

Characteristics, phenotypes, mechanisms and management of severe asthma

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Abstract

Severe asthma is “asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.” The state of control was defined by symptoms, exacerbations and the degree of airflow obstruction. Therefore, for the diagnosis of severe asthma, it is important to have evidence for a diagnosis of asthma with an assessment of its severity, followed by a review of comorbidities, risk factors, triggers and an assessment of whether treatment is commensurate with severity, whether the prescribed treatments have been adhered to and whether inhaled therapy has been properly administered. Phenotyping of severe asthma has been introduced with the definition of a severe eosinophilic asthma phenotype characterized by recurrent exacerbations despite being on high dose ICS and sometimes oral corticosteroids, with a high blood eosinophil count and a raised level of nitric oxide in exhaled breath. This phenotype has been associated with a Type-2 (T2) inflammatory profile with expression of interleukin (IL)-4, IL-5, and IL-13. Molecular phenotyping has also revealed non-T2 inflammatory phenotypes such as Type-1 or Type-17 driven phenotypes. Antibody treatments targeted at the T2 targets such as anti-IL5, anti-IL5R α , and anti-IL4R α antibodies are now available for treating severe eosinophilic asthma, in addition to anti-immunoglobulin E antibody for severe allergic asthma. No targeted treatments are currently available for non-T2 inflammatory phenotypes. Long-term azithromycin and bronchial thermoplasty may be considered. The future lies with molecular phenotyping of the airway inflammatory process to refine asthma endotypes for precision medicine.

Keywords: Severe asthma; Biologic therapies; Eosinophils; Neutrophils; Corticosteroid insensitivity; Type 2-high inflammation

Introduction

Asthma is a global health problem. It has been defined as a heterogeneous disease characterized by airway inflammation usually presenting with a history of wheeze, shortness of breath, chest tightness, and cough that vary with time and in intensity, associated with variable airflow obstruction. It affects around 300 million people globally of all ages and ethnicities, with a death rate of ~250,000 people each year. In China, a recent survey of a representative population of asthma found a prevalence of 4.2% of asthma in adults aged 20 or above, representing 45.7 million Chinese.^[1] Asthma is associated with a high degree of morbidity, part of which is represented by those suffering from asthma despite being treated with anti-asthma medication, although many patients with asthma remain undiagnosed or are not receiving adequate medication. The recent asthma survey in China found

15.5% of asthmatics reporting at least one emergency room visit and 7.2% experiencing at least one hospital admission in the past year. It is likely that this morbidity is accounted for by inadequate treatment of asthma because only 5% to 6% of asthmatics had been treated with inhaled corticosteroids (ICS), suggesting undertreatment.^[1]

It is those asthma patients who experience uncontrolled asthma despite adequate therapy who are now labelled as suffering from severe asthma that represent an important economic burden to healthcare providers. The prevalence of severe asthma has been reported to be 3.6% amongst asthmatics attending a hospital clinic in the Netherlands^[2] and 4% to 6% in a Swedish cohort.^[3] In China, the incidence of severe asthma amongst asthmatics ranges from 3.4% to 8.3%.^[4-6] In terms of death rates from asthma, between 2011 and 2015 in high income countries, these are reported to be the highest in UK, Australia and

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000001990

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Chinese Medical Journal 2022;135(10)

Received: 01-09-2021; Online: 28-05-2022 Edited by: Peifang Wei

US averaging three to five standardized deaths per million population, while those in lower income countries as high as 12 to 25 per million population in Mauritius, South Africa and Philippines (<http://globalasthmareport.org/burden/mortality.php>; checked on October 6, 2021). Data regarding China are sparse, but in 2004 to 2005, a standardized death rate of 24.5 per million population was reported.^[7] It is to be noted that many of these asthma death rates are preventable because of inadequate diagnosis and treatment, and therefore the death rate due to uncontrolled or severe asthma would be lower than that reported. However, it is clear that the costs for uncontrolled or severe asthma are higher than those for controlled asthma. In Europe, the direct costs through hospital care, medication and indirect costs from time out of work range from 509 Euros per patient for those with controlled disease to 2281 Euros for uncontrolled disease per patient.^[8] The costs of asthma in Europe are estimated to be 21 billion Euros for asthmatics aged between 16 and 54 years in 2014. In the United States, \$56 billion is the estimated costs for asthma in 2015 (www.aafa.org/page/cost-of-asthma-on-society.aspx; checked on October 5, 2021).

The last 20 years of research into asthma has improved our understanding of the asthma with the recognition that far from being a single disease entity, asthma is a complex heterogenous disease that presents with several clinical phenotypes driven by a multiplicity of molecular mechanisms. This complexity of the severe asthma diathesis has become fully appreciated following the international agreement of a working definition of severe asthma that has in turn led the foundation towards an increased understanding of the underlying phenotypes and mechanisms. The clarification of the inflammatory processes such as the dominance of the Type-2 (T2) inflammation and the concomitant phenotyping into clinical and molecular phenotypes has contributed to improving the management of these patients.^[9] This has subsequently led to the successful introduction of monoclonal antibody therapies directed at various targets underlying T2 inflammation, an example of precision medicine applied to severe asthma.

In this review, we will start with the agreed definition of severe asthma and the clinical approach to the diagnosis and management of patients with severe asthma. In parallel, we will describe the clinical and molecular phenotypes of severe asthma and the underlying driving mechanisms of severe asthma that underpin these phenotypes. Finally, we will review the new treatments that have been introduced for severe asthma and summarize current on-going research towards more precision medicine for severe asthma.

Defining Severe Asthma

Prior to any consensus on the definition of severe asthma, there has been several terms used by clinicians to characterize these patients such as “brittle” asthma, corticosteroid-resistant asthma, difficult-to-control asthma, difficult-to-treat asthma, difficult chronic asthma, and life-threatening asthma which qualifies the type of

asthma presenting in a particular asthma patient. One of the first international definitions of the World Health Organization (WHO) Consultation on Severe Asthma defined severe asthma as “uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity.”^[10] This definition encompassed three groups of asthmatics: (1) untreated severe asthma representing patients who cannot receive treatment for their asthma because they cannot afford the treatments or do not have access to such treatments, (2) difficult-to-treat severe asthma in patients who are treated for their asthma but are not responsive to the treatments for many reasons including not being adherent to treatments or not receiving the right treatments, and (3) treatment-resistant severe asthma where control is not achieved despite the highest level of recommended treatment and asthma for which control can be maintained only with the highest level of recommended treatment.

A later definition of severe asthma from a task force of the European Respiratory Society (ERS) and American Thoracic Society (ATS)^[11] focused on severe asthma being a treatment-resistant asthma after the patient has been treated effectively and all other cofounders, such as medication compliance and comorbidities have been addressed. The definition was: “When a diagnosis of asthma is confirmed and comorbidities have been addressed, severe asthma is defined as ‘asthma which requires treatment with high dose ICS plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ despite this therapy.’”^[11] Uncontrolled asthma was defined according to the presence of poor symptom control, frequent severe exacerbations, serious exacerbations and presence of airflow limitation.

Diagnosing and Managing Severe Asthma

The diagnosis of severe asthma will be made in clinical practice in patients with asthma who remain uncontrolled despite receiving asthma treatments, at which stage the patient may be qualified as having “difficult-to-control asthma.” Within this cohort of difficult-to-control asthma who are referred to secondary care, a proportion will ultimately receive a diagnosis of severe asthma. This should happen when there has been exclusion of any other diagnoses that could mimic asthma, when the right treatments have been provided according to current guidelines and when the patient has been shown to be adherent to treatment. This approach will ensure that the first two types of patients under the WHO classification (untreated and difficult-to-treat asthma) have been excluded and that we have a patient with severe asthma according to the ATS-ERS definition of severe asthma.

It has been recommended that patients are evaluated within an asthma specialist service by a physician who specializes in asthma with access to the services of a whole multidisciplinary team.^[12] The assessment in a multidisciplinary team environment allows the experienced clinician to ensure that the classical symptoms of asthma (fluctuating dyspnoea, wheezing, cough) are caused by

Table 1: Systematic assessment of difficult-to-treat/severe therapy resistant asthma.

Item	Contents
1	Refer to an asthma specialized service
2	Confirmation of asthma diagnosis: Lung function variability; bronchial provocation test
3	Exclude other conditions masquerading as asthma
4	Assess severity of disease: Poor symptom control, airflow obstruction, frequent exacerbations, life-threatening severe exacerbations
5	Check inhalation technique and adherence to treatments
6	Optimization of treatment according to national guidelines
7	Assess adherence to therapy
8	Adaptation and using self-management plans
9	Identification and avoidance of trigger factors
10	Assessment and management of comorbidities
11	Phenotyping according to clinical-physiological-inflammatory parameters
12	Individualization of management plan

asthma rather than one of the many other conditions that can cause a similar medley of clinical symptoms.

A systematic assessment of the patient with difficult-to-treat-asthma should be performed within a severe asthma service [Table 1]. First, confirmation of the diagnosis of asthma and its severity should be evaluated, a process that can take up to 3 to 6 months of evaluation in the clinic. Bronchodilator reversibility or assessing variability of airflow obstruction with a peak flow diary or, if possible, the measurement of bronchial hyperreactivity may be used to support the diagnosis of asthma. High resolution computed tomography (HRCT) of the lungs is not indicated in the routine management of asthma but it can be used to exclude alternative diagnoses or the existence of additional conditions or co-morbidities of the lung. These conditions include intra- or extra-thoracic airway obstruction, obliterative bronchiolitis, chronic obstructive pulmonary disease, congestive heart failure, hypersensitivity pneumonitis, hyper-eosinophilic syndromes, allergic bronchopulmonary aspergillosis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

Assessing the factors that may underlie symptoms or exacerbations such as poor adherence to treatments and improper inhaler technique, comorbidities, and assessment of risk factors and triggers must be made [Supplementary Table 1, <http://links.lww.com/CM9/A939>]. Anxiety and depression and socio-economic factors may also form the basis of uncontrolled asthma. Social and psychological or psychiatric support may also be provided. The prevalence of treatable pulmonary and non-pulmonary traits is higher in severe asthma compared to non-severe asthma.^[13] Use of a systematic approach and attention to managing comorbidities can improve outcomes, quality of life, asthma control, reduce health care usage, and minimize the amount of oral corticosteroid (OCS) use.^[14,15]

Addressing non-adherence to prescribed inhaled and oral therapies is important since it can exist in 30% to 70% of prescribed medication^[16] in difficult-to-treat asthma, including the adherence to oral prednisolone therapy.^[17,18] For oral prednisolone adherence based on prednisolone-cortisol assays, the adherence varied from 33% to 45% in two specialist asthma centers.^[18,19] Non-adherence has been associated with poorer asthma outcomes, from worsening symptoms scores, increase in hospitalization, exacerbations rates, and mortality.^[16] Unintentional non-adherence can usually be addressed by better education, once a daily inhaler preparations, and ensuring (where possible) that if multiple inhalers in use are of the same type used in the same manner. Intentional non-adherence is a complex problem requiring further evaluation of the reasons behind it and will require other members of the asthma multidisciplinary team to be involved.^[20]

Assessment of the severity of asthma based on the definition of asthma control is necessary. Severity has been defined according to either poor symptom control, or presence of frequent severe exacerbations or serious exacerbations or presence of airflow limitation.^[11] Those patients that do not meet those criteria, but whose asthma control worsens when tapering corticosteroid dose, also meet the criteria of severe asthma. These criteria can predict future risks from asthma as well as side-effects of medications.

Finally, treatments need to be reviewed and optimized. Combination therapy of long-acting beta-agonist (LABA) with medium/high dose ICS should be established, with addition of leukotriene modifier and long-acting muscarinic antagonist (LAMA). Use of daily oral prednisolone can be considered but with the introduction of targeted antibody therapies for severe asthma, resort to the use of OCS therapy may be reduced.

Self-management education should be provided with incorporation of a personalized written or electronic asthma action plan. A review at 3 to 6 months should determine whether the patient has severe asthma, with the diagnosis confirmed if the asthma remains uncontrolled despite optimization of therapy. If the asthma remains well-controlled, stepping-down treatment can be considered, and if asthma symptoms or exacerbations occur on stepping down high dose treatment, then severe asthma can be diagnosed.

Risk Factors and Co-morbidities of Severe Asthma

Severe asthma phenotypes have been associated with genetic factors, age of asthma onset, disease duration, exacerbations, rhinosinusitis, and inflammatory characteristics.^[21-24] Early childhood-onset severe asthma is characterized by allergic sensitization and a strong family history of asthma.^[25,26] On the other hand, late-onset severe asthma is often associated with female gender and reduced lung function, persistent eosinophilic inflammation, nasal polyps and sinusitis, and aspirin sensitivity.^[25,27-29]

Obesity is associated with childhood and adult-onset severe asthma, but its impact may differ by age at onset

and the degree of allergic inflammation.^[30,31] Tobacco smoke and environmental air pollution have been considered as risk factors for more severe asthma.^[32,33] Cigarette smoking, exposure to air pollution and obesity have been linked to corticosteroid insensitivity, also present in severe asthma.^[34-36] Exacerbations in severe asthma are more frequent in those with comorbidities such as rhinosinusitis, gastro-oesophageal reflux disease, recurrent respiratory infections and obstructive sleep apnoea.^[37] Sensitization to the fungus, *Aspergillus fumigatus*, has also been linked to severe asthma development in adults.^[38]

Patients with severe asthma face the risks of lung function decline, recurrent exacerbations, corticosteroid-induced side effects and mortality,^[39] being greater in those with uncontrolled asthma as compared to those with controlled asthma. Future risk of exacerbations can be predicted from a history of exacerbations, in addition to other factors including smoking history, poor lung function, nasal polyps, obesity, and co-morbid depression.^[40-44] Loss of lung function in severe asthma has been associated with exacerbation rate, OCS usage, and age.^[45] Higher mortality has been associated with poor asthma control and presence of severe airflow obstruction.^[46] Severe asthma patients taking OCSs had more comorbidities that may be related to systemic corticosteroid exposure such as T2 diabetes, obesity, osteoporosis, hypertension, cataracts, and dyspeptic symptoms than those with milder asthma.^[47]

HRCT scan can also be used to denote future risks. The presence of air trapping on HRCT has been associated with asthma-related hospitalizations, intensive care unit visits, duration of asthma, airway neutrophilia, and airflow obstruction.^[48] Mucus plugging is another recognized feature of acute severe asthma and fatal asthma.^[49] Using a quantified mucus plugging scoring system, 67% of asthmatics with forced expiratory volume in one second (FEV₁) of less than 60% predicted had plugs present in four or more lung segments.^[50]

Long-term OCS therapy

The co-morbidities that are associated with long-term OCS therapy need to be addressed by monitoring bone densitometry and treating reduced bone density appropriately as well as monitoring for metabolic sequelae of OCS use, such as non-alcoholic fatty liver disease. With the advent of monoclonal antibodies, or biologic therapies, the reliance on long-term OCS for the treatment of severe asthmatics has been reduced. This could occur with the early administration of such biologic therapies prior to considering the use of OCS therapy. In addition, with establishment of biologic therapies particularly anti-interleukin (IL) 5, anti-IL5R α and anti-IL4R α antibodies,^[51-53] the dose of OCS can be reduced and sometimes discontinued.

Corticosteroid-insensitive patients continue to experience side-effects from OCS therapy.^[54] Use of sputum eosinophil counts which has been recommended by the ERS-ATS guidelines may help toward adjusting to the lowest dose of

OCS needed.^[55] Low levels of sputum or blood eosinophil counts indicate a non-eosinophilic phenotype that is likely to be less responsive to OCS therapy, and therefore corticosteroids can be down-titrated. On the other hand, the blood eosinophil count may increase as a result of down-titration of the OCS dosage, in which case this would represent a corticosteroid-sensitive but relatively resistant eosinophilic asthma. A recent expert consensus statement relating to OCS use, tapering, adverse effects, adrenal insufficiency, and patient-physician shared decision-making has been published and will be helpful in the management of OCS therapy in severe asthma.^[56]

Clinical Severe Asthma Phenotypes

Clinicians over the years have described various descriptive phenotypes such as early childhood onset severe allergic asthma, late adult-onset eosinophilic asthma, obesity-associated asthma, aspirin-associated asthma, and smoking-associated asthma. In addition, clinical phenotyping has also been done on the basis of clinical features and the presence of chronic airflow obstruction and exacerbations.^[57]

Unbiased methods of clustering used in the Severe Asthma Research Program have refined these clusters with identification of phenotypes of (1) early onset atopic asthma with mild to moderate severity, (2) obese late onset non-atopic asthma female patients with frequent exacerbations, and (3) those with severe airflow obstruction and use of daily OCS therapy.^[27] In the European Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohort that included severe smoking and ex-smoking patients, three severe asthma phenotypes were described: (1) late-onset asthma with past or current smoking and chronic airflow obstruction, (2) non-smoking severe asthma with chronic airflow obstruction and use of OCS therapy, and (3) obese female patients with frequent exacerbations but with normal lung function.^[58] Inclusion of sputum eosinophilia as a marker of eosinophilic asthma has resulted in two clusters: one of non-eosinophilic inflammation characterized by early-onset, symptom-predominant group in female obese patients, and another of eosinophilic inflammation with late-onset disease, associated with rhinosinusitis, aspirin sensitivity, and recurrent exacerbations,^[25] later described as a severe eosinophilic asthma phenotype.^[59] [Supplementary Table 2, <http://links.lww.com/CM9/A939>].

Molecular Phenotypes of Severe Asthma

Definition of T2-high phenotype

The airway epithelium responds to external stimuli such as allergens, pollutants and infectious agents (eg, viruses) to cause the recruitment and/or activation of cells that are involved in the innate and adaptive immune response (such as dendritic cells, mast cells, and innate lymphoid cells),^[60] which leads to the orchestration of airway inflammation and mechanisms that drive the pathophysiology of asthma.^[61] Thus, it controls the regulation of T2 cytokines through the production of the alarmins such as thymic stromal lymphopietin (TSLP), IL-25, and IL-33,

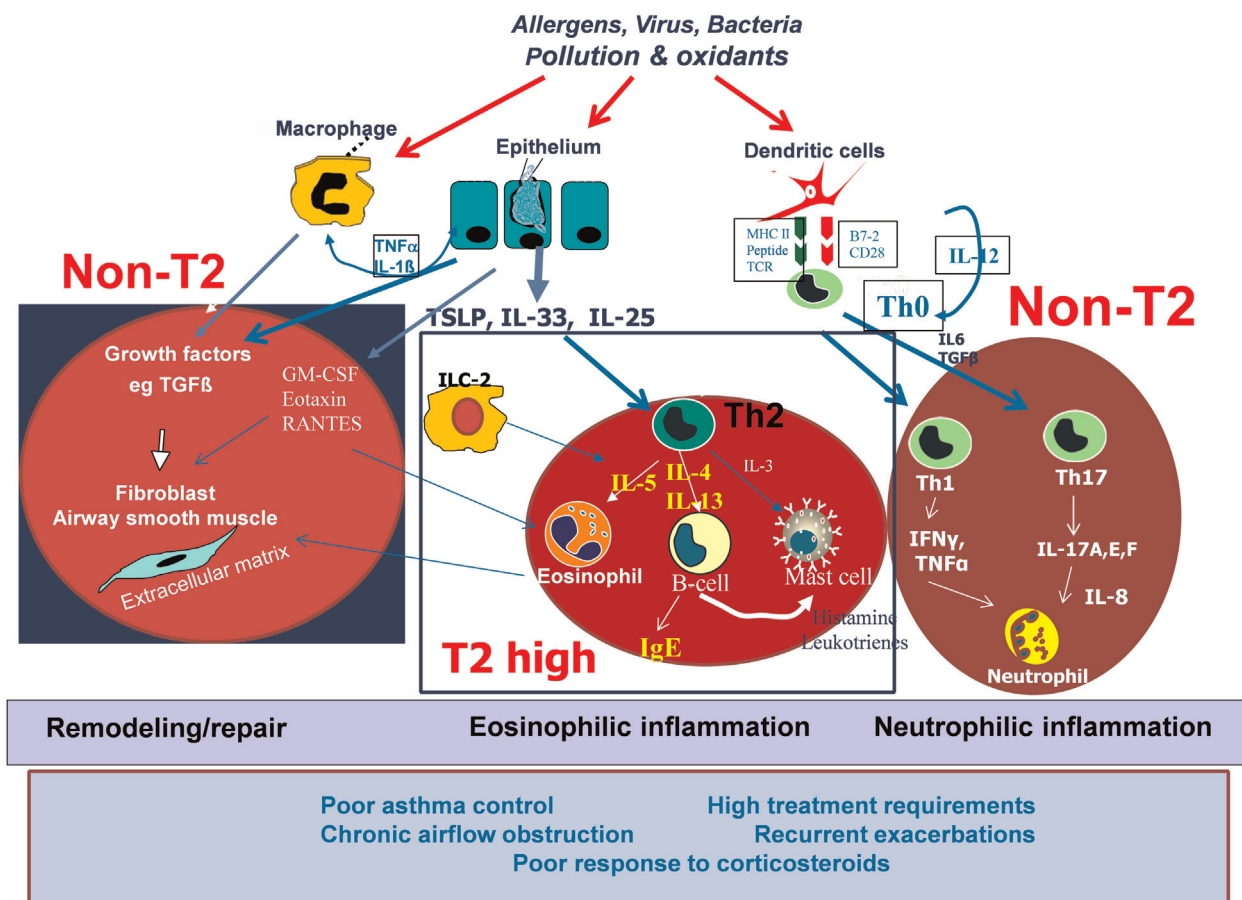


Figure 1: Airway epithelium interactions with environmental factors to induce innate and adaptive immune and inflammatory responses with the release of TSLP, IL-33, and IL-25. Generation of Th2 cells and ILC2s leads to the elaboration of IL-4, IL-5, and IL-13, inducing an allergic eosinophilic inflammation with eosinophil recruitment and activation, and IgE production. Activation of Th1 and Th17 cells may contribute to neutrophilic inflammation. Airway wall remodeling and repair driven by epithelial-mesenchymal transformation and the effects of ILs on airway structural cells such as airway smooth muscle cells and epithelial cells contribute to chronic airflow obstruction and bronchial hyper-responsiveness. Targets for interleukin intervention against IL-4, IL-5, and IL-13 are shown. B7-2: Also known as cluster of differentiation 86 (CD86); GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFN γ : Interferon γ ; IgE: Immunoglobulin E; IL: Interleukin; ILC2: Type 2 innate lymphoid cells; MHC II: Major histocompatibility complex; RANTES: Regulated upon activation, normal T cell expressed and presumably secreted; TCR: T-cell receptor; T2: Type 2 inflammation; TGF β : Transforming growth factor β ; Th0: T helper 0; Th1: T helper 1; Th2: T helper 2; Th17: T helper 17; TNF α : Tumor necrosis factor α ; TSLP: Thymic stromal lymphopoietin.

which can be induced following exposure of epithelial cells to external stimuli including environmental pollutants, viruses and allergens^[62] [Figure 1]. IL-33 is a member of the IL-1 cytokine family and an inducer of chemoattractants for T-helper type 2 cells (Th2). TSLP is an IL-7-related cytokine secreted by airway epithelial cells that activates dendritic cells to release chemokines that attract and activate Th2 cells. Expression levels of both IL-33 and TSLP are increased in airway epithelium of patients with asthma, particularly in those with severe asthma.^[63,64] These alarmins can be produced in response to allergens such as house dust mite and *A. fumigatus* in a Toll-like receptor 4/myeloid differentiation factor 88 (MyD88)-dependent manner,^[65,66] as well as exposure to diesel exhaust particles^[67] and to virus infections.^[68] There is also increased expression of the IL-33 and TSLP receptors in sputum cells from patients with severe asthma.^[69]

The alarmins TSLP and IL-33 direct T-helper cells towards a Th2 phenotype with the secretion of IL-4, IL-5, and IL-13, and also directly stimulate innate lymphoid T2 cells to

produce IL-5 and IL-13.^[62] The Th2 cytokines, including IL-3, IL-4, IL-5, IL-9, and IL-13, are expressed in bronchial submucosa of patients with the disease. IL-5 is involved in the terminal differentiation of eosinophils and in the activation of airway eosinophils. IL-13 increases the activation of inducible nitric oxide synthase (iNOS) enzyme in the epithelium, leading to an increase in exhaled nitric oxide (NO), goblet cell metaplasia and bronchial hyperresponsiveness. IL-4 promotes immunoglobulin E (IgE) synthesis and primes the vascular endothelium for the extravasation of eosinophils.

T2-high and severe eosinophilic asthma

Hierarchical clustering of differentially expressed genes between eosinophilic and non-eosinophilic inflammatory profiles using sputum cell transcriptomics revealed three molecular phenotypes.^[70] The first transcriptomic-associated cluster (TAC1) was characterized by the immune receptors of IL-33, eotaxin (CC chemokine receptor 3), and TSLP with the highest enrichment of gene signatures

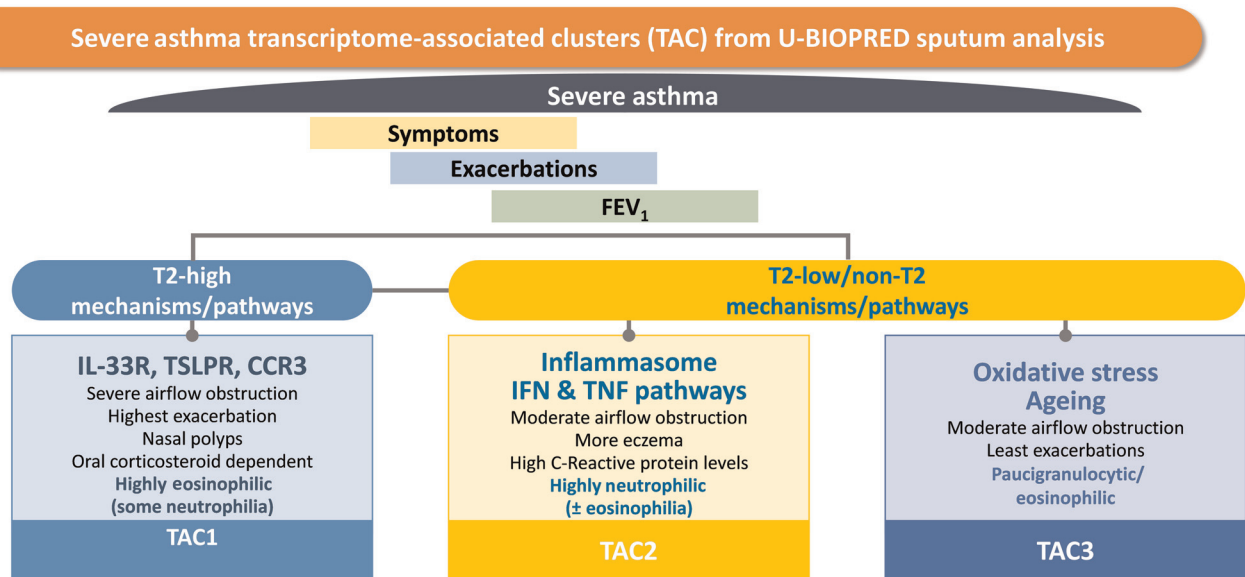


Figure 2: Three transcriptomic-associated clusters (TAC) obtained from hierarchical clustering of differentially expressed genes obtained by comparing the transcriptome of sputum cells obtained from eosinophil-high and eosinophil-low sputum from patients with severe asthma. Each of the lower boxes represent the genes or class of genes that characterize each TAC signature, the salient clinical features and the sputum granulocytic inflammation. CCR3: CC chemokine receptor 3; FEV₁: Forced expiratory volume in one second; IFN: Interferon; IL-33R: Interleukin 33 receptor; TNF: Tumor necrosis factor; T2: Type 2 inflammation; TSLPR: Thymic stromal lymphopoietin receptor; U-BIOPRED: Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes.

for the IL-13/T2-inflammation signature being associated with sputum eosinophilia [Figure 2]. This grouped patients with severe asthma with OCS dependency, frequent exacerbations, and severe airflow obstruction, characteristics of the severe eosinophilic asthma phenotype^[59] [Supplementary Table 2, <http://links.lww.com/CM9/A939>].

Using a different approach to determine the enrichment of an IL-13/T2-high gene expression signature in bronchial epithelial cells of patients with asthma, a T2-high phenotype was found in up to 37% of patients with severe asthma.^[71] The T2-high patients were more symptomatic despite treatment with ICS and most often on OCS therapy, characterized by higher levels of nitric oxide in exhaled breath and of blood and sputum eosinophils. This, therefore, defined the molecular signature of the severe eosinophilic asthma. Using a composite measure of IL-4, IL-5, and IL-13 gene expression in induced sputum cells from severe asthma patients, 70% of patients on high dose ICS had a T2-high phenotype.^[72]

The “T2-high” phenotype^[70] is likely to be driven by activated eosinophils through the production of cytotoxic proteins such as major basic protein, eosinophil peroxidase, eosinophil cationic protein and eosinophil derived neurotoxin, which cause damage to epithelial and other lung structural cells.^[73] Release of proinflammatory cytokines and chemokines and of lipid eicosanoid products may contribute to bronchial hyperresponsiveness and airway wall remodeling. The success of anti-IL5 and anti-IL5R α antibody treatments in reducing exacerbations in severe eosinophilic asthma has firmed up this phenotype as an endotype while the therapeutic effects of anti-IgE antibody support the severe allergic asthma phenotype.

Non-T2 pathways and neutrophilic asthma

The second cluster, TAC2, derived from the U-BIOPRED sputum transcriptomic analysis was characterized by inflammasome-associated genes, interferon- α and tumor necrosis factor- α -associated genes, with sputum neutrophilia, high serum C-reactive protein levels and a higher prevalence of eczema, defining patients with neutrophilic asthma^[69] [Figure 2]. The third phenotype (TAC3) was characterized by metabolic pathway genes, ubiquitination and mitochondrial function which are normally reduced in asthma and with paucigranulocytic inflammation and little airflow obstruction. The non-T2 pathways that could drive asthma pathobiology include type 1 innate lymphoid cells, inflammasome, neutrophil and IL-17 activation, oxidative phosphorylation, and interferon-gamma (IFN γ) activation.^[74] Th1 CD4⁺ T cells produce IFN γ which plays a role in controlling intracellular infections and in autoimmunity. Th1 cells expressing IFN γ are increased in bronchoalveolar lavage fluid, sputum cells and bronchial biopsies from patients with asthma.^[75-77] Bronchoalveolar lavage fluid from severe asthmatic patients showed greater Th1 cells and neutrophil numbers accompanied by higher IFN γ levels than in non-severe asthmatics.^[78]

Th17 cells are CD4⁺ T cells that express IL-17A, IL-17E, IL-17F, and IL-22 mediating neutrophil activation via IL-8 production.^[79,80] Th17-associated cytokines IL-17A and IL-17F have been localized in the airways of patients with severe asthma.^[81] Th17 cells have been implicated as a cause of neutrophilia in severe asthma.^[82] An “IL-17-high” asthma phenotype has been characterized by bronchial epithelial dysfunction and upregulated antimicrobial and inflammatory response.^[83] An IL-6 trans-signaling signature developed in U-BIOPRED also

indicated an IL-6 phenotype that drives non-T2 airway inflammation and epithelial dysfunction.^[84]

Sputum neutrophilia has been associated with severe asthma, corticosteroid insensitivity, and chronic airflow obstruction^[85-88] and is also observed during acute exacerbations.^[89,90] Sputum neutrophilic inflammation associated with inflammasome activation supports the presence of a neutrophilic phenotype of asthma.^[70] In neutrophilic asthma, an elevated gene expression of nucleotide-binding domain and leucine-rich, repeat-containing family, pyrin domain containing 3, caspase-1 and IL-1 β in sputum cells has been reported.^[69,91] Increased airway neutrophilia may be the result of infection, exposure to air pollutants, or treatment with corticosteroids, particularly OCSs.^[92]

Non-T2 pathways: airway wall remodeling

Airway wall remodeling is characterized by an increase in airway smooth muscle mass, subepithelial fibrosis and increased numbers of mucous glands and goblet cells. The epithelium in severe asthma is thicker than in mild-moderate asthma, with increased proliferation, apoptosis and release of pro-inflammatory factors.^[93] Airway smooth muscle mass increase is associated with airflow obstruction and bronchial hyper-responsiveness, with an enhanced proliferation rate.^[85,94,95] Fibrocytes, which can differentiate into myofibroblasts, are increased in blood and in airway smooth muscle bundles in asthma patients with fixed airway obstruction and/or severe disease.^[96-98] Subepithelial thickening of the bronchial reticular layer is a feature of asthma of all severities.^[22,85,99] Patients with severe asthma have increased expression of transforming growth factor- β isoforms and collagen deposition, compared to those with mild asthma, in association with eosinophilia.^[100,101] In severe eosinophilic asthma, the increased subbasement membrane thickness was associated with matrix metalloproteinase 10 and MET protooncogene, receptor tyrosine kinase (MET) which are the most differentially expressed proteins that drive airway wall remodeling.^[102]

HRCT scan studies in asthmatic subjects may reveal abnormal radiologic findings, such as bronchial wall thickening, bronchial wall dilatation, bronchiectasis, mosaic lung attenuation, mucus plugging, prominent centrilobular opacities, emphysema, and atelectasis.^[103,104] Mosaic lung attenuation represents involvement of small airways (<2 mm) and acinar air spaces. Its delineation can be improved by using an expiratory phase computerized tomography (CT).^[105] HRCT scan abnormalities such as bronchial wall thickening (62%), bronchial enlargement (40%), and emphysema (8%) have been shown to be present in 80% of severe asthma subjects.^[106]

Non-T2 pathways: corticosteroid insensitivity

Severe asthma may be considered as having poor therapeutic response to corticosteroid therapy.^[107,108] The defining feature of severe asthma is need for high dose ICS to gain disease control or despite this, the disease is poorly controlled (as previously described in this review), with only 62% of moderate to severe asthma gaining

control with ICS and LABAs inhalers.^[109] Corticosteroid insensitivity has been defined clinically by <15% improvement of peak expiratory flow rates from baseline after receiving 7 to 12 days of 30 mg of prednisolone.^[110] Half of severe asthma patients in the U-BIOPRED cohort were on OCS therapy, and had a higher prevalence of nasal polyps, uncontrolled asthma, and a higher number of exacerbations compared with those not on OCS maintenance,^[111] associated with elevated fractional exhaled nitric oxide (FeNO) and sputum eosinophils, evidence of corticosteroid insensitivity. After treatment with intramuscular triamcinolone, most patients showed little response in terms of lung function (FEV₁), blood eosinophil count or levels of FeNO, accompanied by little change in the expression of IL-4, IL-5, and IL-13 genes in sputum cells, indicating a degree of corticosteroid insensitivity in this group.^[112]

Cigarette smoking, bacterial infections, obesity, and deficiency of vitamin D have been associated with corticosteroid insensitivity.^[107,108] Impaired nuclear translocation of the glucocorticoid receptor, activation of mitogen-activated protein kinase pathways, activation of transcription factors by IFN γ and increased oxidative stress resulting in reduction in histone deacetylase expression and activity are implicated molecular mechanisms.^[108] The observations of overexpression of *Haemophilus parainfluenzae* (*H. parainfluenzae*) in bronchoalveolar lavage fluid and culture of *H. parainfluenzae* with macrophages inducing corticosteroid resistance in these cells link steroid resistance to *Haemophilus* infection.^[113] Th17 cells may be induced by bacterial infections, and have been implicated in corticosteroid insensitivity.^[114,115] The anti-IL5 α antibody, mepolizumab,^[51] anti-IL-5R α antibody, benralizumab,^[52] and anti-IL4Ra antibody, dupilumab^[53] reduced maintenance dose of OCS by 50% in OCS-dependent patients with severe eosinophilic asthma, implicating a role for these T2 cytokines in corticosteroid insensitivity. Therefore, both T2 and non-T2 pathways may underlie corticosteroid insensitivity in severe asthma.

Phenotyping and Biomarkers for Severe Asthma

After the diagnosis of severe asthma has been ascertained, phenotyping in terms of whether the patient falls within the category of severe eosinophilic asthma should be determined [Figure 3]. This is often referred to as a T2 high phenotype asthma because the severe eosinophilic asthma has been linked to T2 inflammation as measured in the bronchial epithelium by the expression of genes involved in T2 inflammation.^[71] Using this measure of T2 inflammation, a blood eosinophil count of 115 cells/mL was found to have the highest sensitivity and specificity for detecting T2 inflammation with a receptor operating curve discrimination of 68.9%.^[71] The reason why this phenotype should be ascertained is that there are biologic treatments that target specific components of the type-2 inflammation (IL-5, IL-4, and IL-13) and provide clinical benefits when given to severe eosinophilic asthma patients.

Blood eosinophil count has been used to identify T2-high status, derived from the clinical trials of these biologic therapies. A level of 300 cells/mL blood eosinophil count

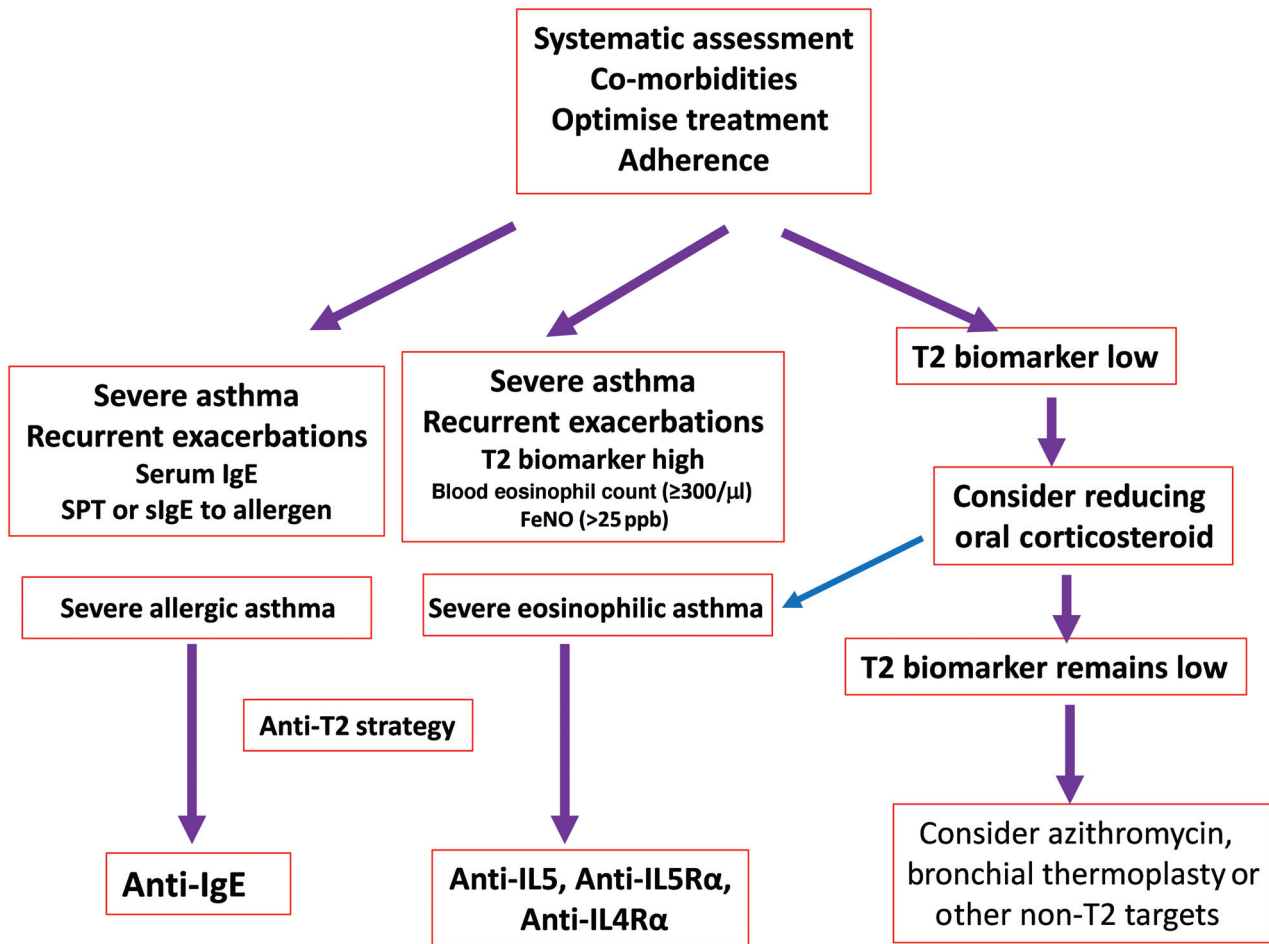


Figure 3: Management algorithm for severe asthma. After confirming the diagnosis of severe asthma, Type-2 (T2) biomarkers which are currently based on blood eosinophil count, fractional exhaled nitric oxide (FeNO) and total serum immunoglobulin E (IgE) and presence of allergies can be used to diagnose severe eosinophilic or severe allergic asthma. Those with high-T2 biomarker and regular exacerbations of asthma can be offered biologic anti-T2 treatments. Those with low T2-biomarker will need to have a reduction in oral corticosteroid dosage (OCS) in case the steroids are suppressing the level of T2-biomarkers. Trial of long-term azithromycin or bronchial thermoplasty may be considered. IL: Interleukin; IL4Rα: Interleukin 4 receptor alpha; IL5Rα: Interleukin 5 receptor alpha; ppb: Part per billion; SPT: Skin prick tests; sIgE: Specific immunoglobulin E.

has been used as the cut-off point although a level of > 150 cells/mL has also been used, with most studies showing that the higher the cut-off point used, the greater the beneficial effects of the biologic therapies (anti-IL5, anti-IL5Rα, and anti-IL4Ra antibodies) in terms of reduction in exacerbation rates. For anti-IgE therapy, a blood eosinophil count > 260/μL is predictive of this response in severe allergic patients.^[116]

Sputum eosinophils are the most sensitive and specific noninvasive biomarker for eosinophilic airway inflammation,^[117] but is difficult to obtain reliably and measure easily. A differential cell count of > 2% to 3% indicates an underlying eosinophilic inflammatory process and is diagnostic of eosinophilic airway disease.^[117]

FeNO is another biomarker of T2 inflammation of the airways, indicating the activity of T2 cytokines IL-4 and IL-13, as these cytokines upregulate the expression of epithelial iNOS.^[118] Recent evidence has confirmed the utility of using FeNO as an indicator of T2 inflammation, with its use as a tool for precision medicine in the management of severe asthma during periods of stability

and instability.^[119] The severe asthma ATS/ERS and Global Initiative for Asthma (GINA) guidelines have indicated that a FeNO > 20 parts per billion (ppb) is enough to indicate T2-high signal and to identify those who are likely to respond to current anti-T2 biologic therapies.^[120]

Therapeutic Approaches for Severe Asthma

Once the patient with severe asthma has been phenotyped, consideration of therapeutic approaches remains the final important aim. Use of currently available controller treatments need to be ascertained irrespective of the phenotype of the asthma. Consideration needs to be given regarding new biologic therapies, particularly if the patient fulfils the criteria of a severe allergic or severe eosinophilic asthma, both being under the umbrella of T2-high inflammation^[121] [Figure 3]. The list of currently available anti-T2 biologic therapies is shown in Figure 4. This represents the start of precision medicine for severe asthma.^[9,122] There are currently no specific therapies for the various T2-low phenotypes, including neutrophilic asthma, airway wall remodeling and corticosteroid

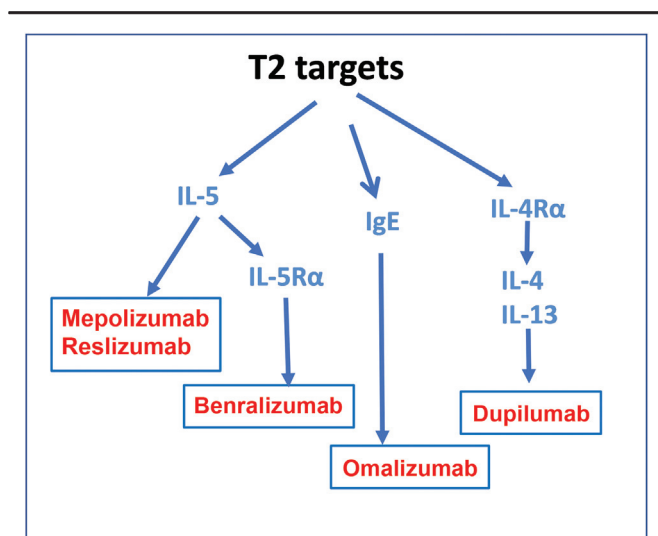


Figure 4: Therapeutic antibodies targeting type 2 cytokines, IL-4, IL-5, and IL-13, and anti-IgE. IgE: Immunoglobulin E; IL: Interleukin; IL4R α : Interleukin 4 receptor alpha; IL5R α : Interleukin 5 receptor alpha; T2: Type 2 inflammation.

insensitivity. However, long-term azithromycin and bronchial thermoplasty may be considered. Currently, anti-TSLP and anti-IL-33 antibody therapies are being developed which might target both T2-high and T2-low phenotypes.

Current Controller Treatments

Patients with severe asthma are by definition usually at steps 4 and 5 of the therapeutic recommendations of the GINA guidelines (<https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf>). Controller therapies using a combination of ICS and LABA remain the backbone of treatment, with the possibility of using the maximum dose of ICS, although the step-up of medium to high-dose ICS may only provide a small improvement in control. Nevertheless, a trial of high dose ICS is recommended with the proviso that if there is little benefit, maintenance ICS dose should revert to the medium dose. The more recent recommendation from GINA is on the use of the maintenance and reliever therapy approach using the single inhaler of formoterol and an ICS, for which there is support for its efficacy in reducing severe exacerbations.^[123] Triple therapy of LABA-LAMA-ICS is now recommended for the treatment of severe asthma, with previous studies showing that the LAMA, tiotropium bromide, added to ICS-LABA inhalation improved lung function and reduced exacerbations compared to ICS-LABA alone.^[124]

Biologic antibody therapies

Omalizumab

Omalizumab, the first approved biologic for asthma, is a recombinant humanized monoclonal antibody that binds to circulating free IgE, thereby preventing IgE binding to its receptor (Fc ϵ R1) expressed on the surface of basophils and mast cells and therefore the release of mediators from

these cells.^[125] Omalizumab is indicated for severe allergic asthma in whom appropriate pharmacotherapy and allergy avoidance have not been helpful and in those with a total serum IgE from 30 to 700 IU/mL (with the possibility of including those with serum IgE levels up to 1300 IU/mL) and raised specific IgE to at least one aeroallergen.^[11] A meta-analysis that included 3000 patients with moderate to severe asthma reported a decreased risk of exacerbation while ICS doses were successfully reduced during omalizumab treatment.^[126] In a study of severe allergic asthma, omalizumab led to a 25% reduction in exacerbations while improving quality of life scores and asthma symptom scores.^[127]

Treatment response should be evaluated at 4 months, using a combination of quality of life, exacerbation frequency and health care use. In a *post hoc* analysis of the EXACT study of omalizumab in subjects with moderate-to-severe persistent asthma, a high blood eosinophil count > 260 cells/mL and a FeNO > 19.5 ppb were found to predict those patients likely to benefit most with a reduction in exacerbation frequency.^[117] However, in a prospective real-world study (PROSPERO study), these biomarkers had minimal predictive value for omalizumab treatment outcomes, particularly for exacerbation reduction,^[128] questioning the need for using these biomarkers to predict responders.

Anti-IL-5/anti-IL-5R α antibodies: mepolizumab, reslizumab, and benralizumab

Mepolizumab, reslizumab, and benralizumab block the IL-5 pathway which is the key cytokine for eosinophil maturation, survival and transition of this granulocyte from the bone marrow into the systemic circulation. Mepolizumab and reslizumab are immunoglobulin G (IgG) 4 humanized monoclonal antibodies that bind IL-5, thus preventing it from binding to the IL-5R α on eosinophils.^[121] On the other hand, benralizumab is an IgG1 humanized monoclonal antibody that targets the α subunit of the IL-5 receptor. It induces apoptosis of eosinophils and basophils through antibody-dependent cell mediated cytotoxicity.

These three monoclonal antibodies (mAbs) have been approved for use in patients with severe eosinophilic asthma that demonstrate a blood eosinophil count of ≥ 300 cells/ μ L and experience frequent exacerbations. They reduce the risk of exacerbations by 40% to 50% with modest effects on lung function,^[129-132] which have been replicated in real-world practice.^[133-135] Mepolizumab and benralizumab also reduced the maintenance dose of OCS in OCS-dependent patients with severe eosinophilic asthma by 50% while reducing the frequency of exacerbations.^[51,52]

The 2019 GINA guidelines for severe asthma recommend the use of an anti-IL-5 and anti-IL-5R α antibody for patients who remain uncontrolled with exacerbations in the past year despite step 4 or 5 therapy and who have a blood eosinophil count > 300 cells/ μ L (<https://ginasthma.org/wp-content/uploads/2021/08/SA-Pocket-guide-v3.0-SCREEN-WMS.pdf>). The ERS-ATS recommendation on

the other hand suggests a blood eosinophil count cut-off point ≥ 150 cells/ μL .^[119]

Anti-IL4R α antibody: dupilumab

Dupilumab is a fully humanized monoclonal antibody directed at the α -subunit of the IL-4 receptor leading to the blockade of the effect of the T2-cytokines, IL-4, and IL-13,^[121] involved in airway recruitment of eosinophils, B cell class switch to IgE production, goblet cell hyperplasia and mucus production, airway remodeling through airway smooth muscle proliferation and collagen deposition and airway epithelial cell expression of iNOS. Dupilumab decreased exacerbations in moderate to severe uncontrolled asthma, with greater improvements in those with higher blood eosinophil levels, reaching 67% in those patients with blood eosinophils ≥ 300 cells/ μL .^[136,137] The greatest treatment benefit in terms of reduction in exacerbation rates and improvement in FEV₁ as compared with placebo was observed in patients with elevated T2 biomarkers (baseline blood eosinophil count of ≥ 150 cells/ μL and baseline FeNO of > 25 ppb).^[128] It is also effective in reducing OCS dose in those with severe OCS-dependent asthma while reducing exacerbation risk.^[53] Dupilumab therapy is also associated with improvements in lung function, asthma control and quality of life.

While the GINA severe asthma guidelines suggest using dupilumab for patients with severe eosinophilic asthma with exacerbations in the past year with either a blood eosinophil count of ≥ 150 cells/ μL or a FeNO > 25 ppb (<https://ginasthma.org/wp-content/uploads/2021/08/SA-Pocket-guide-v3.0-SCREEN-WMS.pdf>; checked on October 5, 2021), the ERS-ATS guidelines advise its use in severe eosinophilic asthma including corticosteroid-dependent asthma regardless of blood eosinophil counts.^[119] However, those with higher blood eosinophil counts and higher FeNO are expected to respond better.

The indications for using these expensive biologic therapies are also dependent on the regulations set by the health care system of each country, which could be determined not only by being medically suitable for such therapies according to biomarker status, but also by other factors such as cost-benefit issues and affordability.

Other Therapies for Severe Asthma

Bronchial thermoplasty

Bronchial thermoplasty is a bronchoscopic procedure whereby intraluminal thermal energy is applied to the airway wall, with the aim of ablating the airway smooth muscle, although epithelial cells and nerves are also affected.^[138] In patients with severe asthma, there is a modest effect in improving asthma-related quality of life scores and bringing some reduction in asthma exacerbations.^[11] A sustained reduction in severe exacerbations over a 3-year follow-up period after bronchial thermoplasty in severe asthma with no improvement in pre- or post-bronchodilator FEV₁ has been reported.^[139] There is limited information on the identity of patients with severe asthma who will benefit most from bronchial thermo-

plasty. It has been suggested that bronchial thermoplasty should be considered for patients with severe asthma associated with non-T2 inflammation and non-eosinophilic inflammation. This procedure in patients with severe asthma resulted in 11.8% of 152 procedures associated with emergency respiratory readmission and in 48.1% having a post-procedural stay in hospital.^[140] A 10-year review of clinical data in patients that have undergone bronchial thermoplasty reported an increased rate of bronchiectasis.^[141]

The Asthma guidelines of the Expert Panel Working Group of the National Heart Lung, and Blood Institute in the US have conditionally recommended against bronchial thermoplasty in individuals aged 18 years and older with persistent asthma.^[142] It advised for the conduct of registered clinical trials and long-term registry studies of bronchial thermoplasty to fully assess the clinical benefits and harms.

Long-term macrolide therapy

An abnormal microbiome has been associated with severe asthma.^[143] The use of antibiotics in the treatment of severe asthma is therefore of interest with a potential two-pronged mode of action using macrolide antibiotics as an antineutrophilic and an anti-bacterial agent. In a placebo-controlled study of patients with symptomatic asthma on ICS and LABA, azithromycin administered three times per week reduced the number of exacerbations (1.86 per patient year in the control group versus 1.07 in the active group) together with an improvement in asthma and quality of life.^[144] It was not clear whether severe exacerbations or hospitalizations were reduced. Patients with eosinophilic asthma benefited as well as patients with non-eosinophilic asthma. Azithromycin reduced airway *H. influenzae* load, with no changes in total or pathogenic bacterial loads. But there is emergence of antimicrobial resistance. It is not known whether this therapy does improve outcomes among patients with severe asthma. The ERS-ATS severe asthma guidelines suggest a trial of macrolide treatment to reduce asthma exacerbations in adult asthma subjects on GINA/National Asthma Education and Prevention Program (NAEPP) step 5 therapy that remain persistently symptomatic or uncontrolled, but they suggest against the use of chronic macrolide treatment in children and adolescents with severe uncontrolled asthma.^[119]

Future directions

The introduction of these T2 targeted biologic antibody treatments for severe asthma remains a big advance in the treatment of asthma. One particular area of therapeutic advance has been in reducing the need for OCS therapy in severe asthma by these biologic therapies. The current development of other biologics such as the anti-TSLP and the anti-IL-33 antibody represents further development as they block the effect of these alarmins, TSLP and IL-33, produced by epithelial cells interacting with environmental factors such as allergens, pollutants, and infectious agents. Patients with severe, uncontrolled asthma who received tezepelumab, a monoclonal antibody to TSLP,

had fewer exacerbations and better lung function, asthma control, and health-related quality of life than those who received placebo irrespective of the blood eosinophil counts.^[145] Thus, these may be targeting not only T2-mechanisms but also non-T2 mechanisms. Once these non-T2 pathways that may be driving severe asthma are defined, specific therapies can be developed to treat patients with non-T2 phenotype. The failure of some non-T2 targeted therapies such as anti-IL-17 or anti-tumor necrosis factor antibody treatments may have resulted from inadequate selection of asthma phenotype. Further advances will result from the application of precision medicine to severe asthma, which is bringing the right treatment to the right patient.^[9] The introduction of these efficacious treatments raises the issue as to whether these may represent disease modifying treatments, particularly if introduced earlier at the onset of severe asthma. Therefore, the best time to introduce these treatments for severe asthma with respect to the available treatments needs to be determined. The future looks very promising for severe asthma.

Funding

SG, JY and KFC are supported by the Sanming Project of Medicine in Shenzhen “Integrated Airways Disease Research Programme” (No. SZSM201612096). PD, HA-W, PB, and KFC are supported by UK Research Innovation projects (No. MRC MR/T010371/1; EPSRC: EP/T003189/1).

Conflicts of interest

KFC has received honoraria for participating in Advisory Board meetings of GSK, AstraZeneca, Roche, Novartis, Merck, Boehringer Ingelheim, TEVA and Shionogi regarding treatments for asthma, chronic obstructive pulmonary disease and chronic cough and has also been remunerated for speaking engagements. PHP has received honoraria for participating in Advisory Board meetings of GSK and AstraZeneca, regarding treatments for asthma and has also been remunerated for speaking engagements. Other authors have no conflicts of interest to declare.

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How to cite this article: Chung KF, Dixey P, Abubakar-Waziri H, Bhavsar P, Patel PH, Guo S, Ji Y. Characteristics, phenotypes, mechanisms and management of severe asthma. *Chin Med J* 2022;135:1141–1155. doi: 10.1097/CM9.0000000000001990