near genes for *CHI3L1* (also known as *YKL40*), *IL6R*, and *DENND1B* on chromosome 1, *IL1RL1–IL18R1* on chromosome 2, *PDE4D* and *RAD50–IL13* on chromosome 5, *HLA-DQ* on chromosome 6, *IL33* on chromosome 9,

*SMAD3* on chromosome 15, *ORMDL3–GSDMB* on chromosome 17, *IL2RB* on chromosome 22, and *PYHIN1* on chromosome 1 in African-Americans. For most of these loci, genes reported in one GWAS have not been replicated in other studies. An exception is *ORMDL3–GSDMB*, which has been repeatedly found to be associated with childhood but not adult asthma. For all loci, effects are weak, accounting for only a small proportion of the heritability of the disease. Loci associated with total IgE concentrations show very little overlap with those related to asthma,<sup>38</sup> supporting the notion that atopy might not be a primary driver of susceptibility.<sup>39</sup> A study of quantitative genetic scores of the combined effect of thousands of common single-nucleotide polymorphisms that individually have a weak influence on asthma risk suggested that asthma has a strong polygenic component,<sup>32</sup> which accords with previous findings in studies of familial segregation of the disease.<sup>40</sup>

Taken together, studies of common genetic variants have yielded important new information on the mechanisms involved in pathogenesis of asthma, although the variants identified have little prognostic utility. Recent reports in which gene exons were sequenced genome-wide in thousands of individuals have suggested that rare genetic variants, seldom detected through GWAS chips, might have a larger effect than common variants on the heritability of complex diseases.<sup>41</sup> **The only study so far to have reported on resequencing of selected genes in patients with asthma yielded promising results,**<sup>42</sup> but these findings need to be confirmed and extended to the whole genome in much larger populations.

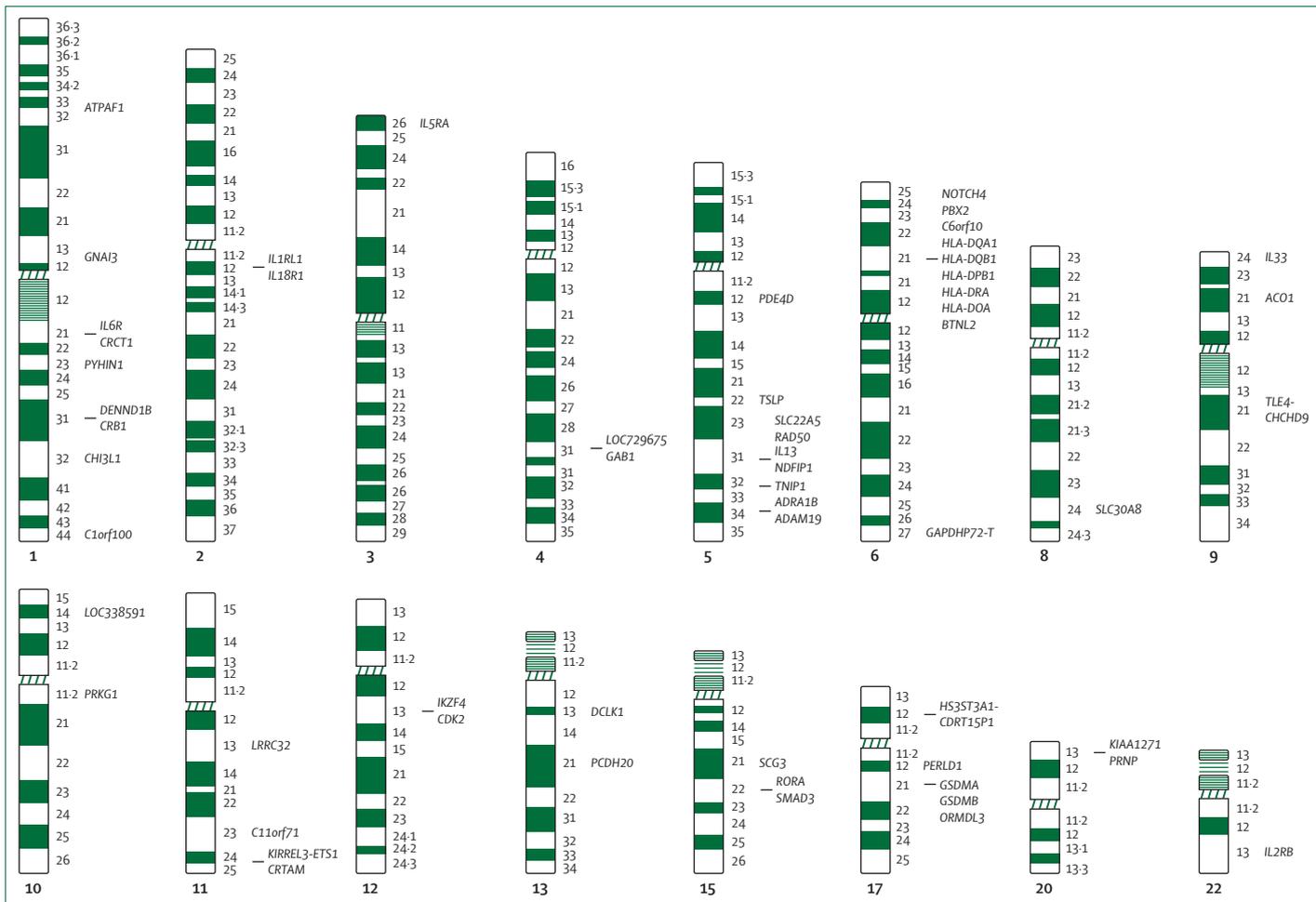
## Environment: bacteria, viruses, and fungi

There has been a striking change in the emphasis of environmental studies of asthma in the past decade; the proportion of studies investigating protective factors has increased markedly compared with the number of



**Figure 1: Changes in lung function during the course of mild and moderate asthma**

In mild disease, change in lung function is not substantially different from that in people without asthma. In more severe asthma, deficits have already been detected at birth, but most of the postnatal loss in lung function seems to occur during the preschool years.



**Figure 2: Asthma genes identified through genome-wide association studies (GWAS)**  
 The National Human Genome Research Institute catalogue of published GWAS was searched using asthma as disease, and childhood asthma as trait.<sup>37</sup>

studies assessing factors that increase risk of the disease. The most influential studies were those in which children in advanced societies who were raised on farms were compared with those raised in the same rural communities but away from farms, or those raised in cities.<sup>43,44</sup> These surveys consistently found that the protective effects of living on a farm are stronger if they occur in utero and during early life, that protection against asthma might be associated with microbial diversity, a hallmark of the farm environment, and that protective factors for asthma are different from those for allergic sensitisation. A parallel finding is that exposure to day care in early life is associated with decreased risk of asthma during school years.<sup>45</sup> Also, the microbial communities of house dust differ significantly depending on whether the household includes children exposed versus unexposed to day care.<sup>46</sup>

The specific environmental factors that account for these effects have not been identified, but the most accepted hypothesis is that exposure to a range of mainly

innocuous micro-organisms, largely bacteria, triggers protective responses in the developing immune system. Strong support for this hypothesis has come from studies with animals, which have shown that mice raised under germ-free conditions were more likely to develop experimental allergic asthma than animals exposed to normal microbial flora.<sup>47</sup> After germ-free young mice were exposed to standard mouse-colony bacteria and intestinal microbiota were re-established, predisposition for asthma was reversed; this effect was not achieved in adult, germ-free mice. Similarly, oral exposure to bacterial extracts protects animals against the development of experimental models of asthma.<sup>48,49</sup> These studies suggest that exposure to environmental micro-organisms might affect asthma risk by modifying the type of bacteria that colonise the gut, and these changes could have profound effect on the risk for asthma and other diseases.<sup>50</sup> These effects are probably activated through innate immune receptors such as TLR2,<sup>51</sup> and might affect the development of responses mediated by several cell types, including basophils and

natural killer cells,<sup>47</sup> dendritic cells,<sup>49</sup> and T-regulatory (Treg) cells.<sup>48</sup>

Susceptibility to asthma also seems to be associated with microbial colonisation of the airways. One study reported increased detection of pathogenic bacteria in the upper airway of infants who later developed asthma symptoms in preschool years, compared with those who did not.<sup>52</sup> Metagenomic studies of samples obtained from the lower airways through bronchoscopy showed that, by contrast with long-held belief, microbial flora do colonise the bronchi in healthy individuals. However, the composition of the flora found to be colonising the upper airway was similar to that present in the lower airway,<sup>53</sup> thus, contamination via instruments used for the procedure cannot be excluded. Two studies in adult patients with asthma recruited from tertiary care centres showed predominance of Proteobacteria in the lower airways, a feature not seen in non-asthmatics.<sup>54,55</sup> Similar predominance of Proteobacteria was found in adult patients with mild asthma, most of whom were not taking inhaled corticosteroids.<sup>56</sup> It remains to be determined whether the microbes preferentially detected in people with asthma are directly involved in its pathogenesis, or are otherwise markers of an underlying, pre-existing change in the immune system in these patients.

Viruses, especially rhinovirus, are often isolated from the upper airways of patients with asthma during clinical exacerbations.<sup>57,58</sup> **Studies in which rhinovirus was experimentally inoculated into the airways convincingly showed that, compared with non-asthmatics, patients with asthma have increased susceptibility to developing chest symptoms when infected.**<sup>59</sup> Birth cohorts have shown that infants and young children who wheeze during episodes in which rhinoviruses were detected have a substantially higher risk than those who did not have rhinovirus-induced wheezing episodes as infants of having asthma during the school years.<sup>60,61</sup> It is unknown whether this increased susceptibility to rhinovirus infection is a cause or consequence of asthma.<sup>62</sup> In children with a strong family history of allergies, atopic sensitisation is more likely to occur before than after rhinovirus-induced wheezing,<sup>63</sup> suggesting that susceptibility to the latter might be induced by allergy-related mechanisms. Whether children without a family history of allergies experience atopic sensitisation leading to rhinovirus susceptibility is unknown. Newborns and young infants at risk for subsequent development of asthma have been consistently found to have diminished interferon- $\gamma$  responses to non-specific stimuli,<sup>64,65</sup> and to have other changes in immune markers<sup>65</sup> in peripheral blood cells. These changes could be a common antecedent for allergic sensitisation and susceptibility to viral infection. In-vitro and ex-vivo studies in patients with asthma have shown deficits in interferon type I and III responses by airway epithelial cells and macrophages,<sup>66,67</sup> especially in patients with chronic airflow obstruction.<sup>68</sup> Whether these deficits, and subsequent increased susceptibility to acute airway

obstruction, are the result of allergic sensitisation or develop independently is still to be determined.

**Results of recent longitudinal studies have suggested that exposure to indoor mould, specifically *Aspergillus ochraceus*, *Aspergillus unguis*, and *Penicillium variable*, during the first year of life is positively associated with asthma incidence by age 7 years.**<sup>69</sup> Only a small proportion of participating children were allergic to moulds; thus, it is possible that mould induce asthma by non-allergic mechanisms. Activation of protease-activated receptors<sup>70</sup> and induction of eosinophilic inflammation by fungal chitin<sup>71</sup> have been proposed as potential mechanisms.

### Pathogenesis

Over the past decade, understanding of asthma pathogenesis has undergone a significant shift. The 2002 *Lancet* Seminar<sup>1</sup> on asthma presented the classic view that asthma is a T-helper-type-2 (Th2)-cell-dependent, IgE-mediated allergic disease. This view was largely based on the observation that asthmatic patients are more likely to be sensitised to local aeroallergens.<sup>72</sup> Moreover, the pathology of asthma (especially the most severe cases) is characterised by mucus-cell hyperplasia and infiltration of inflammatory cells, among which CD4+ T cells, eosinophils and mast cells predominate.<sup>73</sup> Infiltrating T cells express the signature Th2 cytokines interleukin 13, interleukin 4, and interleukin 5,<sup>74–76</sup> which coordinately regulate many aspects of allergic inflammation.<sup>77</sup> More recently, this T-cell-centric paradigm has been enriched by the identification of Treg cells with the capacity to control Th2 responses.<sup>78–80</sup> A protective role of Treg cells in asthma is supported by the epidemiological and immunological studies in the farming families described above.<sup>81,82</sup> In these populations, farm exposure is associated with increased number and function of cord blood Treg cells and lower Th2 cytokine secretion.<sup>83</sup>

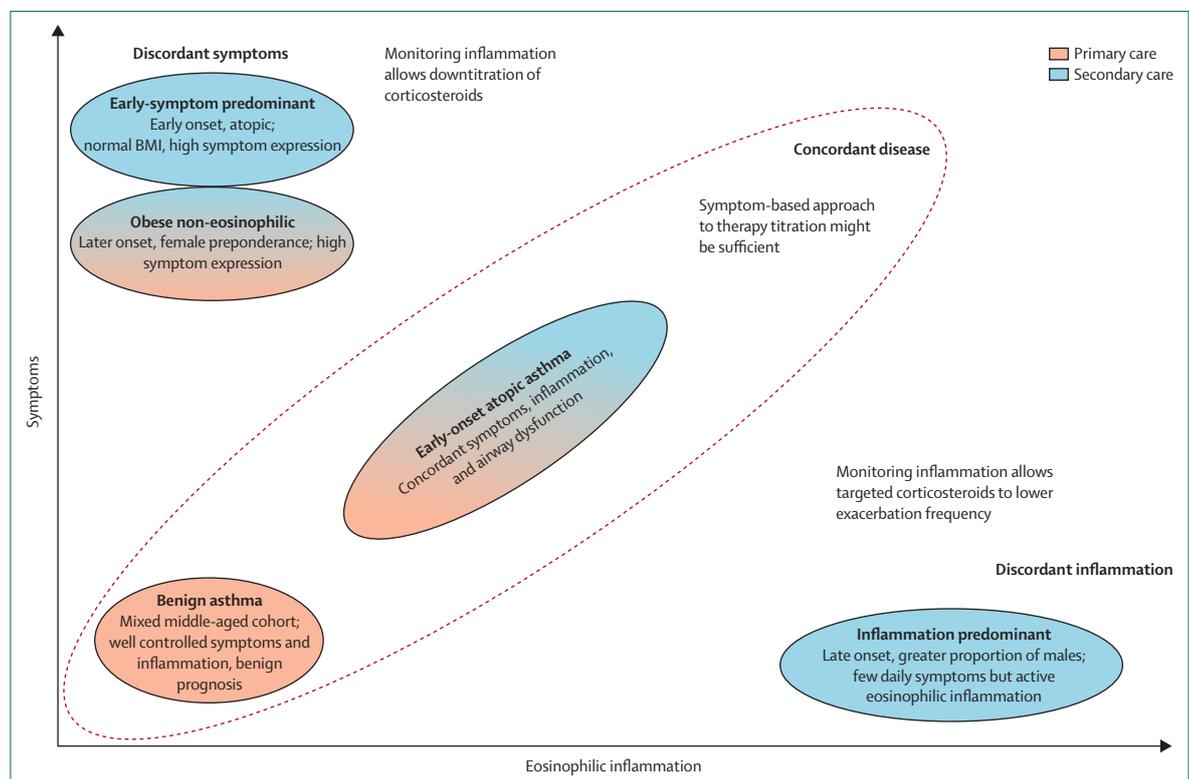
In mouse models, Th2 inflammation also promotes long-term airway remodelling with fibrosis and an increase in smooth muscle.<sup>77</sup> Similarly, structural changes in the airways of asthmatic individuals contribute to the development and progression of disease; in severe cases, airway obstruction from mucus-cell hyperplasia is common, the subepithelial basement membrane is thickened, smooth-muscle mass is increased through hypertrophy and hyperplasia, the airways undergo fibrosis with increased deposition of connective tissue, and fibroblast and myofibroblast proliferation occurs.<sup>84,85</sup> It is unclear whether inflammation precedes or coexists with airway remodelling, but remodelling can occur early in the disease, in some cases in the absence of inflammation. Research has highlighted intriguing relationships between mechanical stress and airway remodelling in asthma.<sup>86</sup> Activation of airway smooth muscle during bronchoconstriction abruptly changes airway size and mechanical stress within the airway wall. Airway epithelial cells, smooth-muscle cells, and fibroblasts respond to their mechanical environment.

The epithelium in particular transduces mechanical stresses, and in both fetal and mature airways, epithelial cells interact with mesenchymal cells to coordinate remodelling of tissue architecture in response to the mechanical environment.<sup>86–88</sup> The ability of mechanical stress by itself to regulate airway structural changes might contribute to the dissociation between airway remodelling and inflammation, and might also explain why patterns of fluctuations in airway function seem to predict asthma exacerbations<sup>89,90</sup> and loss of asthma control after withdrawal of inhaled corticosteroids.<sup>91</sup>

Despite the complexity of asthma pathogenesis, confidence in the fundamental role of Th2 cells in asthma pathobiology has led pharmaceutical and biotechnology companies to develop new asthma treatments that target Th2 cytokines or their receptors. These therapies have consistently blocked Th2 inflammation and associated structural changes in the airways of antigen-challenged animal models; however, few have been successful when moved to the clinic.<sup>85</sup> Recent findings might help explain these results. Phenotypic heterogeneity—probably a reflection of the diverse genetic and environmental factors that underpin asthma pathogenesis—is an evolving concept that has clinical implications.<sup>92</sup> Early clinically-based definitions of asthma focused on two main phenotypes; extrinsic asthma is defined as typically developing in childhood and accompanied by IgE-mediated allergic

disease, whereas intrinsic asthma typically develops later in life and is not associated with allergic sensitisation. Concerns over the ability of these biased definitions to capture the diversity of asthma characteristics, and the continued lack of biomarkers for asthma phenotypes, prompted efforts to develop alternative, unbiased strategies that sought to define asthma phenotypes based on statistical methods, such as cluster analysis<sup>93,94</sup> and latent class analysis.<sup>95</sup> Figure 3 shows results obtained using cluster analysis, a method that combines variables so that objects in the same group, or cluster, are more similar to each other than to those in other clusters. In a study of clinical phenotypes of adult asthma,<sup>93</sup> clusters of patients were defined according to their relative expression of symptoms and eosinophilic inflammation. Patients with greater discordance between symptoms and inflammation were more difficult to treat and required treatment in specialised asthma centres. Although the reasons for this discordance were unclear, measures of airway inflammation in these subgroups were clinically informative; management aimed at reducing eosinophilic inflammation was better than usual treatment in both discordant groups.

The results of unbiased studies of asthma phenotype are more similar than they are different, even though the statistical methods and variables analysed are not the same. Moreover, results overlap with those obtained using earlier, biased phenotype approaches. All studies of asthma



**Figure 3:** Clinical phenotypes of adult asthma, identified by cluster analysis<sup>93</sup>

Clusters of patients are plotted according to their relative level of symptoms and eosinophilic inflammation. The plot highlights that patients with greater discordance between symptoms and inflammation are more difficult to treat and should usually be followed up in specialised asthma centres.

phenotype found age at disease onset to be a crucial differentiating factor. Early-onset disease is consistently associated with a more allergic condition over a range of severities, whereas later-onset disease is associated with eosinophilic inflammation and obesity, is more common in women, and is generally less allergic. Despite the association of early-onset disease with atopy and allergy, none of the unbiased approaches found variables associated with these conditions (such as atopy and total IgE) to be key distinguishing features of subgroups.<sup>92</sup>

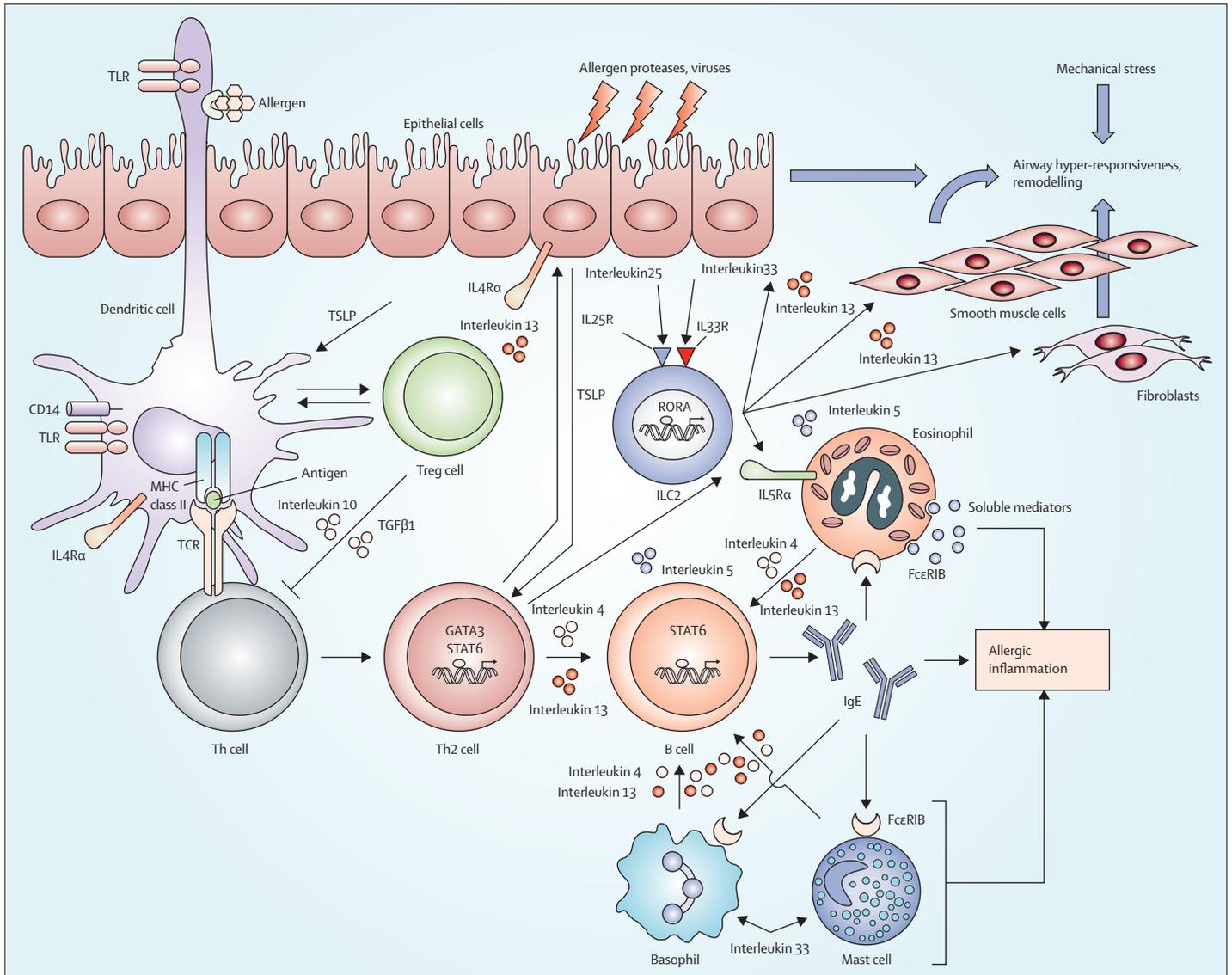
An important step towards integrating asthma phenotypes and pathogenesis was made by a 2009 analysis of molecular phenotyping in adult patients with mild, corticosteroid-naïve asthma.<sup>96</sup> Expression profiling of bronchial biopsies identified a Th2-high asthma phenotype that is detectable in around 50% of adults with asthma, and is marked by overexpression of interleukin-13-dependent genes (ie, *POSTN*, *CLCA1*, and *SERPINB2*). Patients classified as Th2-high were subsequently found to have higher amounts of tissue interleukin 13 and interleukin-5 mRNA, greater numbers of eosinophils and mast cells, and showed more atopy and thickening of the subepithelial basement membrane. These patients responded to inhaled corticosteroids, whereas the Th2-low group did not.<sup>97</sup> Moreover, asthmatics with high serum concentrations of the interleukin-13-induced biomarker periostin were more likely than those with low concentrations of periostin to show improved lung function in response to anti-interleukin-13 treatment.<sup>98,99</sup> Although long-term studies are needed to assess the stability of these phenotypes, understand them in more detail, and further integrate them with relevant pathobiology and appropriate biomarkers, these results suggest that combining clinical and molecular approaches might move us closer to the identification of true asthma endotypes—ie, disease subtypes that are defined by distinct pathophysiological mechanisms and can be treated accordingly.<sup>100</sup> The table presents an integrated view of major clinical and molecular asthma phenotypes with relevant pathobiology and biomarkers.

A truly modern view of asthma pathogenesis should also incorporate the notion that a Th2 cytokine signature might not simply reflect an adaptive Th2 cellular response; thus, there might be more to asthma than Th2-cell-dependent, IgE-mediated allergic inflammation. Indeed, asthma is increasingly seen as a disease that has a strong innate immune component and begins at the airway epithelium. Far from being just a structural barrier, the airway epithelium responds to environmental insults such as protease-containing allergens, pathogens, cigarette smoke, and pollution by secreting inflammatory mediators and antimicrobial peptides.<sup>101</sup> Moreover, a damaged epithelium releases interleukin 25, interleukin 33, and the cytokine protein TSLP, which activate natural-killer T cells, mast cells, eosinophils, and basophils, and stimulate newly discovered lineage-negative cells (ILC2, also known as natural type-2 helper cells

or nuocytes).<sup>102–105</sup> ILC2 cells require the transcription factor ROR $\alpha$  for their development,<sup>106</sup> reside in the mucosa, and respond to epithelial distress signals by rapidly releasing large amounts of Th2 cytokines (mainly interleukin 13 and interleukin 5).<sup>107,108</sup> ILC2 are also activated by interleukin 33 released by alveolar macrophages during influenza virus infection,<sup>109</sup> providing a common pathway for allergen-induced and virus-induced Th2-type responses. ILC2 have been shown to be necessary for allergic lung inflammation in mice,<sup>110,111</sup> although their role in human asthma remains to be determined. These cells have been found in human fetal and adult lung tissue, and in human peripheral blood.<sup>112</sup>

The identification of innate lymphoid cells that secrete Th2 cytokines in response to airway epithelial damage might fill a crucial gap in our understanding of asthma pathogenesis, by providing a long-sought link between Th2 inflammation and lung-based mechanisms of disease initiation. The ability of these cells to produce interleukin 13 and interleukin 5 is consistent with the classic cytokine signature of asthma, but emphasises the role of innate mechanisms in promoting adaptive Th2 responses. An altered epithelial barrier could allow the entry of otherwise innocuous antigens that, in the pro-Th2 milieu created by epithelium-activated innate type-2 cytokines, could promote Th2 differentiation eventually leading to IgE production. Continued stimulation of epithelial cells, smooth muscle cells, and fibroblasts by Th2-cell-derived and ILC2-derived interleukin 13 would lead to airway hyper-responsiveness and remodelling (figure 4). This updated view of asthma pathogenesis still emphasises the role of Th2 cytokines, but focuses on both their innate and adaptive cellular sources. Genetic evidence from GWAS has independently pointed to the importance of the

	Natural history	Clinical and physiological features	Pathobiology and biomarkers	Response to therapy
<b>Th2-high phenotype</b>				
Early-onset allergic	Early onset, mild to severe	Allergic symptoms and other diseases	Thick subepithelial basement membrane, specific IgE, Th2 cytokines	Corticosteroid-responsive, Th2-targeted
Late-onset eosinophilic	Adult onset, often severe	Sinusitis, less allergic	Corticosteroid-refractory, eosinophilia, interleukin 5	Responsive to antibody to interleukin 5 and cysteinyl leukotriene modifiers, corticosteroid-refractory
<b>Th2-low phenotype</b>				
Obesity-related	Adolescent and adult onset	Women mainly affected, very symptomatic, airway hyper-responsiveness less clear	Lack of Th2 biomarkers, oxidative stress	Responsive to weight loss, antioxidants, and possibly to hormonal therapy
Neutrophilic	Adult onset	Low FEV1, more air trapping	Sputum neutrophilia, Th17 pathways, interleukin 8	Possibly responsive to macrolide antibiotics
Th2=T-helper-type-2 cytokine. FEV1=forced expiratory volume in 1 s.				
<b>Table: An integrated view of clinical and molecular asthma phenotypes<sup>92</sup></b>				



**Figure 4: Major immune pathways involved in asthma pathogenesis**

Innate and adaptive components of allergic inflammation are shown, including the recently discovered ILC2 cells that release Th2 cytokines in response to epithelial damage. The links between immune responses and structural changes in the lung are also depicted. TLR=toll-like receptor. TSLP=thymic stromal lymphopoietin. TGFβ1=transforming growth-factor β1. TCR=T-cell receptor. Treg=regulatory T cell. Th=T-helper cell. Th2=T-helper-type-2 cell.

epithelium–ILC2 axis in asthma pathogenesis by identifying *IL33*, the IL33 receptor *IL1RL1* (*ST2*), *TSLP*, *RORA*, and *IL13* as major asthma susceptibility genes.<sup>33,113</sup>

Cytokine profiles resembling a typical T-cell-derived, adaptive response but sustained by innate lymphoid cells are not limited to the Th2 type. A parallel system of cells lacks antigen receptors yet produces an array of effector cytokines (interferon  $\gamma$ , interleukin 17, and interleukin 22) that match the variety of cytokines secreted by subsets of T-helper cells. These cells function in lymphoid organogenesis, tissue remodelling, and antimicrobial immunity and inflammation, particularly at barrier surfaces. Their ability to promptly respond to insults inflicted by stress-

causing microbes suggests these cells are crucial for first-line immunological defenses.<sup>114</sup> Changes in these innate mechanisms might also be involved in asthma pathogenesis, by contributing to lower airway vulnerability to otherwise innocuous respiratory tract viral infections, particularly those caused by rhinoviruses.

### Prevention

There is currently no established strategy for primary prevention of asthma or for preventing the development of airflow limitation in patients with asthma. Avoiding exposure to house dust mite during pregnancy and early infancy had no effect on asthma outcomes by age 8 years

in Australia or the Netherlands.<sup>115,116</sup> Two trials in which high-risk infants (defined by parental history of allergic disease) were randomly assigned to extensive environmental and dietary interventions or to usual care showed reductions in prevalence of asthma, as assessed by questionnaire, by age 18 years and age 7 years;<sup>117,118</sup> however, the generalisability of these results is limited by small numbers, highly selected populations, unfeasibility to mask the interventions, and losses to follow-up. The consistent protection against development of asthma seen with exposure to high microbial burden in early life has suggested the possibility that innocuous surrogates of such exposure could be used to prevent asthma,<sup>119</sup> but no data is yet available to support this hypothesis.

Results of several trials have disproved the contention that chronic use of inhaled corticosteroids could block the natural course of asthma and the development of airflow limitation. 4 years of twice daily treatment with inhaled corticosteroids in school-age children with asthma had no effect on lung function or clinical outcomes 4 years after discontinuation of therapy.<sup>13</sup> In preschool children with wheezing, administration of inhaled corticosteroids for several years and with different methods had no effect on long-term, asthma-related outcomes.<sup>120–122</sup>

### Treatment

The two most important aspects of asthma therapy are environmental control and pharmacological therapy. For severe asthma, treatment of comorbidities is also crucial. Most asthma trials have been done in developed countries. In less-developed countries, treatment of asthma faces many challenges, including underdiagnosis, access to care, ability of health-care workers to manage asthma, and availability and affordability of inhaled therapy.<sup>123</sup> These obstacles might substantially increase asthma-associated morbidity and mortality in developing countries,<sup>124</sup> but studies specifically addressing this issue are lacking.

Although there is consensus that environmental exposures are important causative agents in asthma, the role of environmental control and allergen avoidance in the treatment of asthma remains controversial. Even in cases of occupational asthma, where the offending agent can often be directly identified, only a third of patients show symptomatic recovery after cessation of exposure.<sup>25</sup> A comprehensive environmental intervention to reduce exposure to indoor allergens among children with asthma who live in inner cities, including reducing exposure to cockroach and dust mite allergens, resulted in reduced asthma-associated morbidity.<sup>125</sup> Data from adult studies are less convincing, with most studies showing that use of allergen-avoidance measures as a single intervention is clinically ineffective in asthma management.<sup>126</sup>

### Therapeutic approaches to mild and moderate asthma

Inhaled corticosteroids, with or without long-acting beta agonists (LABA), continue to be the mainstay of

pharmacological treatment for mild to moderate asthma. When taken regularly, inhaled corticosteroids effectively control everyday asthma symptoms, improve lung function, and decrease the risk for exacerbations.<sup>127</sup> Controlled trials have consistently shown that inhaled corticosteroids are better than leukotriene receptor antagonists, such as montelukast, at controlling symptoms, improving lung function, and reducing exacerbations,<sup>128,129</sup> yet results of a pragmatic trial, in which the study settings attempted to mirror those of usual medical practice, suggested that montelukast seems to be as effective as inhaled corticosteroids.<sup>130</sup> In this real-life setting, adherence to once daily oral therapy was better than adherence to twice daily inhaled therapy,<sup>130</sup> suggesting that adherence to inhaled therapy is a key obstacle to achieving success with asthma treatment. In community-based studies, adherence to such therapy can be as low as 20%. In well controlled trials, adherence is very high initially but wanes thereafter; several months into trials, participants do not take more than 50% of their prescribed doses.<sup>131</sup> Evidence suggests that taking at least 75% of inhaled corticosteroid doses is necessary to attain the expected decrease in exacerbations.<sup>132</sup> Although behavioural and other interventions have been proposed to increase medication adherence, results are not encouraging.<sup>133</sup>

Three approaches to improve or circumvent daily administration of asthma medicines have been proposed. Supervised therapy for children, in which use of inhaled corticosteroids was overseen by study staff members each school day for 15 months, showed some improvement in asthma outcomes,<sup>134</sup> but the cost of such an approach would probably only make it worthwhile for severe cases. In patients with milder asthma, replacing a daily dose of inhaled corticosteroids with inhaled corticosteroids taken together with albuterol (salbutamol) whenever the latter is needed showed improved rates of asthma exacerbations compared with placebo, and similar exacerbation rates to those seen with daily inhaled corticosteroids.<sup>127,135</sup> By contrast, a strategy based on doubling the daily dose of inhaled corticosteroids when asthma control deteriorates has proven ineffective,<sup>136</sup> although quadrupling the dose showed some evidence of decreased exacerbation risk.<sup>137</sup> Although the role of these as-needed approaches in asthma therapy remains controversial,<sup>138,139</sup> it is well established that patients often have different asthma control goals and different views of the importance of medication side-effects than those of practitioners and in guidelines.<sup>140</sup> Considering the patient's perspective when developing treatment plans could help solve the conundrum of inhaled corticosteroids therapy—ie, that high efficacy in clinical trials is not matched by a similar improvement in community-based asthma outcomes.

Several clinical trials have shown that patients who are still symptomatic after treatment with inhaled corticosteroids benefit from the addition of a LABA, and a larger

proportion of such patients respond better to adding LABAs than to doubling the dose of inhaled corticosteroids or adding a leukotriene receptor antagonist.<sup>129</sup> In a small proportion of patients, reduced responsiveness to inhaled corticosteroids might be explained by corticosteroid resistance.<sup>141</sup> For patients in whom exacerbations are a main source of morbidity, as-needed use of inhaled corticosteroids plus formoterol, a fast-onset LABA, has proven effective in preventing exacerbations.<sup>142</sup> However, daily use of inhaled corticosteroids plus LABA is not better than inhaled corticosteroids alone in controlling exacerbations in inhaled-corticosteroid-naïve patients.<sup>143</sup> Nevertheless, in more than 60% of asthma patients in the USA<sup>144</sup> and in other countries,<sup>145</sup> the inhaled corticosteroid formulation most widely used to treat asthma consists of an inhaled corticosteroid plus LABA, with inhaled corticosteroids alone being used by a smaller proportion of patients. A possible explanation for the excessive use of inhaled corticosteroids plus LABA combinations is insufficient asthma control due to lack of adherence to inhaled corticosteroids, which could lead patients and practitioners to believe that taking inhaled corticosteroids alone leads to an insufficient response, warranting the addition of another medicine. This use of combination treatments over inhaled corticosteroids alone markedly increases drug costs,<sup>9</sup> and could unnecessarily expose patients to rare but potentially deleterious side-effects of LABAs. Increased risk for severe asthma attacks and death has been reported in patients taking LABAs alone, and it is uncertain whether inhaled corticosteroids completely prevent such unwanted outcomes.<sup>146,147</sup>

These safety concerns have prompted the search for alternative add-on therapies in patients whose asthma is not well controlled with inhaled corticosteroids alone. In a 14-week crossover study, tiotropium, a long-acting anticholinergic agent approved for use in COPD when added to inhaled corticosteroids, showed similar clinical improvements to those obtained when salmeterol, a LABA, was added to inhaled corticosteroids, and greater improvements than those achieved with higher doses of inhaled corticosteroids.<sup>148</sup> Larger and longer studies are needed to determine if this drug could be an effective alternative to LABAs.

#### **Therapeutic approaches to severe asthma: targeted drugs on the horizon**

Treatment for patients with severe asthma, who remain uncontrolled and have frequent exacerbations even with high-dose inhaled corticosteroids plus LABA or with oral corticosteroids, remains a significant challenge. These patients account for a high proportion of the direct financial costs of asthma, and this societal burden, added to the debilitating morbidity of severe asthma, justifies continued efforts to find new treatments. A major shift in potential treatment approaches to severe asthma has come from advances in our understanding of disease pathogenesis. There is now clear evidence that severe

asthma is heterogeneous, and unbiased hierarchical clustering methods have described several subphenotypes in adults and children.<sup>149</sup> One hypothesis is that different asthma subphenotypes have unique pathogenic mechanisms, and identifying such mechanisms could allow for more targeted and specific therapy.

Many patients with severe asthma, especially children, are highly atopic. Omalizumab, a humanised monoclonal antibody against IgE, decreased asthma exacerbations by 30% in a large, inner city study of patients of all severities,<sup>150</sup> with effects being particularly strong in patients sensitised and exposed to cockroaches. In adults with severe asthma, omalizumab also decreased exacerbations, but had less impressive effects on everyday symptoms.<sup>151</sup> High costs and unfeasibly large doses in patients with very high serum IgE concentrations limit the use of this drug.

The finding that several asthma subphenotypes had evidence of sputum eosinophilia<sup>94</sup> and were prone to exacerbations suggested the possibility that humanised monoclonal antibodies against interleukin 5, the most potent eosinophil stimulant and chemoattractor, could have a role in preventing such exacerbations. A recent study supported this hypothesis; patients 12 years or older with severe asthma and direct or indirect evidence of eosinophilic inflammation showed a substantial decrease in exacerbation rates with different doses of mepolizumab, an anti-interleukin 5 antibody, compared with placebo.<sup>152</sup> The effects were specific for exacerbations, the primary outcome, and there was no significant improvement in measures of global asthma control or lung function.

The central role of interleukin 4 and interleukin 13 in the pathogenesis of some cases of asthma has also prompted studies using humanised monoclonal antibodies against these cytokines and against the common component of their receptors, the interleukin 4R $\alpha$  chain. Although these studies have shown less impressive results than those with anti-interleukin 5 antibody, specific subgroups of patients did show benefits. For example, compared with patients with low concentrations, patients with high concentrations of serum periostin, a marker of interleukin 13 activation,<sup>153</sup> showed larger improvement in lung function when treated with lebrikizumab, a humanised monoclonal antibody to interleukin 13.<sup>99</sup> Similarly, those with more severe disease showed some clinical improvement after administration of AMG317, a monoclonal antibody against interleukin 4R $\alpha$ .<sup>154</sup>

Therapies targeting other possible inflammatory mediators have been developed, but none have shown clear evidence of clinical benefit. Anti-tumour-necrosis-factor  $\alpha$  drugs are highly effective in other inflammatory conditions but showed few clinical benefits and substantial unwanted effects in patients with severe asthma.<sup>155</sup> Pharmacological advances have occurred in the development of phosphodiesterase-4 (PDE4) inhibitors, which are effective against neutrophilic inflammation<sup>156</sup> and could be effective in treatment of severe

asthma. Roflumilast is an oral PDE4 inhibitor that has been shown to decrease allergen-induced inflammation<sup>157</sup> and is currently approved for use in severe COPD. However, PDE4 inhibitors cause frequent nausea, vomiting, and diarrhoea, which limit their clinical usefulness. In summary, the development of therapies specifically targeted to inflammatory pathways and mediators, identified by use of biomarkers, is the most promising approach to treatment of severe forms of asthma that are refractory to available treatment.

### Severe asthma: thermoplasty

In patients with severe, refractory asthma, reduction of hypertrophied bronchial muscle might induce symptom relief and improvement in lung function. Bronchial thermoplasty, an outpatient procedure in which controlled thermal energy is applied in consecutive sessions through a bronchoscope, has been used with this goal in mind. A study that compared thermoplasty versus a control group without sham procedure showed benefits in exacerbation rates and symptoms; however, hospitalisation for adverse respiratory events was more frequent shortly after thermoplasty procedures than in the control group.<sup>158</sup> A larger clinical trial, in which bronchial thermoplasty was compared with a sham procedure, showed modest improvements in asthma symptoms and exacerbations after treatment.<sup>159</sup> Bronchial thermoplasty was approved for use in severe asthma by the US FDA in 2010, but it remains unclear whether its benefits outweigh its potential risks.<sup>160</sup>

### Conclusions

There have been major advances in the past decade in our understanding of the genetics, natural history, and pathogenesis of the diverse clinical syndromes identified as asthma. There is renewed hope that novel prevention strategies, and therapies targeted specifically against the mechanisms responsible for disease processes, will decrease the worldwide burden in health-care costs and morbidity caused by this still mysterious disease.

#### Contributors

The authors contributed equally to the literature search, writing and editing of the manuscript, and the generation of figures and table.

#### Conflicts of interest

FDM has received honoraria from Abbott Laboratories for invited lectures. DV has participated in peer discussion groups supported by Merck.

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