Severe asthma: novel advances in the pathogenesis and therapy

Ruth Hartley, Rachid Berair, Christopher E. Brightling
Institute for Lung Health, Department of Infection, Immunity & Inflammation, University of Leicester, Leicester, United Kingdom

KEY WORDS
advances, asthma, pathogenesis, therapy

ABSTRACT
Asthma affects an estimated 300 million people worldwide and is severe in approximately 10% of sufferers. Asthma, especially severe asthma, is a heterogeneous disease that results from complex host–environment interactions. This review article outlines recent advances in both the understanding of pathogenesis and novel therapies. The pathogenesis of severe asthma can be broadly thought of in four domains: Th2 inflammation, non-Th2 inflammation, airway remodeling, and airway smooth muscle dysfunction. They can develop independently or partly as a consequence of each other. Interactions between these domains, their causation, and consequent impact upon disordered airway physiology and clinical expression are poorly understood. Recent advances in specific Th2- and non-Th2-targeted therapy, bronchial thermoplasty targeting airway remodeling and advances in therapies for airway smooth muscle dysfunction present new opportunities for treatment and inform our understanding of asthma pathogenesis. As our understanding of the pathogenesis increases, the need for individualized investigation, treatment, and management of asthma becomes more apparent.

Introduction
Asthma is characterized by symptoms of breathlessness, wheeze, and cough together with episodes of marked worsening of symptoms known as exacerbations. Symptoms occur on the background of disordered airway physiology characterized by variable airflow limitation, airway hyper-responsiveness, and, in more severe disease, persistent airflow obstruction. Asthma affects an estimated 300 million people worldwide and is severe in approximately 10% of sufferers.1 Severe asthma requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller or systemic corticosteroids or both to prevent it from becoming “uncontrolled” or remain “uncontrolled” despite therapy. Uncontrolled disease is determined by 1 or more of the following: poor symptom control, frequent severe exacerbations requiring high-dose corticosteroid therapy or resulting in hospital admissions, and/or persistent airflow limitation. Morbidity and mortality are the highest in severe asthma consuming over 50% of the health care costs attributed to asthma.2

Prior to confirming a diagnosis of severe asthma, it is critical to confirm adherence to therapy and optimize treatment of comorbidities. Whether treatment of comorbidities modulates asthma severity directly or indirectly, through improving asthma control, remains controversial. Intriguingly, recent evidence has suggested that in obese asthmatics with severe disease, there is increased eosinophilic infiltration of the airway wall, perhaps suggesting, in this example, a direct effect upon the underlying pathogenesis.2

Less controversial is the increasing recognition that asthma, particularly severe asthma, is a complex heterogeneous condition encompassing several underlying pathologies that develop as a consequence of a variety of gene–environment interactions that give rise to a clinical phenotype. This review will first consider our current understanding of the pathogenesis of severe asthma across the temporal and spatial scales of the disease from genes to cells, cells to tissue, and tissue to organ. Second, we shall describe how current therapies affect different aspects or domains of the disease. Finally, we shall describe how current and future treatments are changing to go beyond target specificity to also become phenotype- and outcome-specific as we move towards stratified medicine.
Pathogenesis of severe asthma  

Genes to cells: functional 'omics'. A number of genes have been implicated in modulating the response of epithelial repair in response to damage in genome-wide association studies. Single nucleotide polymorphisms (SNPs) have been associated with airflow obstruction and lung function impairment, and SNPs in the interleukin (IL)-4 receptor are associated with persistent airway inflammation and severe asthma exacerbations.

Cell to tissue: airway inflammation and remodeling

Persistent airway inflammation despite full treatment is one of the hallmarks of severe asthma. However, critically, there is no clear pathological definition of severe asthma. In allergic asthma, airway inflammation is orchestrated by dendritic cell–T2 cell interactions mediated by epithelial derived-thymic stromal lymphopoietin leading to mast cell activation and eosinophil recruitment. Evidence is emerging, particularly in severe asthma, that T1i1/T1 and T1i17 pathways with activation of neutrophils may play a role. Importantly, although these inflammatory profiles may coexist to varying degrees within an individual, they do not necessarily occur independently. Cellular interactions considered to play important roles in airway inflammation and remodeling are summarized in Figure 1. It is unclear whether these inflammatory profiles are a consequence of environmental exposure to pollutants, smoking, and infection, or primary abnormalities. Indeed, persistent bacterial colonization, which is traditionally associated with chronic obstructive pulmonary disease (COPD), is also evident in some subjects with asthma. Fungal colonization and sensitization is also observed in severe disease.

A consequence of inflammation is epithelial damage and ciliary dysfunction. Impaired ciliary function, goblet cell hyperplasia, and mucus gland enlargement all lead to increased mucus production, which is likely to perpetuate exacerbations and lead to further epithelial damage. Activated epithelium releases various growth factors including transforming growth factor-β (TGF-β) and pro-angiogenic factors such as vascular endothelial growth factor (VEGF). In concert with proinflammatory cells, TGF-β activates subepithelial mesenchymal cells to release matrix and proliferate. Fibrocytes, which are blood-borne mesenchymal progenitors, are recruited to the airway in response to the "chronic wound", and differentiation of these cells together with local proliferation of resident mesenchymal stem cells promotes an increase in airway smooth muscle (ASM) mass. ASM mass is the strongest predictor of airflow obstruction. Once activated, ASM in asthma recruits mast cells by releasing chemoattractive factors. Mast cells interact with the ASM to promote airway hyper-responsiveness, whilst mast cells and neutrophils localize to glands and are associated with increased mucus plugging.

In addition to the pathogenesis of persistent disease, recurrent exacerbations are an important component of severe disease and are often associated with pathogens, suggesting abnormalities in innate/adaptive immunity. In asthma, the secretion of interferon-β and interferon-λ from the airway epithelium is impaired in response to rhinovirus. This leads to decreased viral clearance and is associated with worsening symptoms at exacerbation.

Tissue to organ: image functional modeling

Both large and small airway disease leads to airflow obstruction and airway hyper-responsiveness in asthma. Large airways account for the majority of airflow resistance behaving effectively like resistors in series. The small airways provide parallel resistance pathways and contribute to less than 10% of total airway resistance. Consequently, there may be no detectable changes in spirometry until advanced small airway disease is present. In severe asthma, quantitative computed tomography (CT)
has shown that there is proximal airway narrowing without changes in wall volume,\textsuperscript{18} small airway disease with gas trapping, and minimal emphysema. These changes in airway geometry assessed by CT have been related to structural changes observed in endobronchial biopsies.\textsuperscript{19}

**Temporal scales of severe asthma** Interactions across the spatial scales occur over different timescales. Airway inflammation is diverse but results in a common pathway of airway wall remodeling, alterations in geometry and biomechanical properties, airway obstruction with mucus plugging, and small airway closure. Together these processes result in airway obliteration, impaired airflow and gas exchange, and increased susceptibility to exacerbations. Traditionally, these events are considered to occur sequentially over years, but this is inconsistent with some observations related to severe asthma. For example, whether severe asthma represents a distinct disease entity or part of the asthma spectrum remains controversial. The basis of this controversy is largely our lack of understanding of whether severe asthma develops over time in sufferers with initially mild disease or whether severe disease presents de novo. The natural history of the disease is poorly understood and severe disease can occur very early in life (early onset) or later in life (late onset). Both hospital admission and need for intensive care can be the first presentation of asthma without any apparent history of mild disease. Remodeling might occur largely in parallel with inflammation or the development of remodeling might occur over shorter timescales than previously considered. To fully understand the dynamics of the interactions between the spatial scales described above, we need to focus future attention on the natural history of disease.

Perhaps much will be learnt by response to therapy particularly if emerging therapies are able to modify disease.

**Therapy for severe asthma** There have been a paucity of novel therapies for asthma over the last 20 years despite increased understanding of asthma pathogenesis. ICS and long-acting bronchodilators have remained the mainstay of therapy in asthma. Current therapies and treatments in late-phase development predominately target specific severe asthma domains. The greatest focus has been upon T\textsubscript{2}-mediated eosinophilic airway inflammation and ASM dysfunction. However, new targets are emerging as it has become apparent that there is a complex role for inflammation beyond TH2. Critically, in addition to persistent symptoms and exacerbations, severe asthma is also characterized by progressive decline in lung function and development of persistent airflow obstruction, as a consequence of remodeling. To date, this is largely refractory to current therapy. Therefore, targeting airway remodeling remains a major challenge of severe asthma. These domains and the role of current and future therapies approaching the clinic in targeting these domains are presented in Figure 2.

**T\textsubscript{2}-directed therapies** Current therapies Corticosteroids ICS have been well studied and convincingly demonstrate a reduction in exacerbation frequency across the spectrum of severity. However, studies consistently show that the major benefit occurs in patients with eosinophilic airway inflammation.\textsuperscript{20} Indeed, a meta-analysis of randomized controlled trials looking at titrating corticosteroid dose according to sputum eosinophilia concluded that sputum-based strategies were effective in reducing exacerbations in adults...
with asthma without a net increase in a mean ICS dose.25 Therefore, the recent American Thoracic Society/European Respiratory Society guidelines have stated that using sputum cell counts to direct corticosteroid therapy, as part of asthma management strategy, has benefits above standard care.2

**Antileukotriene drugs** Antileukotriene drugs are an adjunctive in the management of chronic asthma. They are primarily used in patients who are not controlled on ICS. Evidence suggests that antileukotriene drugs may be particularly effective in exercise-induced bronchoconstriction and aspirin-intolerant asthma.22

**Future therapies** Anti-interleukin 5 IL-5 is vital for eosinophil survival, maturation, and activation. Mepolizumab and reslizumab, both biological treatments targeting IL-5 itself, and benralizumab, which targets the IL-5 receptor, are effective in reducing blood, sputum, and tissue eosinophilic inflammation.24,25

The first phase 2a randomized placebo controlled trial26 of mepolizumab in 362 asthmatic patients showed no statistically significant clinical benefit for the whole cohort, but a trend was seen towards a reduction in exacerbation rates, raising the possibility of benefit in a subgroup. Subsequent phase 2 trials24,27 in subjects with refractory eosinophilic asthma, despite high-dose corticosteroids, mepolizumab significantly reduced exacerbation frequency, improved Asthma Quality of Life Questionnaire (AQLQ) scores, and allowed oral prednisolone dose reduction. Following cessation of therapy, the benefits were lost within 3 months.24

Similarly, in a placebo-controlled trial of reslizumab, sputum eosinophil levels were reduced and lung function improved with a non-significant trend towards reduced exacerbations.28 Benralizumab binds to the alpha subunit of the IL-5 receptor and enhances antibody-dependent cell-mediated cytotoxicity, and early studies are promising.29 They found a trend to a reduction in eosinophil count in the airways, measured from biopsy specimens as well a strong decrease in peripheral eosinophils and bone marrow eosinophils. A recent phase 2b study demonstrated reduced exacerbations and improved lung function and asthma control in moderate-to-severe asthmatics with peripheral blood eosinophilia.30

**Anti-interleukin 4** Pitrakinra, an IL-4 antagonist, reduced the allergen-induced late-phase response and the need for rescue medication in asthmatic patients.31 AMG-317, an IL-4Rα monoclonal antibody, demonstrated an improvement in the number and time to exacerbation in 147 moderate-to-severe asthmatics.32 Similarly, in a study on ICS reduction in moderate-to-severe asthmatics, dupilumab, another IL-4Rα antibody, resulted in improved lung function and the reduction of both T_{H2}-2-associated markers and asthma exacerbations compared with placebo.33

**Chemokine antagonist** AMG-427, an IL-13 neutralizing antibody, is in development. AMG-427 in a phase 2 trial has shown that it significantly reduced exacerbation rates and improved lung function in severe asthmatics with elevated eosinophils.34

**Antileukotriene drugs** Antileukotriene drugs are an adjunctive in the management of chronic asthma. They are primarily used in patients who are not controlled on ICS. Evidence suggests that antileukotriene drugs may be particularly effective in exercise-induced bronchoconstriction and aspirin-intolerant asthma.22

**Future therapies** Anti-interleukin 5 IL-5 is vital for eosinophil survival, maturation, and activation. Mepolizumab and reslizumab, both biological treatments targeting IL-5 itself, and benralizumab, which targets the IL-5 receptor, are effective in reducing blood, sputum, and tissue eosinophilic inflammation.24,25

The first phase 2a randomized placebo controlled trial26 of mepolizumab in 362 asthmatic patients showed no statistically significant clinical benefit for the whole cohort, but a trend was seen towards a reduction in exacerbation rates, raising the possibility of benefit in a subgroup. Subsequent phase 2 trials24,27 in subjects with refractory eosinophilic asthma, despite high-dose corticosteroids, mepolizumab significantly reduced exacerbation frequency, improved Asthma Quality of Life Questionnaire (AQLQ) scores, and allowed oral prednisolone dose reduction. Following cessation of therapy, the benefits were lost within 3 months.24

Similarly, in a placebo-controlled trial of reslizumab, sputum eosinophil levels were reduced and lung function improved with a non-significant trend towards reduced exacerbations.28 Benralizumab binds to the alpha subunit of the IL-5 receptor and enhances antibody-dependent cell-mediated cytotoxicity, and early studies are promising.29 They found a trend to a reduction in eosinophil count in the airways, measured from biopsy specimens as well a strong decrease in peripheral eosinophils and bone marrow eosinophils. A recent phase 2b study demonstrated reduced exacerbations and improved lung function and asthma control in moderate-to-severe asthmatics with peripheral blood eosinophilia.30

**Anti-interleukin 4** Pitrakinra, an IL-4 antagonist, reduced the allergen-induced late-phase response and the need for rescue medication in asthmatic patients.31 AMG-317, an IL-4Rα monoclonal antibody, demonstrated an improvement in the number and time to exacerbation in 147 moderate-to-severe asthmatics.32 Similarly, in a study on ICS reduction in moderate-to-severe asthmatics, dupilumab, another IL-4Rα antibody, resulted in improved lung function and the reduction of both T_{H2}-2-associated markers and asthma exacerbations compared with placebo.33

**Anti-interleukin 13** Lebrikizumab, a humanized IL-13 antibody improved lung function in a trial of 219 poorly controlled asthmatics.34 This effect was more pronounced in patients who had high serum levels of periostin, an extracellular protein produced by epithelial cells in response to IL-13 activation. A trend to a reduction in exacerbations was also observed in the group with high periostin levels.34 Tralokinumab, another anti-IL-13 antibody, also improved lung function in moderate-to-severe uncontrolled asthmatics,35 and benefits were greatest in those with high levels of periostin or dipeptidyl peptidase 4.36

**Chemokine antagonist** A phase II trial has shown that blocking this receptor can reduce sputum eosinophilia and improve lung function.39 Further small molecules targeting this receptor are in development and results are eagerly awaited (NCT01545726).

**Tyrosine kinase inhibitors** The enzyme tyrosine kinase is important for cell signaling of several key proinflammatory mediators. Tyrosine kinase inhibitors, imatinib and masitinib, inhibit stem cell factor, which is critical for mast cell maturation and survival. A phase 2a study in 44 subjects with severe corticosteroid-dependent asthma showed that after 16 weeks of treatment with masitinib, there was an improvement in asthma control.40 A phase 3 trial of masitinib in severe asthma is currently ongoing.

**Non-Th2 inflammation** Current therapies Antifungal agents Allergic bronchopulmonary aspergillosis (ABPA) is relatively uncommon and responds favorably to antifungal therapy.2,41 Similarly, itraconazole is beneficial in severe asthma with fungal sensitization without ABPA.42 Whether the efficacy from antifungal therapy is a consequence of a direct effect on fungal colonization or an indirect effect of increased corticosteroid bioavailability remains controversial. A recent study of voriconazole in sensitized severe asthmatics found no benefit after 3 months of treatment suggesting...
that previous benefit of antifungal therapy was probably largely due to its pharmacokinetic effects on corticosteroids.41

Macrolides  Macrolides are known to possess anti-inflammatory properties over and above their antimicrobial activity, and are of proven benefit in diffuse panbronchiolitis.41 Conflicting results for asthma have emerged from clinical trials.45 Nevertheless, there is some evidence to suggest that macrolides specifically target neutrophilic airway inflammation. A study of 45 refractory asthmatics showed that 8 weeks of clarithromycin at a dose of 500 mg twice daily significantly reduced airway neutrophilia and sputum IL-8 and significantly improved AQLQ scores compared with placebo.46 These differences were accentuated in the subgroup of patients with noneosinophilic asthma, suggesting that macrolides may be employed in specific subgroups. In a recent randomized controlled trial, azithromycin was used as an add-on treatment in severe asthma. It was beneficial in those without compared with those with high blood eosinophilia.47

Future therapies  Non-T_2 cytokine and chemokine therapy  Direct inhibition of neutrophil inflammatory via blockade of the chemokine receptor, CXCR2, reduced neutrophil inflammation and demonstrated small improvements in asthma control and mild exacerbations.48

Early studies using antibodies against tumor necrosis factor-α (TNF-α) were encouraging with improvements in asthma control, health status, lung function, and airway hyper-responsiveness. However, later studies were less conclusive in terms of efficacy and raised major safety concerns with increased frequency of infection and malignancy.49 It remains likely that some patients do benefit from anti-TNF-α, but without simple tools to stratify asthmatics reliably to maximize the likelihood of benefit and reduce harm, this approach has not been continued.

Th17 cells and cytokines, in particular IL-17A and IL-17F, promote neutrophil inflammation and their role within asthma has been investigated. Studies have reported that IL-17A and IL-17F are increased in the bronchial submucosa in moderate-to-severe asthmatics.50 The only clinical trial of an IL-17 antagonist reported in asthma is brodalumab, a human anti-IL-17 receptor monoclonal antibody. Busse et al.,51 in moderate-to-severe asthmatics, reported no improvement in lung function or asthma control with a 12 weeks of treatment with brodalumab; however, a prespecified subgroup analysis showed improvement in asthma control in patients with high reversibility of forced expiratory volume in 1 second (FEV₁).51

Airway smooth muscle dysfunction  Current therapies  Long-acting β₂ adrenergic agonists  The addition of long-acting β₂ adrenergic agonists (LABAs) to ICS improves symptoms and lung function and reduces exacerbations. Evidence suggests that clinical response to LABAs may be affected by polymorphisms in the β₂-adrenergic receptor gene. Most commonly seen polymorphisms are at codons 16 (Arg16Gly) and 27 (Gln27Glu).52 Patients who are Arg/Arg homozygous at codon 16 may be at increased risk of exacerbations, particularly when treated with LABAs.

Macrolides in asthma are mainly used as an add-on maintenance therapy option. Occasionally, they are used in an acute setting for severe asthma exacerbation. They exert both bronchodilator and anti-inflammatory effects on the airways and improve airway hyper-responsiveness and lung function. The exact mechanism of action of macrolides is not fully understood; however, the nonspecific inhibition of phosphodiesterase enzyme is strongly suspected of driving most of the clinical therapeutic effects. The inhibition of phosphodiesterase type VI isoenzyme has been shown to relax human ASM and also to have a direct anti-inflammatory effect.53 Methylxanthines also increase corticosteroid responsiveness through their stimulatory action on histone deacetylase-2.54 However, the use of methylxanthines in asthma has always been limited by their significant adverse event profile and a narrow therapeutic index.

Anticytokine therapies modulating airway smooth muscle function  Both anti-IL13 and anti-IL17 increase agonist-provoked ASM contraction in vitro and have the greatest benefit in vivo in asthmatics with bronchodilator reversibility suggesting these cytokines might exert some of their potential clinical benefit through effects upon the ASM. This further supports the concept of developing other approaches to modulate ASM function.
Airway remodeling  Current therapies  Mechanotransduction and breathing exercises  Mechanotransduction refers to the effects mechanical forces have on cellular function. In asthma, this particularly refers to the mechanical distortion of airway mucosa during bronchoconstriction. Grainge et al. 59 looked at 48 mild atopic asthmatics. They were divided into 4 challenge groups: those to receive an allergen, methacholine, saline, or methacholine preceded by albuterol, a short-acting β2-adrenergic agonist. They found that irrespective of the stimulus of bronchoconstriction, airway remodeling was evident and it was independent of eosinophil recruitment. 60 Another study, which focused more on clinical measures, found that attending personal breathing training improved AQLQ scores more than attending nonpersonalized asthma teaching sessions. 61Bronchial thermoplasty  The therapeutic use of radiofrequency is well established in cardiology for treating arrhythmias. Bronchial thermoplasty (BT), a novel technique that uses radiofrequency to heat the airways, is the only asthma therapy approved by the Food and Drug Administration that directly targets airway remodeling. BT is directed to the proximal conducting airways and aims to reduce the ASM mass as demonstrated in earlier studies. 62 The first human trial was in 9 cancer patients who had BT applied to lung segments that were due for resection. This showed a 50% reduction in the ASM mass. 63 The AIR trial showed improvements, following BT, in asthma control and AQLQ scores in mild-to-moderate asthmatics, but not in lung function. 64 Similar benefits were confirmed in patients with severe asthma. 65 The AIR2 trial studied 288 asthmatics and showed beneficial effects in the BT group when compared with the sham treatment, including health status and reduced exacerbations. 66 Initial follow-up studies suggest that the improvement in symptoms seem to last at least 5 years. All studies have shown a small increase in short-term adverse events in patients undergoing BT, including higher rates of pneumonia, hospitalization, and lobar collapse. Therefore, predictors of benefit and risk are required.

Future therapies  Treating inflammation to reduce remodeling  The effects upon features of remodeling in response to T2-directed anti-inflammatory therapies described above, particularly corticosteroids, have been reported. Corticosteroids reduce reticular basement membrane thickening and vascularity. Similar effects are reported for anti-IgE and anti-IL5. The effects on the ASM mass are unknown and, consistently, withdrawal of therapy results in worsening of airway remodeling. Therapies available or in development for other diseases such as cancer and fibrosis might present suitable targets for remodeling in asthma such as anti-VEGF, but these approaches have not been tested in asthma. More importantly, whether these treatments are also unable to demonstrate sustained benefit after their withdrawal is uncertain.

Conclusions  As our knowledge of the pathogenesis of asthma increases, so does our awareness that it is a very complex disease with numerous effectors and a wide variety in disease expression. It is already apparent that the “one size fits all” approach to asthma management is not sufficient, especially for those with severe asthma. Research into the pathogenesis of asthma is revealing distinct heterogeneous patient groups, and the challenge for the future of asthma management is to be able to personalize care at an individual level. This means the right patient needs to be identified to receive targeted treatment and response needs to be monitored using appropriate outcome measures.

Acknowledgments  C.E.B is funded by AirPROM (FP7 270 194). This article is supported by the National Institute for Health Research Leicester Respiratory Biomedical Research Unit. The views expressed are those of the authors and not necessarily those of the National Health Service, National Institute of Health Research, or Department of Health.

REFERENCES
Severe asthma: novel advances in the pathogenesis and therapy


Ciężka astma – postępy w patogenezie i terapii

Ruth Hartley, Rachid Berair, Christopher E. Brightling
Institute for Lung Health, Department of Infection, Immunity & Inflammation, University of Leicester, Leicester, Wielka Brytania

SŁOWA KLUCZOWE
astma, leczenie, patogeneza, postępy

STRESZCZENIE
Ocenia się, że na astmę choruje 300 milionów ludzi na całym świecie, w tym około 10% ma astmę ciężką. Astma, zwłaszcza ciężka, jest heterogenną chorobą wynikającą ze złożonych interakcji organizmu gospodarza i środowiska. W niniejszym artykule przeglądowym omówiono ostatnie postępy w rozumieniu patogenezy tej choroby oraz najnowsze metody leczenia. W patogenezie astmy ciężkiej można z grubsza wyróżnić 4 zjawiska: zapalenie T_{H2}, zapalenie nie-T_{H2}, remodeling dróg oddechowych oraz dysfunkcja mięśni gładkich dróg oddechowych. Te patologie mogą się rozwijać niezależnie lub w powiązaniu ze sobą. Interakcje między nimi, ich przyczyny oraz ostateczny wpływ na zaburzenia czynności dróg oddechowych i obraz kliniczny choroby pozostają słabo poznane. Najnowsze postępy w zakresie swoistej terapii ukierunkowanej na mechanizmy T_{H2}-zależne i niezależne, termoplastyka oskrzeli korygująca remodeling oraz nowe leki wpływające na dysfunkcję mięśni gładkich dają nowe możliwości lecznicze oraz pozwalają lepiej zrozumieć patogenezę astmy. W miarę poszerzania się wiedzy o patogenezie astmy coraz wyraźniej dostrzegamy potrzebę zindywidualizowanej diagnostyki i leczenia.