A Comprehensive Guide to Obstructive Airway Diseases

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By

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Cambridge
Scholars
Publishing

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This book first published 2026

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-1-0364-6762-3
ISBN (Ebook): 978-1-0364-6763-0

Govt. Medical College, Kozhikode, South India

This book is dedicated to our alma mater, *Government Medical College, Kozhikode*. It was here that the foundations of medical science were firmly laid in our young, eager minds, shaping our thinking and guiding us on our professional journey. The values and knowledge imparted by this esteemed institution have been instrumental in helping us reach our current position.

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PREFACE

Over the past decade, advancements in research have significantly deepened our understanding of the pathophysiology underlying airway diseases. This enhanced knowledge has paved the way for clinicians to develop and implement targeted therapies for conditions such as asthma and chronic obstructive pulmonary disease (COPD). Consequently, the management strategies for these diseases have undergone a transformative shift, presenting both new opportunities and challenges for practising physicians.

The book *Airway Diseases: A Comprehensive Guide to Obstructive Airway Diseases* is designed to serve as an all-encompassing resource for clinicians, researchers, and students engaged in the care of patients with obstructive airway conditions. By integrating insights from both aetiology and pathophysiology, this guide offers a multidisciplinary perspective that is essential for the understanding and effective management of airway diseases.

We dwelled upon this subject to review the newer aetio-pathological basis of these diseases and to provide a detailed and up-to-date guide that reflects the current best practices and emerging trends in the diagnosis and management of obstructive airway diseases. Each chapter deals with different airway diseases, their diagnostic approaches, and therapeutic options.

The authors recognise that the diagnosis and treatment of airway diseases can be complex and challenging, especially diseases like bronchiectasis and bronchiolitis. Therefore, focus is given to presenting the material in a clear and accessible manner, with practical insights and illustrations that underscore key points. The integration of multidisciplinary perspectives ensures that readers gain a holistic understanding of various airway diseases, which is essential for optimising patient outcomes.

The authors explore the impact of identifying the phenotypes and endotypes of airway disorders and biomarkers responsible for identifying these entities. This will help in patient-centred approaches to managing these diseases. By highlighting these areas, we hope to inspire continued innovation and collaboration in the field.

As you read through this book, we encourage you to consider how the guidelines and recommendations presented can be applied in your practice. Our ultimate aim is to empower healthcare professionals with the knowledge and tools needed to improve the lives of patients with obstructive airway diseases. We are confident that this book will be a valuable addition to your professional library and a reliable reference for years to come.

We extend our deepest gratitude to all our colleagues and students from whom we could gather more insights and experiences. Their encouragement is the inspiration for this work.

Sincerely,
Ravindran Chetambath,
Professor & Senior Consultant in Pulmonology

Gayathri Karedath
Specialist in Pulmonology

CHAPTER 1

OVERVIEW OF OBSTRUCTIVE AIRWAY DISEASES

Introduction

Obstructive airway diseases are a diverse group characterised by reductions in airflow at any level of the bronchial tree due to intrinsic airway narrowing. Many obstructive diseases of the lung result from narrowing (obstruction) of the smaller bronchi and bronchioles, often because of excessive contraction of the smooth muscles. It is generally characterised by inflamed and easily collapsible airways and airflow obstruction. Obstructive airway diseases include chronic obstructive pulmonary disease (COPD), Asthma, Bronchiectasis, and Bronchiolitis (Table 1). Although COPD shares similar characteristics with all other obstructive lung diseases, they are distinct condition in terms of disease onset, frequency of symptoms, and reversibility of airway obstruction. Cystic fibrosis is also sometimes included in obstructive pulmonary diseases. Symptomatic similarity between different obstructive airway diseases makes diagnosis and effective management difficult. Diagnosis of obstructive disease is based on several factors, depending on the type of disease. Spirometry and imaging are widely used for the diagnosis. However, one common factor between them is an FEV1/FVC ratio less than 0.7, i.e., the inability to exhale 70% of their breath within one second. Chronic obstructive pulmonary disease is mainly a combination of chronic bronchitis and emphysema, but may be more or less overlapping with all other conditions. Modern technologies can enable the identification of important biomarkers for efficient disease endotyping and subsequent development of precision medicine for obstructive airway diseases.

Condition	Main site	Major changes	Causes	Symptoms
Asthma	Bronchus	Smooth muscle hyperplasia Excessive mucus Inflammation Constriction	Immunologic or idiopathic	Episodic wheezing, cough, and dyspnea
Chronic bronchitis	Small airways	Hyperplasia and hypersecretion of mucous glands	Tobacco smoking and air pollution.	Productive cough
Emphysema	Parenchyma	Enlargement of the airspaces distal to the terminal bronchiole	Tobacco smoking, air pollution, and genetic factors.	Progressive dyspnoea
Bronchiectasis	Bronchus	Dilation and scarring of airways	Persistent severe infections	Cough, purulent sputum, and fever
Cystic Fibrosis	Medium-sized airways and parenchyma	Dilatation, increased secretions, Mucus plugging, Collapse	Persistent infections and colonization	Cough, breathlessness
Bronchiolitis (subgroup of chronic bronchitis)	Bronchiole	Inflammatory scarring and bronchiolitis obliterans	Idiopathic, Tobacco smoking, and air pollutants.	Cough, dyspnea

Table 1.1: Main obstructive airway diseases describing the pathophysiology and symptoms

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic progressive disorder characterised by air flow limitation. It comprises chronic bronchitis and emphysema. Chronic bronchitis is predominantly an airway disease with inflammation and obstruction of small airways, presenting with symptoms such as cough and sputum production. Emphysema is essentially a parenchymal disease characterised by enlargement of airspaces distal to the terminal bronchioles. There is destruction of the alveolar wall with loss of elasticity and air trapping. Both diseases are irreversible and progress slowly, leading to deterioration of respiratory function.

Prevalence

A study from Nigeria in 2002 and a study from South Africa in 2009 reported the prevalence of airway obstruction as 9.3% and 26 %, respectively.[1,2] In the USA, the prevalence of bronchial obstruction based on a fixed pre-bronchodilator ratio has been reported to be about 20.9 %[3]. Globally, the prevalence of airway obstruction is estimated to be between 9 and 24 % in the 40-year-old and above age group. Based on a more appropriate definition for the younger population to diagnose COPD, the prevalence was 2.1 % in the general population and 3.2 % among those aged 40 years and above.[4,5] COPD is more frequent in men than in women, as per many studies from developed countries[6]. Smoking is the prime risk factor for COPD; other known risk factors are exposure to biomass, pulmonary tuberculosis, and HIV infection.

Pathophysiology

Chronic obstructive pulmonary disease (COPD) is a disease of pulmonary inflammation and poorly reversible airflow obstruction. It is caused by an immune response to long-term inhalation of particles and gases. Cigarette smoking and other noxious inhalants cause inflammation in the small airways of all individuals. The immune system has an innate defence system against these toxins. An epithelial barrier provides a physical blockade to foreign materials entering the body through the lungs. Mucociliary clearance removes many inhaled particles that make it past the upper airways. An acute inflammatory response to these foreign molecules removes pathogens from causing further damage. But this response has no memory. The humoral and cellular components of the immune system develop slowly but produce memory of these previous injuries. The tissue

is healed through microvascular changes and the addition of connective tissue matrix. Both the lung parenchyma and airways are typically affected by this inflammation and remodelling. Differing mechanisms of injury and recovery may lead to chronic bronchitis, emphysema, and bronchiolitis.[7] COPD patients have increased numbers of neutrophils, macrophages, and T lymphocytes (CD8 > CD4) in their lungs. These inflammatory cells release several cytokines and chemotactic factors that cause further inflammation. Macrophages, neutrophils, and epithelial cells release leukotriene B4, which attracts additional neutrophils and T cells. Chemotactic factors such as CXC chemokines, interleukin (IL)-8, and growth-related oncogene α are produced by macrophages and epithelial cells that stimulate cellular migration. Additional proinflammatory cytokines such as tumour necrosis factor α (TNF-α), IL-1β, and IL-6 are released, which further worsen the inflammatory injury. Growth factors such as transforming growth factor β release connective tissue growth factor, which causes scarring and subsequent fibrosis of the lung.[8] Environmental toxins, such as the free radicals in cigarette smoke, produce oxidative stress. In addition to causing the inflammation described earlier, this oxidative stress releases proteases and inactivates several antiproteases. Neutrophils release elastase, cathepsin G, and protease [9], whereas macrophages release cysteine proteases, cathepsins E, A, L, and S, and matrix metalloproteases such as MMP-8, MMP-9, and MMP-12. When these proteases are activated, they cause alveolar wall destruction, mucous hypersecretion, and abnormal tissue repair. Antiproteases typically protect lung tissue and include α1-antitrypsin (AAT), secretory leucoprotease inhibitor, and tissue inhibitors of metalloproteases, which are inactivated. Long-term inflammation causes metaplasia of the bronchial epithelial goblet cells through inflammation, oxidative stress, protease imbalance, and signal transduction pathways. There is hypertrophy and hyperplasia of submucosal bronchial glands. These obstruct airflow and accelerate the decline in lung function, leading to an increase in acute exacerbations. The biochemical properties of the excreted mucus change, making it mucus plugs. These mucus plugs block the airways and cause constant colonisation of the airway with bacterial pathogens[9]. The amount of sputum production has been shown to correlate with forced expiratory volume in the first second of expiration (FEV1).[5,6] Patients with chronic bronchitis have lower quality-of-life scores and worse physical limitations.

The main areas of airflow obstruction occur at the airways that are less than 2 mm in diameter, or the 4th to 12th generation of bronchi. [7] The narrow diameter of these airways causes inhaled irritants to collide with the bronchial walls and cause damage.[10] These airways show mucus plugs.

They have increased numbers of neutrophils, macrophages, CD4 cells, CD8 cells, B cells, and lymphoid follicles. Thickening of the airways and the number of lymphoid follicles has been shown to correlate with disease progression.[7] There is both narrowing and a loss of terminal bronchioles. The reduced number and the smaller diameter of airways decrease the total cross-sectional area for airflow, increasing resistance to airflow. This airway destruction of the terminal bronchioles tends to predate the emphysematous changes seen in the alveoli.[11,12,13] The emphysematous tissue results in a decreased number of alveolar walls attached to the terminal bronchioles. This can reduce airway patency, making the airways close during expiration, causing obstruction.[10] On pathology, respiratory bronchiolitis is seen with an increase in macrophages in the lumen of the respiratory bronchioles and alveolar spaces. They contain finely granular golden-brown pigment.

Pulmonary hypertension is an important comorbidity of COPD as it is linked to mortality and morbidity. This typically develops late in the course of COPD. Chronic hypoxia causes pulmonary arterial constriction.[8] There is intimal thickening of the arteries adjacent to the bronchioles due to smooth muscle proliferation and deposition of elastin and collagen. These arteries are unable to dilate fully in response to exercise, acetylcholine, or increases in airflow.[14] Long-term smoking is associated with a decrease in nitric oxide response, further reducing arterial vasodilatation in COPD.

α1-Antitrypsin (AAT) deficiency is present in 1% to 2% of COPD patients.[15] About 60% of those with AAT deficiency develop airflow obstruction.[16] The severity of obstructive lung disease is variable, suggesting that the environment and modifier genes are also clinically important.[15] AAT is a protease inhibitor encoded by the SERPINA1 gene[17] on chromosome 14q32. It is synthesised in the endoplasmic reticulum of liver hepatocytes and then released into the bloodstream. It protects tissue from the enzymes released during inflammation, notably the protease neutrophil elastase. Its levels rise 3 to 5 times in acute inflammation. Symptoms of the disease typically develop between 20 and 40 years of age.

Pathophysiology of COPD exacerbations

COPD exacerbations may be caused by bacterial or viral infection, air pollution, and changes in the weather. They are associated with an increased number of neutrophils and sometimes increased eosinophils in the lungs. Inflammation in the lungs may cause oedema, mucus hypersecretion, and bronchoconstriction. This, along with respiratory muscle fatigue, may

worsen gas exchange. Worsening oxygenation may lead to worsening perfusion due to autoregulation of the pulmonary vasculature. This may increase pulmonary vasculature pressures and lead to right ventricular volume overload. Respiratory muscle fatigue and diminished alveolar ventilation from obstruction also cause worsening hypercapnia and respiratory acidosis and eventually may lead to death.

Asthma

Asthma is a chronic inflammatory condition affecting the airways and is characterised by symptoms of intermittent dyspnea, cough, and wheezing. Asthma often presents in childhood, and the development involves a complex interplay of genetic and environmental factors associated with atopy. Despite treatment advancements, disparities persist in asthma care, with variations in access to diagnosis, treatment, and patient education across different demographics. The most substantial known risk factor is atopy, which is characterised by the genetic tendency to produce specific immunoglobulin E (IgE) antibodies in response to common environmental allergens. Nearly one-third of children with atopy will develop asthma later in life.

Pathogenesis

Asthma is induced by mixed airway inflammation. It is classified into Th2-high and Th2-low asthma. Patients can have Th2-high asthma and Th2-low asthma concurrently.

Th2-High Asthma

Th2 cells are a distinct lineage of $CD4^+$ effector T cells that secrete interleukin (IL)-4, IL-5, IL-13, and IL-9. More than 50% of asthma is induced by Th2-dependent inflammation [18]. When allergens enter the airways, antigen-presenting cells process and present the allergens to Th2 cells, which secrete Th2 cytokines, including IL-5, IL-4, and IL-13. IL-4 and IL-13 activate B cells, which produce IgE and bind to FcεRI of mast cells (Figure 1). When the same allergens enter the airways for the next time, they bind to IgE, which induces mast cells to release mediators, such as leukotrienes (LTs), histamine, and ILs. Allergens also act on cholinergic nerves to release acetylcholine. These mediators and neurotransmitters irritate

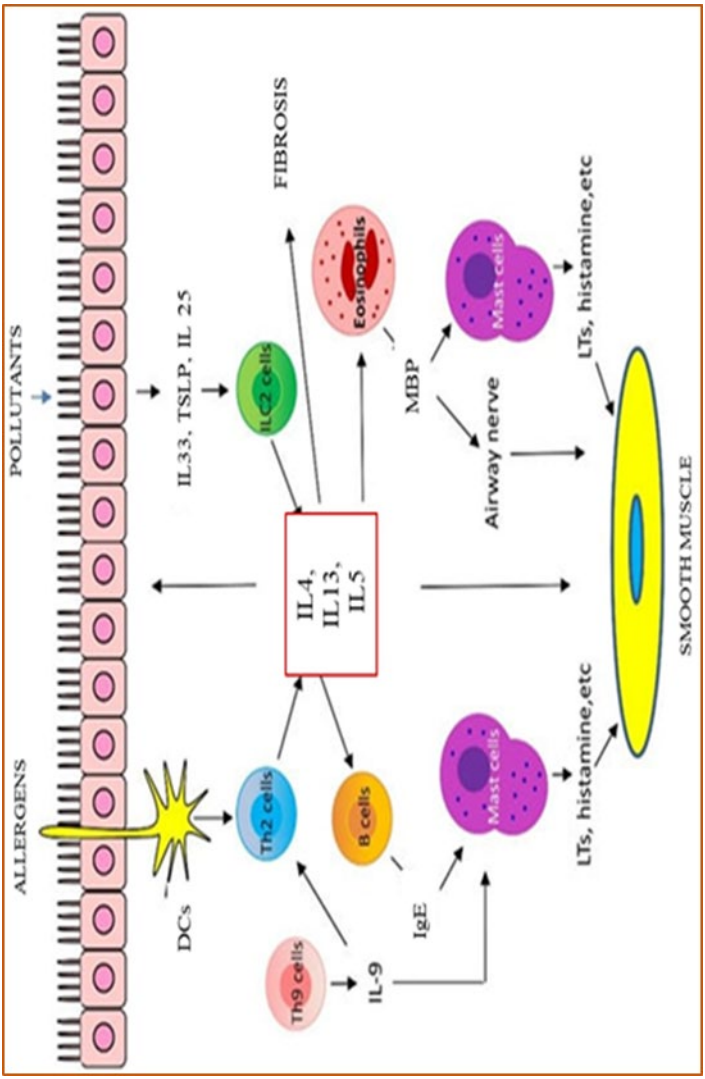

Figure 1.1: Pathogenesis of T2 High Asthma (Inflammatory Cascade)

airway smooth muscle and induce bronchoconstriction[19]. In addition, IL-5 induces eosinophil production, maturation, and recruitment to the lungs[20]. Eosinophils release mediators, like major basic protein (MBP), which stimulate mast cells to release histamines and LTs. MBP also inhibits M_2

receptor, promotes acetylcholine release from cholinergic nerves, and induces bronchospasm [21]. IL-13 directly sensitises airway smooth muscle contraction, stimulates epithelial cells to secrete mucins, and induces fibrosis [22].

Recent studies demonstrated that the airway epithelium produces cytokines in response to injury, infection, and pollutants. These epithelial-derived cytokines include thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. TSLP, IL-25, and IL-33 activate type 2 innate lymphoid cells (ILC2), which generate Th2 cytokines, such as IL-5 and IL-13, and induce Th2 lung inflammation [18]. Additionally, there is evidence to suggest that IL-33 may directly affect mast cell activation, airway smooth muscle migration, and asthma phenotype [23]. Natural killer T (NKT) cells are a distinct subset of lymphocytes that are abundant in the lungs as well as lymphoid organs. It was proposed that NKT cells secrete IL-4 and IL-13 or facilitate Th2 cells to increase production of IL-4 and IL-13 [24]. However, other studies do not support this notion[25].

One of the targets of Th2 cytokines is periostin, a matricellular protein that is dynamically expressed as a non-structural protein present in the extracellular matrix. Periostin expression is upregulated by IL-4 and IL-13 in cultured bronchial epithelial cells and bronchial fibroblasts[26] and is one of the most differentially expressed bronchial epithelial genes between asthmatic patients and healthy control subjects [27]. The role of periostin in asthma is still under investigation. There are reports to suggest that periostin supports adhesion and migration of IL-5-stimulated human eosinophils and Th2 inflammation in asthma [28]. On the other hand, other studies suggest that periostin plays a protective role, rather than a detrimental role, in asthma. Periostin positively regulates TGF-β production, which promotes T-regulatory cell differentiation. Differentiated T cells inhibit airway inflammation and IgE production[29].

Th2-Low Asthma

IL-17 has been proposed to play an important role in Th2-low asthma[30]. Variants in the IL-17 pathway genes may be related to asthma pathology[31]. Higher levels of IL-17 are found in serum, sputum, and bronchoalveolar lavage fluid (BALF) of patients with asthma, which is associated with asthma severity[30]. There are several cell types secreting IL-17 cytokines. $CD4^+$ Th17 cells are one of the major sources of IL-17. Other cellular sources include major histocompatibility complex class I-restricted $CD8^+$ T-cells, Natural killer T cells, mucosal-associated invariant T (MAIT) cells,

ILC3 cells, and B-cells [32].

The role of IL-17 cytokines in asthma is still under investigation. IL-17 cytokines may stimulate epithelial cells and fibroblasts to release neutrophil chemoattractants CXCL1/5/8 and granulocyte–macrophage colony-stimulating factor, which recruit neutrophils to the lungs. Furthermore, IL-17A, but not IL-17F, enhances airway smooth muscle contraction, migration[33], and proliferation[34], which facilitates airway hyperresponsiveness (AHR) and airway remodelling, key characteristics of asthma. However, it has been proposed that IL-17 cytokines are important for maintaining the integrity of the epithelium, and IL-17 cytokines may play a protective role against asthma [32].

Th2-High-Related Biomarkers

1. Sputum Eosinophils

Eosinophils in induced sputum provide important information on asthma phenotyping and understanding of asthma pathophysiology [35]. Increased sputum eosinophil levels (>3%) have been associated with high airway inflammation, frequent asthma exacerbation, and poor asthma control [36].

2. Blood Total Eosinophil Count (TEC)

TEC has also been considered as a non-invasive biomarker for eosinophilic inflammation [35,37]. The use of blood eosinophil counts as a diagnostic biomarker for airway eosinophilia has been evaluated by assessing the relationship between blood and sputum eosinophil counts[38]. TEC increases $\geq 0.30 \times 10^9$/L when Th2 lung inflammation and asthma exacerbations occur. If a blood count is $<0.15 \times 10^9$/L, sputum eosinophilia may not be found, especially when FeNO is low (<25 ppb)[39]. However, higher TEC is also seen in patients with atopic dermatitis and other allergic diseases. Thus, eosinophilia is not a specific marker of Th2 low airway inflammation. These caveats prompt physicians to use FeNO measurement, which is associated with airway inflammation [40].

3. Serum IgE

Serum IgE is an immunoglobulin that induces type 1 hypersensitivity reactions and anaphylaxis. As described earlier, IgE also plays a key role in the pathogenesis of allergic asthma. Elevated IgE levels are correlated with asthma[41]. There is an association between IgE levels, skin testing, and lung function in asthmatics. Clinical studies show that asthmatics have an inverse

relationship between IgE and FEV1/FVC ratio[42]. Various clinical trials have used IgE as a biomarker to identify Th2-high asthma. Omalizumab, a recombinant human anti-IgE antibody that binds to circulating IgE at the IgE receptor binding site, blocks the activation of the mast cells and basophils. A large phase III study that recruited over 500 patients with asthma found that IgE levels ranged from 30 to 700 IU/mL. Treatment with Omalizumab was able to reduce exacerbation rates and improve quality-of-life scores [43]. However, a Cochrane review published in 2014 on the use of omalizumab questions whether there is a clear threshold level of IgE for optimal efficacy. The authors note a wide variation in the mean serum IgE levels of patients included in clinical trials, ranging from 141.5 to 508.1 IU/mL[44].

4. Nitric Oxide

Nitric oxide is produced by airway epithelial cells as a result of IL-13 induced upregulation of nitric oxide synthase in the airway epithelium and is, therefore, a more specific marker of Th2 airway inflammation [45]. FeNO is a reproducible, easily measurable biomarker, indicative of AHR and a good predictor of inhaled corticosteroid (ICS) response [46]. FeNO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously, considering the clinical context. FeNO greater than 50 ppb (>35 ppb in children) can be used to indicate eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroid treatment. However, FeNO may be affected by several confounders, including demographics, smoking, diet, nasal polyps, and atopic status[47]. Although most patients with raised FeNO respond to corticosteroids, some patients are resistant to corticosteroid treatment. Their FeNO is not suppressed, and they have high Th2 cytokines and chemokines in sputum [40]. However, FeNO level is a useful indicator of Th2-high asthma and helps to use appropriate doses of inhaled ICS [48].

5. Periostin

Periostin is upregulated by recombinant IL-4 and IL-13 in cultured bronchial epithelial cells and bronchial fibroblasts [26,27,49]. Periostin is proposed as a surrogate marker of Th2 inflammation. Serum periostin levels are significantly higher in asthmatic patients with eosinophilic airway inflammation. A logistic regression model, including sex, age, IgE levels, blood eosinophil numbers, body mass index, FeNo levels, and serum periostin levels, in 59 patients with severe asthma, showed that the serum periostin level was the best predictor of airway eosinophilia [50].

6. Cytokines

Levels of IL-4, IL-5, and IL-13 in sputum and BALF are higher in asthmatics. TSLP, IL-33, and IL-25 in epithelium are elevated in asthmatic patients[49]. These cytokines are the gold standard biomarkers for Th2-high asthma in clinical research. However, it may not be feasible for routine practice because of high costs.

These Th2-high biomarkers are being used to choose adequate biologic therapy and monitor the patients' response to asthma treatment. For instance, higher levels of FeNO, blood eosinophils, and serum periostin (Th2-high asthma) are indications for the use of the IgE antibody Omalizumab. Omalizumab treatment reduces asthma exacerbation rates and improves quality of life for this group of patients [43]. Lebrikizumab is an IgG4 humanised monoclonal antibody that specifically binds to IL-13 and blocks its function. Lebrikizumab administration was able to improve lung function. Patients with higher pretreatment levels of serum periostin had greater improvement in lung function with lebrikizumab[51]. Despite ICS therapy and an additional controller, some patients still had uncontrolled asthma. Lebrikizumab administration reduced the exacerbation rate by 60% compared with a placebo in periostin-high patients and by 5% in periostin-low patients. However, lebrikizumab administration did not lead to clinically meaningful placebo-corrected improvements in asthma symptoms or quality of life [52].

Th2-Low-Related Biomarkers

1. Sputum Neutrophils

Th2-low asthma includes late-onset asthma in middle-aged females, obesity-associated asthma, smoking-associated asthma, infection-associated asthma, and ozone-associated asthma[53]. Another common feature seen in Th2-low asthma is poor response to inhaled and oral corticosteroids [54]. Using induced sputum coupled with cytology, patients with Th2-low asthma are classed as pauci-granulocytic and neutrophilic. In healthy subjects, neutrophils and macrophages are the major leukocytes in the induced sputum (median neutrophil percentage 37%). Cigarette smoking, ozone, infection, and endotoxin all increase sputum neutrophil counts. In asthma patients, sputum neutrophil count increased to 40–76%.[53]

2. IL-17

As described earlier, IL-17 promotes neutrophilic inflammation in asthmatics. IL-17 levels in induced sputum, BALF, and bronchial biopsies are increased in severe asthma [30]. Due to technical challenges and costs, measurement of sputum IL-17 has not been widely used to characterise asthma phenotype.

3. Other Potential Biomarkers

TNF-α and IFN-γ contribute to the progression of Th2-low asthma [18]. IL-6 and C-reactive protein have been linked to severe asthma [53]. More studies are required to assess whether these potential biomarkers are practical in clinical settings.

Genetic Risk for Asthma Development and Treatment

GWAS have implicated genetic variants in developing asthma. In particular, childhood asthma is associated with the 17q21 locus alleles. Polymorphisms of 17q21 are associated with an increased risk of exacerbations in children with asthma, despite ICS use. Single-nucleotide polymorphism (SNP) rs7216389 frequency was higher in East Asians, African Americans, and Hispanics, compared to patients of European ancestry[55]. In addition, the *ORMDL3* gene is located at the 17q21 region and plays an important role in asthma pathogenesis [56, 57]

In addition to genetic risk, many environmental factors are also important risks for asthma, although most experts do not consider environmental risks to be "biomarkers' for asthma. Allergens (e.g., house dust mite, pollen), pollutants, bacteria, viruses, and fungi are well-known environmental risks for asthma[58]. Exposure to different environmental factors may affect different mechanisms and asthma progression. For example, IL-17A is a potential mediator to link Candida albicans sensitisation and poor outcomes for asthma [59].

Phenotypes of Th2-High Asthma

Phenotypes of Th2-high asthma are classified into three groups: early-onset allergic asthma, late-onset eosinophilic asthma, and aspirin-exacerbated respiratory disease (AERD) [60].