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The Role and Immunobiology of Eosinophils in the Respiratory System: a Comprehensive Review

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Abstract The eosinophil is a fully delineated granulocyte that disseminates throughout the bloodstream to end-organs after complete maturation in the bone marrow. While the presence of eosinophils is not uncommon even in healthy individuals, these granulocytes play a central role in inflammation and allergic processes. Normally appearing in smaller numbers, higher levels of eosinophils in the peripheral blood or certain tissues typically signal a pathologic process. Eosinophils confer a beneficial effect on the host by enhancing immunity against molds and viruses. However, tissue-specific elevation of eosinophils, particularly in the respiratory system, can cause a variety of short-term symptoms and may lead to long-term sequelae. Eosinophils often play a role in more commonly encountered disease processes, such as asthma and allergic responses in the upper respiratory tract. They are also integral in the pathology of less common diseases including eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, and drug reaction with eosinophilia and systemic symptoms. They can be seen in neoplastic disorders or occupational exposures as well. The involvement of eosinophils in pulmonary disease processes can affect the method of diagnosis and the selection of treatment modalities. By analyzing the complex interaction between the eosinophil and its environment, which includes signaling molecules and tissues, different therapies have been discovered and created in order to target disease processes at a cellular level. Innovative treatments such as mepolizumab and benralizumab will be discussed. The purpose of this article is to further explore the topic of eosinophilic presence, activity, and pathology in the respiratory tract, as well as discuss current and future treatment options through a detailed literature review.

Keywords Eosinophil · Respiratory system · Intrinsic asthma · Extrinsic asthma · Severe Asthma · Acute eosinophilic pneumonia · Chronic eosinophilic pneumonia · Eosinophilia · Asthma phenotype · Asthma endotype · Allergic bronchopulmonary aspergillosis

Introduction

The eosinophil is an end-stage granulocyte derived from primordial stem cells in the bone marrow and is known to circulate through the peripheral bloodstream and tissues. While normally appearing in smaller numbers in healthy people, eosinophils play a central role in inflammation and allergic processes [1–3]. Known for its characteristic appearance after staining processes with acid aniline dyes, the eosinophil is composed of many granules containing enzymes and proteins [4]. Concentration of these cells varies throughout the day and night in the bloodstream. Typically, eosinophil levels will be elevated in the evening and lowest in the morning [5]. Half-life in serum is about 8 to 18 h [3]. Degree of eosinophilia in the peripheral blood can be defined according to the absolute eosinophil count (AEC). Normal absolute eosinophil levels in the serum may be as high as 499 cells/μL. Eosinophilia can be graded into three categories of severity, ranging from mild (500 to 1500 cells/μL), to moderate (1500 to 5000 cells/μL), to severe (greater than 5000 cells/μL). Certain disease processes are associated with increased levels of eosinophils in the peripheral

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bloodstream, sputum, and tissues [5]. Elevated levels of eosinophils may correlate with the protective mechanism of the body against asthma, allergies, atopic dermatitis, parasitic infections, gastrointestinal disorders, and other more rare diseases [1, 2, 5]. There is evidence that eosinophils may enhance immunity via an antiviral effect, as seen in experimental mice models in association with various respiratory viruses [6]. Eosinophils may also encourage clearance of molds, such as aspergillus [7].

Pulmonary eosinophilic processes involve elevated levels of eosinophils in the peripheral blood stream, mucosal fluid, and/or respiratory tissues [8–10]. Eosinophil recruitment and production is due to Th2 lymphocyte stimulation, with the help of cytokines including IL-3, IL-4, IL-5, IL-13, and granulocyte macrophage colony-stimulating factor (GM-CSF) [3]. According to Stone et al., these interleukins function in different ways. IL-4 and IL-13 stimulate immunoglobulin (Ig) E production and promote eosinophil recruitment by increasing expresssion of eotaxin (CCL11 and CCL26) and endothelial cell vascular cell adhesion molecule 1 (VCAM1). IL-5 mediates enhanced eosinophil production, eosinophil egress from the bone marrow, and eosinophil activation and survival. This cytokine is specific to eosinophil development but is not responsible for fostering eosinophil infiltration of specific tissues. Precursors to eosinophils reside in the bone marrow and have the potential to differentiate into either basophils or eosinophils. It is only after pluripotent stem cells express IL-5 receptor, CD34, and CCR3 that they are designated to eosinophil development. IL-5 receptor expression is specific for eosinophil differentiation as it is almost exclusively exhibited on eosinophils. Most eosinophils that enter circulation from the bone marrow traffic to specific tissues and never return to circulate in the peripheral bloodstream. The process of extravasation through vascular endothelium is aided by a system of molecules that function in chemotaxis and adhesion. These include α4 (CD49d) and β2 (CD18) integrins as well as CC chemokines (CCL11/eotaxin) [5]. The CC chemokine family is essential for promoting eosinophil trafficking to areas of inflamed tissue. This is a result of eosinophils highly expressing CCR3, a receptor that binds eosinophil-specific chemokines, including eotaxin, eotaxin-2, monocyte chemoattractant protein (MCP-3, MCP-4), and regulated on activation, normal T cell expressed and secreted (RANTES or CCL5) [11]. The process of eosinophils trafficking to tissues is thought to be overseen by T cells responding to antigen-presenting cells. In healthy individuals, mucosal surfaces of the lower gastrointestinal tract, thymus, and uterus are the major targets for eosinophil tissue migration. However, when inflammation regulated by Th2 cells is present, eosinophils will home to other organs including the lungs and skin. Once trafficking to tissues is complete, the eosinophil attaches to extracellular matrix protein, fibronectin, which binds the eosinophil to specific tissues. Subsequently, the eosinophil receives a signal to degranulate and releases the preformed components of its granules, such as major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO), as well as cytokines and chemokines [5]. The cytokines and chemokines released promote longevity of eosinophils in tissues, which leads to the cyclical nature of signaling, activation, and survival. Additionally, these proteins target any foreign antigen, promote inflammation to the area, and may cause significant damage to surrounding structures [2, 3, 5]. For example, eosinophils have the ability to perform collagen degradation through the use of a self-contained protease [12]. Another mode of eosinophilic toxicity includes oxidative damage to normal cells by release of oxygen radicals and other oxidants by EPO [13, 14]. Lastly, MBP, one of the polypeptide components of the preformed granules, is gravely harmful to airway endothelial cells and the tracheal lining [15–17].

The topic of eosinophilic presence, activity, and pathology in the respiratory tract will be explored in the following sections. Table 1 displays the differential diagnosis of respiratory diseases resulting from eosinophilia.

Primary Causes

Idiopathic Acute Eosinophilic Pneumonia

Lung disease and injury secondary to eosinophils in the respiratory system are generally characterized by abnormal findings on imaging modalities. These conditions are typically associated with elevated levels of eosinophils in the blood, sputum, and lung tissue. One such disease is eosinophilic pneumonia, which can be divided into two distinct categories: acute and chronic. Acute eosinophilic pneumonia (AEP) is notable for diffuse pulmonary infiltrates and elevated pulmonary eosinophils in the presence of high-grade fevers and may rapidly progress to acute respiratory failure. In addition to fever, nonproductive cough, shortness of breath, fatigue, myalgias, night sweats, and pleuritic chest pain may be present [8]. Clinical exam findings include tachypnea, tachycardia, and crackles or rhonchi on lung auscultation. Radiographic findings on chest X-ray (CXR) include pulmonary edema, Kerley B lines, pleural effusions, and diffuse pulmonary infiltrates, which are more central and not characteristically seen in peripheral lung fields. Characteristic findings on computed tomography (CT) of the chest include diffuse interstitial and patchy alveolar infiltrates leading to a ground glass appearance [19]. Bilateral pleural effusions and interlobular septal thickening are distinctive of the disorder, and pulmonary lymphadenopathy may also be present (Fig. 1) [9, 19]. Pulmonary function tests may show findings consistent with restrictive lung disease with a low diffusion capacity, though

Table 1 Eosinophilic respiratory diseases

Primary and secondary causes of eosinophilic respiratory disease	
Primary causes	Secondary causes
Idiopathic acute eosinophilic pneumonia	Asthma
Chronic eosinophilic pneumonia	Hypersensitivity pneumonitis
Idiopathic pulmonary fibrosis	Aspirin-related disease
Systemic disorders	DRESS syndrome
Eosinophilic granulomatosis with polyangiitis	Heiner syndrome
Hypereosinophilic syndromes	Occupational asthma
Eosinophils in the upper respiratory tract	Infection
Nonallergic rhinitis with eosinophilia syndrome	Allergic bronchopulmonary aspergillosis
Sinonasal eosinophilic angiocentric fibrosis	Parasitic disease
	Neoplasm
	Leukemia, lymphoma, lung cancer

Source: [3, 8, 18]

the acute nature and severity of disease may limit the effectiveness of utilizing this testing for diagnosis [9].

AEP affects males twice as often as females and can occur at any age, though the average age of onset is about 30 years [20]. Patients do not typically have a previous history of asthma. The etiology of the disease is unknown, but it is thought to be associated with environmental exposures. For example, a 2002 case report by Rom et al. described AEP in a firefighter exposed to a large amount of dust (silica particles and asbestos fibers) after the collapse of the World Trade Center in New York City [21]. A case series published in 2002 characterized 22 patients with AEP, of which several had preceding inhalant antigen exposures including tobacco smoke, gasoline, tear gas, and indoor allergens such as dust. The pathological mechanism of AEP is thought to be related to cell death and inhibition of cell function. Bronchoalveolar lavage (BAL) is helpful for diagnosis, and identification of a concentration of greater than 25 % eosinophils is characteristic of the disorder [22–24]. Eosinophils may be detected in BAL of normal individuals, though the concentration is typically <2 %. A concentration of 2–25 % eosinophils in BAL is nonspecific and can be noted in conditions other than eosinophilic pneumonia, such as asthma [25]. Interestingly, eosinophils are not elevated in the bloodstream on presentation of AEP. Serum concentrations can be high later in the course of the disease, but typically only rise to a level of mild or moderate eosinophilia [20]. AEP is a diagnosis of exclusion, and other causes of acute respiratory failure such as infection or drugs must be ruled out.

While a portion of affected patients may spontaneously recover, treatment with corticosteroids and respiratory support typically leads to improvement, usually without recurrence of disease. Abnormalities on imaging studies and pulmonary function tests usually return to normal once the disease is resolved [20, 22–24].

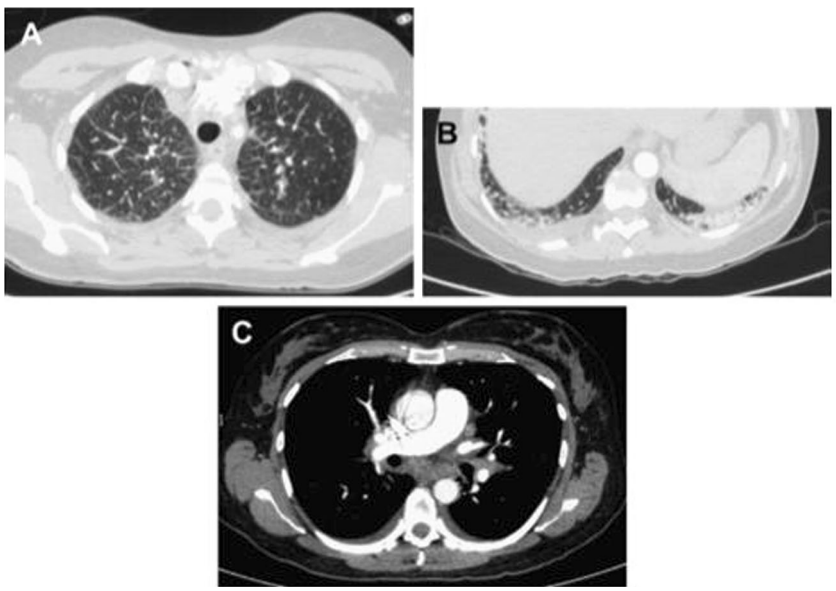

Fig. 1 CT scan of the chest of a patient with acute eosinophilic pneumonia, showing **a** interlobular thickening in the upper lung fields, **b** consolidation in the lung bases, and **c** bilateral pleural effusion and mediastinal lymphadenopathy. **a**, **b** Lung parenchymal windows. **c** Mediastinal window. Reproduced with permission from Elsevier [9]

Chronic Eosinophilic Pneumonia

First described by Charles B. Carrington in the New England Journal of Medicine in 1969, chronic eosinophilic pneumonia (CEP) is a rare disorder, with many reports of this illness being limited to case studies [26, 27]. Though the exact etiology is unknown, the disease is often associated with a high eosinophilic presence in lung tissue [8, 25, 28]. In contrast with AEP, the majority of patients with CEP have a previous history of asthma or atopy (see Table 2) [23, 25]. The presentation of CEP is variable, but tends to be a subacute or chronic course of mild symptoms [8, 25, 27]. Pulmonary and hematologic eosinophilia are typical, and imaging studies reveal peripheral pulmonary infiltrates [8, 25]. Most patients are diagnosed in their third or fourth decade of life, though CEP may present in any age group. CEP has a predilection for women with a ratio of 2:1 female to male diagnoses [23, 25]. The disease is more often seen in nonsmokers. Symptoms include cough, progressive dyspnea, chest pain, weight loss, night sweats, and fever [8, 23, 25]. Patients with CEP, unlike patients with AEP, are likely to present with a slightly elevated temperature that is less than 38 °C. Clinical exam findings include wheeze and crackles on lung auscultation in approximately 30 % of cases. About 20 % of patients will have a history of chronic sinusitis or rhinitis [23, 25]. Diagnostic criteria for CEP includes pulmonary symptoms of at least 2-week duration, eosinophilia in the lung or bloodstream, peripheral pulmonary infiltrates on imaging studies, and exclusion of other common eosinophilic lung diseases [28]. BAL eosinophil count of >40 % and blood AEC of >1000 cells/μL are typical. Blood and alveoli eosinophils may be elevated to over 5000 cells/μL and 60 %, respectively. Laboratory findings in addition to leukocytosis and peripheral eosinophilia include elevated serum IgE and markers of inflammation, such as erythrocyte sedimentation rate and C-reactive protein [23, 25]. In contrast to AEP, CEP does not progress to acute respiratory failure [28]. Characteristic imaging findings in CEP include dense, multifocal consolidations in a bilateral and peripheral distribution on CXR. This classic finding in CEP has been labeled the "photographic negative of pulmonary edema," though central consolidation can occur in up to 30 % of patients [8, 23, 25]. Findings on chest CT include bilateral consolidations and a ground-glass appearance (Fig. 2) [9, 25]. Treatment regimens include systemic corticosteroid therapy, which typically produces a favorable response and rapid improvement. The course may be relapsing and remitting in some patients, with up to 50 % of patients experiencing a relapse of symptoms one or more times after treatment [23, 25]. Management also involves good control of underlying asthma, and some patients may require long-term oral corticosteroid treatment to keep both asthma and CEP well controlled [23].

As eosinophilia is a common occurrence in both AEP and CEP, studies have examined the role of IL-5 in these disorders. A study by Okubo et al. in 1998 investigated whether IL-5 concentrations would vary in the two types of eosinophilic pneumonia. IL-5 concentrations were found to be notably higher in both BAL and peripheral blood samples in patients with AEP as compared to patients with CEP [29]. A study by Jhun et al. examined serum and BAL IL-5 levels and the correlative degree of peripheral eosinophilia during treatment of AEP in 21 patients. Elevated serum IL-5 levels were initially detected in all subjects, improved dramatically with clinical resolution, and inversely correlated with the degree of

Table 2 Comparing acute and chronic eosinophilic pneumonia

Acute vs. chronic eosinophilic pneumonia		
	AEP	CEP
Etiology	Unknown, though associated with environmental exposures	Unknown, though associated with environmental exposures
Presentation	Acute symptoms which progress rapidly	Subacute, milder symptoms
Sex	Male predominance 2:1	Female predominance 2:1
Risk	Higher incidence in smokers	Higher incidence in nonsmokers
Labs	Normal eosinophil count to mild/moderate peripheral eosinophilia	Leukocytosis, peripheral eosinophilia (absolute eosinophil count >1000 cells/μL)
BAL	>25 % eosinophils	>40 % eosinophils
Imaging	Diffuse hazy infiltrates on chest imaging	Bilateral, dense multifocal consolidation on chest imaging
Course	Rapid progression to acute respiratory failure	Indolent course which may be relapsing and remitting, without respiratory failure
Atopy	Asthma does not predispose individual	Asthma predisposes individual
Management	Systemic corticosteroids	Systemic corticosteroids

Source: [3]

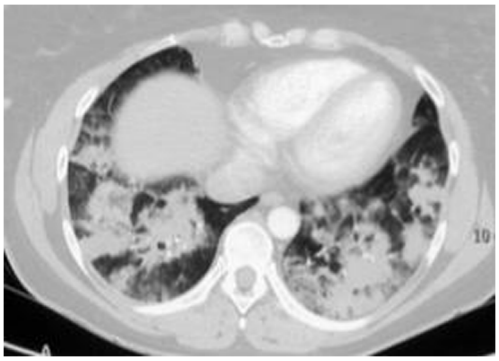

Fig. 2 Characteristic findings of CEP on chest CT demonstrating alveolar opacities with dense airspace consolidation and ground-glass opacities. Reproduced with permission from Elsevier [9]

peripheral eosinophila. The authors speculate that IL-5 is essential for eosinophilic migration to the lung and that a high serum AEC may actually signal disease recovery [30]. These studies highlight the importance of the interaction between IL-5 and the eosinophil in the pathophysiology of specific disease processes such as AEP.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is defined as a state of inflammation in the lungs that results in interstitial collagen deposition producing a fibrotic lining which ultimately leads to irreparable damage. The etiology of this disorder remains unknown [31]. IPF typically affects individuals between the ages of 60 to 80 years and is seen largely in men and cigarette smokers. Common symptoms include chronic cough, exertional dyspnea, digital clubbing, and end-inspiratory crackles at bilateral lung bases on auscultation [32–34]. IPF is often associated with eosinophilia of the blood and respiratory tract, and these findings can confer a worse prognosis. Rudd et al. noted that subjects with IPF and elevated levels of eosinophils on BAL had poor responses to treatment with corticosteroids [15]. A study by Peterson et al. examined BAL contents and found that eosinophilia may be an indicator of worsening IPF. Although neutrophils were also elevated in the BAL fluid of patients, only the degree of eosinophilia correlated with disease severity [12]. Kroegal et al. speculate that eosinophils are likely activated during the process of infiltrating or adhering to the airway in IPF [35]. The detrimental effects of eosinophils on normal airway cells involve release of toxic components including MBP, EPO, collagen-degrading protease, and oxidants. Therefore, eosinophils may play a very important role in IPF, specifically inducing more severe disease progression and hindering treatment course. Therapies for IPF are similar to other eosinophilic lung diseases and include systemic corticosteroids [15, 25]. In general, prognosis remains poor, ensuring the need for early diagnosis and initiation of treatment [32].

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a small vessel, necrotizing vasculitis that may involve antineutrophil cytoplasmic antibody (ANCA). The disease can affect multiple organ systems, but the cardinal feature is respiratory tract involvement. Eosinophils are the major player in systemic, granulomatous inflammation, and associated allergic disease includes rhinitis, nasal polyposis, and asthma. Initially described by J. Churg and L. Strauss in 1951 and defined at the 1994 Chapel Hill Consensus Conference (CHCC), EGPA was previously referred to as Churg-Strauss Syndrome. The disease was renamed by the 2012 Revised International CHCC to EGPA [9, 36]. EGPA primarily affects patients between the ages of 30 and 60 years, with no predilection for gender. The clinical course typically begins with sinusitis and asthma, followed by peripheral eosinophilia and progression to systemic vasculitis. Diagnosis is based on clinical findings, though laboratory and chest imaging studies may be of utility. The etiology of the disorder remains unknown, and treatment is largely targeted at reducing inflammation with corticosteroids and cyclophosphamide [9].

Hypereosinophilic Syndromes

The hypereosinophilic syndromes (HES) include a group of disorders characterized by severe eosinophilia and associated end-organ dysfunction, in which secondary causes for the eosinophilia have been ruled out. This topic will be covered in detail in a separate chapter. Summarily, HES involves markedly elevated and persistent blood eosinophilia (≥1500 cells/μL) that causes damage to a variety of organs. According to a study by Ogbogu et al. summarizing a large group of HES patients, the most common organ affected was the skin. Lung complications were the second most frequent complaint, followed by gastrointestinal disease, and cardiac involvement was variable. Corticosteroids remain the current gold standard of therapy. Alternative and supplemental therapies include hydroxyurea, imatinib, monoclonal antibody therapy, and interferon among others [8, 23, 37–39].

Eosinophilic Involvement in the Upper Respiratory Tract

Eosinophilic presence in the upper respiratory tract can produce a number of conditions. Two such disease processes are nonallergic rhinitis with eosinophilia syndrome (NARES) and sinonasal eosinophilic angiocentric fibrosis (EAF).

Originally described by Mullarkey et al. in 1980, NARES is a common condition characterized by perennial rhinorrhea, congestion, sneezing, and nasal pruritus. Infrequent complaints of sporadic anosmia may occur. NARES is usually seen in adults and seldomly in children and is the cause of

about one third of cases of nonallergic rhinitis. Analysis of nasal cytology exhibits >20 % eosinophils; however, skin testing and serum specific-IgE testing are negative. It is hypothesized that patients with NARES might experience a local rather than systemic IgE-mediated response to allergens [3, 40, 41]. It is also thought that NARES may be a precursor to the triad of intrinsic asthma, nasal polyposis, and intolerance to aspirin [42]. Approximately half of patients with NARES without previous lower respiratory tract symptoms have an elevated number of eosinophils in the sputum regardless of eosinophil level in nasal lavage fluid [43]. The pathophysiology of NARES is thought to involve a cyclical process of chronic nasal inflammation secondary to eosinophilia and possibly mast cell involvement. First-line therapy for NARES is intranasal corticosteroids, with adjuvant therapy involving leukotriene-receptor antagonists (LTRAs) and antihistamines [44].

EAF is a rare nonmalignant lesion in the mucosa of the upper respiratory tract often resulting in a symptomatic obstructive mass [45, 46]. EAF most commonly involves the sinuses and nasal septum, though it may occur in other tissues [47]. Case studies in the literature associate a small percentage of affected patients with a history of trauma or surgery; however, the etiology remains unknown [45]. Symptoms occur as a result of nasal obstruction with patient reported nasal fullness, watery eyes, and proptosis [48]. EAF is more commonly seen in middle-aged women and the diagnosis is made histologically. Characteristic findings include infiltration of eosinophils and other secondary inflammatory cells in a perivascular distribution, which eventually leads to fibrosis of the tissue. Bundles of collagen surround blood vessels, resulting in an appearance likened to "onion-skin" [47]. Treatment involves surgical resection, with occasional adjuvant use of intranasal corticosteroids [45].

Secondary Causes

Asthma

Commonly encountered in children and adults alike, asthma is a multifaceted condition with variability in symptomatology, clinical course, associated illnesses, and response to treatment. Since it was first recognized, asthma has been regarded as a complex disorder involving chronic, reversible, and variable airflow obstruction as a result of bronchial inflammation. A common theme in diagnosis, however, is the recognition that patients with asthma may not exhibit all of the aforementioned features [49]. The purpose of this section will be to examine the pathophysiology and characteristics of asthma, with special emphasis on the role of the eosinophil in the disease process.

Pathophysiology

The pathophysiology of asthma involves a variety of changes at the cellular level, due to the activity of eosinophils, mast cells, neutrophils, and T lymphocytes [3]. Acutely, allergen binds specifically to IgE, which initiates a cascade of inflammation and activation of inciting biomarkers. Eosinophils, mast cells, and Th2 lymphocytes migrate to the area in response to specific cytokines including IL-3, IL-4, IL-5, IL-9, and IL-13 [50]. Mast cells contribute to the release of acute-phase mediators and cytokines, which promote deleterious effects to healthy tissue. Eosinophils release cytokines, growth factors, and leukotrienes which cause further inflammation and produce the characteristic and recurrent symptoms of the disorder, including hyperreactivity in response to various provocative factors. With time, swelling and deposition of inflammatory cells, mucus, and debris ultimately denude the epithelium of the airway. Smooth muscle hypertrophy and neovascularization occur as a form of remodeling, mostly to detrimental effects as they cause airway wall thickening. Additionally, deposits of collagen promote constriction and obstruction [3, 50–52].

Asthma Classification: Phenotype vs. Endotype

Due to the variability of asthma, the question arises as to whether it is a single disease with inconsistent presentation or several related diseases with a common feature of airflow obstruction. This issue sparked the phenotype and endotype movement for asthma classification. The phenotype model of asthma refers to observable clinical and physiological characteristics which describe the varying presentations of the disorder. These phenotypes can be used to help predict treatment response. One limitation to this model is that phenotypes are typically unable to provide answers in terms of etiology of the underlying mechanism causing asthma [49]. For example, different pathogenic mechanisms might cause similar asthma symptoms and may all occur in a certain phenotype. Asthma as a disease process is related to a multitude of factors, which produce symptoms ranging from periodic to persistent obstruction of the airway and correspond with a mild to severe classification. Categorizing asthma into distinct phenotypes can thus be difficult as there are overlapping common features. These characteristics and corresponding phenotypes may change with continued research. Traditionally, the phenotyping of asthma has produced two separate groups: extrinsic and intrinsic asthma (Table 3). Both of these phenotypes involve an inflammatory process mediated by eosinophils. Extrinsic asthma is triggered after allergen inhalation and is frequently seen in younger populations with positive response to treatment. Intrinsic asthma typically does not involve specific allergens, is seen later in life, and is often difficult to treat [53]. In a study by Haldar et al., mathematical cluster analysis

Table 3 Comparing extrinsic and intrinsic asthma

Extrinsic asthma	Intrinsic asthma
Inflammation secondary to eosinophilia	Inflammation secondary to eosinophilia
Allergic	Nonallergic
Childhood-onset, more common in males	Adult-onset, more common in females
More likely to improve with treatment such as inhaled corticosteroids	More likely to have precipitous decline in lung function and association with nasal polyps, aspirin sensitivity, and chronic rhinosinusitis
Increase in Th2-type cytokines, IgE, and eosinophils in airway	Eosinophils predominate in airway; neutrophils also present in airway

Source: [53, 54]

of patients with asthma was performed to determine resulting phenotypic identification. Patients with mild asthma were compared to those with refractory asthma. The research identified two clusters, an early-onset and eosinophilic cohort and an obese and nonatopic cohort, that were common among both severity groups, similar to the traditional extrinsic and intrinsic classification [55]. One important aspect in categorizing asthma based on phenotypes involves the possibility of grouping patients to determine disease prognosis and predict response to treatment. For instance, sputum cytology may be helpful to determine whether the patient has intrinsic versus extrinsic asthma and the optimal medications to use for management. Sputum cytology may expose a variety of cellular components in which certain cell lines predominate. The most common are eosinophils, neutrophils, mixed granulocytes, and paucigranulocytes [53, 56, 57]. Each cellular constituent may contribute to the distinction between different asthma phenotypes [53, 57]. For example, while eosinophils predominate in both extrinsic and intrinsic asthma, neutrophils are more often present in intrinsic asthma [58, 59]. Though the phenotype model is helpful in illustrating the multifactorial components contributing to the presentation of asthma, a limitation to this system is that the inflammatory characteristics may change with time. Asthma phenotypes thus represent an unstable and constantly evolving mode of asthma classification [53, 57].

In contrast with phenotypic characterization of asthma, the endotype model proposes that asthma may be separated into subtypes which correlate to a distinct pathophysiological etiology producing a certain clinical presentation. Asthma endotypes describe disease categories at a cellular and molecular level. An endotype can correlate to various aspects of the disease, such as pathophysiology, genetics, environmental factors, and response to treatment [53, 60–63]. Importantly, certain phenotypes may fit with more than one endotype, while a particular endotype may be comprised of several phenotypes [49] (see Table 4). When endotypes are considered, treatment regimens can target specific etiologies, leading to more precise management options [53]. Lotvall et al. described six asthma endotypes. The first four groups include airway disease exacerbated by aspirin, allergic bronchopulmonary mycoses, early-onset allergic asthma, and late-onset persistent eosinophilic asthma, all of which produce severe asthma endotypes. The other two endotypes include exercise-induced asthma as seen in cross-country skiers and recurrent wheezing as seen in children age 3 years and younger with asthma predictive indices (APIs) [49]. The pathophysiology of each endotype may involve different causative factors. For example, it has been hypothesized that in early-onset allergic asthma, Th2 cells produce an inflammatory process, which contributes to this specific endotype [54, 60, 64]. Exposure to inhaled allergens, viral

Table 4 The link between asthma phenotypes and endotypes

- I. Allergic asthma
  - a. Eosinophilic
  - b. Steroid responsive
  - c. Immunoinflammatory
  - d. Immunotherapy responsive
    - i. Allergen specific
    - ii. Anti-IgE
    - iii. Anti-IL-5
- II. Intrinsic asthma
  - a. Eosinophilic
  - b. Neutrophilic
  - c. Steroid responsive
  - d. Steroid resistant
- III. Neutrophilic asthma
  - a. Medication responsive
    - i. Antibiotics
    - ii. Antioxidants
    - iii. Biologics
    - iv. Theophylline
  - b. Triggered by innate immune response
  - c. Prolonged neutrophil longevity
- IV. Aspirin-exacerbated respiratory disease
  - a. Eosinophilic
  - b. Steroid responsive
  - c. Leukotriene receptor antagonist (LTRA) responsive

Source: [53]

pathogens, and environmental triggers (e.g., cigarette smoke) activate a signaling cascade involving toll-like receptor 4 (TLR4) in the airway epithelium [65, 66]. The ensuing inflammation is produced by activation of stimulating factors, including GM-CSF, thymic stromal lymphopoietin, and interleukins (IL-25 and IL-33), which incite dendritic cells to prevent IL-12 production and subsequently increase Th2 activity levels [67–69]. Cytokines also trigger the innate immune system, including eosinophils, mast cells, lymphoid cells, and basophils, to further stimulate Th2 cell production, leading to a positive feedback loop. Once Th2 cells are abundant, the epithelium exhibits the inflammatory characteristics of asthma [67, 70–75]. Thus, possible treatment options may involve utilizing medications to target the specific components of the inflammatory cascade in asthma. These include Th2 modifiers such as antibodies to IL-13 or IL-4 receptor antagonists, or monoclonal antibodies to IgE [60].

Asthma and the Role of the Neutrophil as Compared to the Role of the Eosinophil

Comparing asthma pathophysiology at the cellular level is helpful in further classifying the disease process. Asthma development can alter tissue structure by the recruitment of various inflammatory cells to areas of irritation. In contrast to normal tissue seen in healthy individuals, the airway mucosa of patients with asthma has a higher amount of CD4+ T (helper) lymphocytes, eosinophils, and mast cells [76, 77]. In patients with more severe disease or during an acute exacerbation of asthma, there is a greater prevalence of neutrophillic inflammation (Fig. 3) [79, 80]. This is due, in part, to upregulation of neutrophil-specific chemoattraction in the airway by IL-8 (CXCL8) and epithelial-derived neutrophil attractant-78 (CXCL5) as they act on receptors (CXCR1 and CXCR2) on various cell surfaces (Fig. 3) [81–83]. In a study by Qiu et al., comparing tissue histological sections of adult patients between the ages of 20–64 years with intermittent versus severe asthma, neutrophils and eosinophils were present in the bronchial mucosa in both patient groups. There was a significantly higher prevalence of epithelial and subepithelial neutrophils in the severe asthma population as compared to those patients with intermittent asthma. Patients with intermittent asthma had six times more eosinophils in the subepithelium biopsies than neutrophils. Thus, bronchial mucosa in intermittent asthma with a stable course is ultimately characterized by a predominance of eosinophils and CD4+ T lymphocytes with occasional neutrophils, though the presence of all three cell types are greater than in nonasthma bronchial mucosa. Alternatively, patients with severe asthma had a larger accumulation of neutrophils and eosinophils in the airway mucosa when compared to the intermittent asthma and control groups, with both cell types being present in an equal ratio [77, 78]. The phenomenon of both neutrophils and eosinophils being elevated in severe asthma has been seen in pediatric patients as well. This finding suggests that neutrophils and eosinophils are both relevant inflammatory mediator cells in more severe asthma [56, 60, 78].

Severe Asthma

On one end of the spectrum, severe asthma is notable for requiring high doses of inhaled corticosteroids and long-acting beta-agonists for management. It affects a much smaller proportion of patients with asthma, approximately 5–10 %; however, the toll

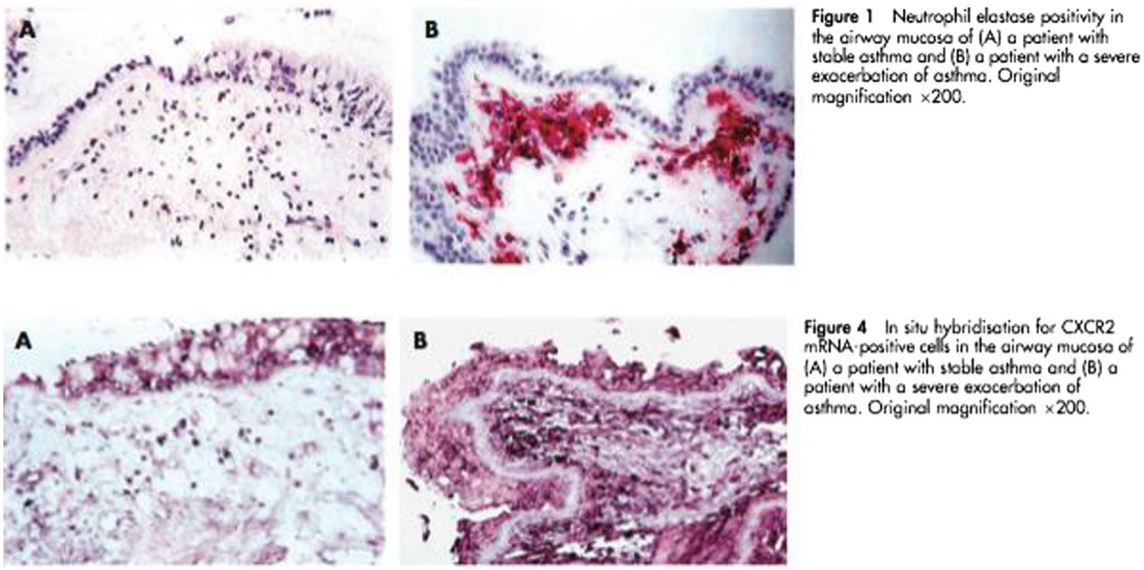

Fig. 3 Airway mucosa inflammatory cells in asthma. Reproduced with permission from Professor Peter Jeffery as noted in "Bronchial mucosal inflammation and upregulation of CXC chemoattractants and receptors in severe exacerbations of asthma" [78]

on healthcare costs and resources is much higher when compared to more mild types of asthma [61]. Severe asthma is distinguished from less complicated forms by increased airway obstruction, poor control of symptoms, greater allergic sensitization, and the propensity for fatal outcomes. Children with severe asthma are found to have increased frequency of exacerbations, airway hyperreactivity, and air trapping than patients with milder forms of the disorder [60]. Individuals with severe asthma have unique differences in their symptomatology and disease course, making subcategorization of this type of asthma challenging. Campo et al. suggest that there are three relevant clinical phenotypes for patients with severe asthma. One phenotype includes patients who experience recurrent severe exacerbations with relatively stable periods between flares. A second group of patients with severe asthma includes those who have fixed and permanent airway obstruction. Lastly, there is a group of patients requiring daily systemic corticosteroid therapy for asthma control. Not all patients in a specific group will have the same course and/or prognosis, making it important to individualize therapies targeted for each specific patient [61]. Cluster analysis of pediatric and adult patients with severe asthma has been performed via the Severe Asthma Research Program (SARP). In this study, patients with severe asthma fell into all phenotypic categories, totaling to five clusters of asthma. Cluster 1 was comprised of predominantly female younger patients with childhood onset atopic asthma and normal lung function. About 40 % of these patients did not use daily controller medications, and about 1/3 reported daily symptoms requiring short-acting rescue therapy despite infrequent hospitalizations or visits to urgent care. Cluster 2 was the largest group, comprising almost half of the research participants. Similar to cluster 1, this group was predominantly female with atopic asthma onset in childhood. Forced expiratory volume in 1 s (FEV1) was either normal or reversed to normal with beta agonist. In contrast to cluster 1, the patients in cluster 2 were generally older and required greater controller medication usage. Cluster 3 was the smallest group and consisted of middle-aged women with nonatopic asthma, later age of onset, elevated body mass index (BMI), poor control despite medical management, and abnormal lung function. Patients in cluster 4 had primarily atopic asthma with childhood onset, no gender predominance, and abnormal lung function with good response to bronchodilators. Cluster 5 was similar to cluster 3 with female predominance, nonatopic asthma, and later-onset, though patients in cluster 5 had the worst lung function of all of the groups with limited response to bronchodilators. Duration of disease was longest in clusters 4 and 5, and quality of life of patients in these groups was more notably affected by frequent and severe exacerbations despite multiple controller medications [84–86]. With a wide range of symptom diversity, severe asthma is notoriously difficult to control; fixed and invariable management can be fatal for these patients [61]. For example, two patients who both have a diagnosis of severe asthma may respond quite differently to the same treatment and thus their therapies should be personalized for optimal results. Severe asthma has variable characteristics and patients may fit into one or many subcategories of asthma. Mortality can be seen particularly in severe asthma; however, fatal outcomes can occur in mild to moderate forms as well. The importance of recognizing the various types of severe asthma is due in part to the potential implementation of life-saving therapies. [54, 87–90]. Medications that target eosinophilic and neutrophilic inflammation, including the different cytokines involved in recruitment of these cells, may be helpful in this type of asthma as discussed below.

Asthma Variability Across Age Groups

Asthma has variable presentations among individuals as well as among different age groups. This can be secondary to asthma severity from a phenotypic standpoint or divergence of cellular predominance with eosinophilic or neutrophilic presence. Often times, young children (defined as birth to 5 years old) may have milder and less frequent symptoms. This is secondary to better baseline control and less time for accumulation of detrimental effects of airway inflammation and remodeling. Exacerbations may be less frequent, however, not necessarily less severe. There are children who experience more chronic and recurrent symptoms at this age. These children typically have early-onset atopy, including atopic dermatitis and sensitization to environmental allergens. Symptoms indicative of severe asthma in young children are more frequently seen in the first 2 years of life, further confirming early-onset symptoms. This contrasts to an average onset age of 60 months for children who have mild or moderate asthma. Young children with asthma have significant variability in histopathology. A subset of this population may have normal pulmonary reticular basement membrane depth, with no thickening appreciated, whereas other children this age may develop tissue damage due to a more dominant neutrophil presence and elevated IL-8 levels. Airway inflammation in this age group is thought to be mostly related to viral infections. Despite neutrophilic predominance, increased eosinophil counts may be identified in bronchial samples and eotaxin-related inflammation may also occur [61, 91, 92].

The next group of patients includes school-age children between the ages of 6 and 11 years. Persistent wheezing during the preschool age often develops into obstructive airway disease during the school-age years and adolescence. Furthermore, bronchospasm in patients of this age group may predispose to bronchial remodeling in adulthood. Pulmonary inflammation results in increased presence of smooth muscle, thickening of the basement membrane, and vascular compaction of the airway. School-age children with severe asthma have a higher amount of eosinophilia and neutrophilia in the respiratory tissue and peripheral CD4+ T lymphocytes in circulation [61, 93].

Adolescence, which includes children 12 to 17 years of age, is a time when asthma symptoms abate in some individuals, persist in others, or may even develop for the first time [94]. Persistent symptoms likely signify atopic asthma [61, 95]. A recent longitudinal study by Arshad et al. following children for the first 18 years of life found that patients with persistent symptoms and onset of symptoms in adolescence had higher sputum eosinophilic and neutrophilic presence. Patients with resolution of symptoms had the lowest amount of eosinophils [94]. For patients with significant and persistent symptoms, airway remodeling is thought to have already begun prior to the transition into adolescence, especially for patients with severe asthma. This is illustrated by pulmonary function testing revealing lower baseline FEV1 compared to typical values seen in subjects without asthma in this age group. These changes may continue to advance into adulthood or may improve as the patient ages [96].

The pathophysiology of asthma in the transition to adulthood is interesting in its continued variability. In adult patients, asthma inflammatory processes are determined by the presentation of the disease process in stages, acute versus chronic. According to Lemanske and Busse, most adults have early-onset asthma and this is commonly associated with allergic inflammation and a Th2 response, which can contribute to a chronic and persistent state. This disease state is a result of IgE binding to an allergen and directly contributing to an increase in eosinophils, in addition to mast cells, Th2-type CD4+ T lymphocytes, and concomitant cytokines (including IL-5). Each inflammatory-associated cell line contributes to the cycle of damage to the airways. Eosinophils are initially drawn to the airway due to chemotaxis and once there, they release their cellular contents causing injury to the respiratory tract. Mast cells and Th2 cells release cytokines, such as IL-4, IL-5, and IL-13, with mast cells also releasing cysteinyl leukotrienes, all of which further produce tissue trauma. During the chronic and persistent phase, airway remodeling produces a decrease in lung function. Cells that reside in the airway contribute to persistent inflammation even when not provoked by an acute process. Smooth muscle cells and epithelial cells in the airway contain and may release cytokines, exacerbating the inflammatory cascade. Mucous glands may respond to these chemical processes, resulting in hypertrophy and mucus release, which can cause airway plugging and congestion. Additionally, growth factors may stimulate airway blood vessels to regenerate and occlude the airway [50]. Although eosinophilic asthma is common in adults, two studies by Gibson et al. showed that about 50–60 % of symptomatic adult asthma patients had sputum analyses consistent with neutrophil predominance [97, 98].

The progression of acute stage to severe stage asthma can be seen in all age groups. Similarities between severe asthma in childhood and adulthood include a multifactorial etiology and airway obstruction that is not easily reversible with treatment [86]. However, differences between age groups abound. First, the degree of airway obstruction is much higher in adults as compared with children. Additionally, severe asthma in children is associated with atopy and an overall allergic process, such as an allergen-induced response resulting in peripheral eosinophilia and elevated IgE [60, 99]. According to Jenkins et al., children with severe asthma are more likely than adults to respond to steroids and are more commonly male [99].

Medical Management of Asthma

When considering the phenotypes and endotypes of asthma, the goal is to determine what factors and symptoms predominate in order to develop an effective treatment plan for the individual patient. Commonly utilized management regimens focus on the initiation of beta-agonists with or without the addition of corticosteroids and/or LTRAs such as montelukast for daily control. In scenarios where patients do not respond to these medications, alternate treatments, such as immunomodulators and biological agents, may be warranted. Cyclosporine is an example of an immunomodulator that can be effective in the treatment of severe asthma. This drug blocks the activation of T lymphocytes, a key factor in the propagation of asthma [100]. Biological agents inhibit specific cytokines or inflammatory cells/markers underlying asthma inflammation. These include anti-IgE (omalizumab), anti-tumor necrosis factor-alpha (anti-TNF-α), chemokine inhibitors, and anti-interleukin-specific treatments. Omalizumab is a recombinant IgG monoclonal antibody that works by binding circulating unbound IgE on the FC region that binds to FcεRI [101, 102]. This in turn prevents IgE from binding these high-affinity receptors on mast cells. By downregulating the inflammatory cascade, omalizumab results in decreased total IgE and IgE receptor expression, lower eosinophilic proliferation, and subsequent decrease in inflammatory mediators secondary to the antagonizing of mast cell degranulation [102]. Anti-interleukin-specific treatments primarily block the signaling cascade before more significant tissue damage can occur. Anti-TNF-α agents, such as infliximab and etanercept, have shown efficacy in reducing exacerbations, though further research is still needed [103]. Chemokine inhibitors, such as modified oligonucleotides (TPI ASM8), prevent CCR3 receptor binding, thereby decreasing airway eosinophil recruitment by impeding eotaxin release after allergen exposure [104]. Another class of medications for anti-interleukin targeted therapy are antibiotics, specifically macrolide antibiotics such as clarithromycin. Studies have shown that macrolide antibiotics can produce immunomodulation by inhibiting IL-8 and the neutrophil cascade, thereby decreasing inflammation. This class of medications may be helpful in supplementing treatment, particularly for neutrophil-predominant asthma [105].

Innovations in Anti-IL-5 Therapy

While many components contribute to the production of inflammation in asthma, IL-5 is viewed as an essential constituent in this process and medications targeting this cytokine are rising to the forefront of innovative asthma research. As previously discussed, IL-5 is a cytokine mediator of eosinophils, mast cells and Th2 cells. By primarily interacting with the IL-5 receptor on eosinophils, IL-5 is integral to eosinophilic maturation and stimulation, and thus, is involved in the inflammatory cascade. Anti-IL-5 therapies continue to show promise in the treatment of severe eosinophilic asthma. A 2014 multicenter, randomized, placebo-controlled study by Ortega et al. showed significant improvement in asthma control with mepolizumab therapy. Mepolizumab, a monoclonal antibody targeting IL-5, decreases eosinophilic concentration and production in the airway and peripheral blood. IV and subcutaneous formulations of mepolizumab were administered to 576 patients with asthma experiencing frequent exacerbations and peripheral eosinophilia. Patients were randomized to receive monthly doses of 75 mg IV mepolizumab, a subcutaneous dose of 100 mg mepolizumab, or a placebo for approximately 8 months. Both forms of mepolizumab were shown to be safe when compared to placebo and resulted in reduced eosinophilic concentration and asthma sequelae, including exacerbations, hospitalizations, and emergency room visits [106]. A study by Bel et al. also investigated the use of mepolizumab, in 135 patients with asthma and peripheral eosinophilia. Patients were randomized to receive either 100 mg of subcutaneous mepolizumab or placebo monthly for approximately 5 months in order to determine dose reduction in glucocorticoid usage, in addition to improvement in asthma control and reduction of asthma exacerbations. Patients who received mepolizumab had an average reduction of 50 % in glucocorticoid dose as well as a 32 % decrease in rate of exacerbations per year [107]. Comparatively, Laviolette et al. observed the effects of benralizumab, a similar humanized monoclonal antibody, on eosinophilic asthma. Benralizumab is also aimed at binding the IL-5 receptor alpha subunit and subsequently decreases both eosinophils and basophils via apoptosis. The authors peformed a multicenter, double-blind, placebo-controlled phase I study on a small cohort of 27 patients to determine effectiveness and safety of this anti-IL-5 medication. There was no significant difference in efficacy between single IV dosing or multiple subcutaneous dosing, with both medication formulations significantly decreasing serum and pulmonary eosinophil concentration [108]. A larger study including 324 participants treated with benralizumab was conducted by Castro et al. The randomized, placebo-controlled, double-blind study investigated the effects of benralizumab (in doses of 2, 20, or 100 mg) versus placebo in patents with eosinophilic asthma and compared these regimens to 100 mg benralizumab versus placebo in patients with noneosinophilic asthma. Patients were treated with monthly injections for the first three doses and subsequently received subcutaneous injections every 2 months for 1 year. Benralizumab at higher doses (20 and 100 mg) showed a reduction of exacerbations, specifically in individuals with eosinophilic asthma [109]. The overall benefit of anti-IL-5 therapy lies in its ability to decrease the long-term use of medications, such as systemic glucocorticoids. With less adverse effects and the ability to decrease frequency of exacerbations, anti-IL-5 therapy is poised to become a safe and effective form of asthma treatment.

Alternative Mechanisms to Monitor Disease

In addition to novel therapies targeting the pathogenesis of asthma, alternative modes for monitoring airway remodeling, disease control, and risk for subsequent exacerbations are continually developing. Some of these methods include measurement of exhaled nitric oxide (FeNO), assessment of sputum cytology, specifically for eosinophils, and collection of urinary bromotyrosine. In a 2006 study by Fitzpatrick et al., a positive correlation between FeNO and asthma severity was observed, with elevated FeNO concentration being associated with more severe disease [110]. Sputum cytology is a noninvasive procedure to determine the cellular components of airway inflammation, though the usefulness of this test may be limited due to the length of time and technical expertise required to obtain, process, and analyze samples [111]. While FeNO and sputum cytology measurements are not easily obtainable in young children, urinary bromotyrosine was found to be useful in predicting risk of future asthma exacerbations and assessing asthma control in a study completed by Wedes et al. [112]. Continued research in this field is warranted, as a quick and reliable laboratory test may be helpful in standardizing categorization of asthma.

Concluding Thoughts on Asthma

Asthma is the most commonly encountered eosinophilic disorder of the respiratory system. With such a multifactorial disease process, individualizing therapy to known endotypes and phenotypes is necessary for an ideal outcome. There remains a broad range of disease categorization and diverse research opportunities for optimized diagnosis and treatment.

Hypersensitivity Pneumonitis

Eosinophilia related to allergic, drug and toxin exposure can produce a variety of disease states. Hypersensitivity pneumonitis (HP) is a pulmonary disorder involving respiratory symptoms upon contact with an antigen to which an individual was previously sensitized. Patients typically develop acute cough and dyspnea, which may eventually become chronic with continued exposure to the causative agent. The disease occurrence is rare and

there is no gender or genetic predilection. Many different antigens may trigger HP, including various types of bacteria, fungi, molds, and chemicals. For example, sensitivity to the bacteria *Saccharopolyspora rectivirgula* produces a type of HP called "farmer's lung," while sensitivity to *Mycobacterium avium intracellulare* is linked with "hot-tub lung." HP is diagnosed by the presence of clinical symptoms, such as cough, dyspnea, wheezing, fever, and fatigue, crackles on lung exam, positive testing to the specific causative antigen, and radiographic findings. CXR may show nonspecific, diffuse ground glass infiltrates or variable opacities during acute illness, though one fifth of patients with acute disease may have normal findings [113–115]. Other imaging modalities such as chest CT may also show nonspecific findings, though the appearance of several general findings together can prompt a more likely diagnosis of HP. These include micronodules in a central position, evidence of air trapping, and ground-glass opacities. Inhalation challenge, another useful diagnostic measure, involves repeat environmental exposure to the offending agent to reproduce symptoms. Specific antibody testing, BAL, and lung biopsy are integral to the HP work-up, as certain features can make the diagnosis more or less likely. For instance, the presence of lymphocytes in normal quantities in BAL can help to rule out HP [114, 116]. Moreover, lung biopsies in acute disease show lymphocytic infiltrates with resultant fibrosis and granulomatous changes with edema, whereas findings in chronic disease include fibrotic tissue in the upper lung fields [114]. Additionally, pulmonary function tests (PFTs) can be useful in monitoring disease course, though this procedure is less helpful for diagnosis, as findings are similar to other interstitial lung diseases and are therefore nonspecific. Typical findings are consistent with a restrictive pulmonary process and diffusing capacity of the lungs for carbon monoxide (DLCO) is reduced [117]. Treatment includes antigen avoidance and corticosteroids, the latter of which can facilitate recovery in acute disease but will not likely change long-term prognosis [114, 118].

Aspirin-Related Disease

First elucidated by Widal and colleagues in 1922, and further by Samter in the 1960s, respiratory disease triggered by aspirin ingestion is characterized by symptoms known as Samter's Triad. The triad includes asthma, chronic sinusitis with nasal polyps, and hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs). The pathophysiology is thought to be secondary to a dramatic eosinophilic response in the upper airway and lung mucosa as a result of dysregulated arachidonic acid metabolism. NSAIDs inhibit the enzyme cyclooxygenase, thereby diverting arachidonic acid to an alternate breakdown pathway leading to increased leukotrienes. Leukotienes are pro-inflammatory mediators and attract eosinophils to the lungs, promoting mucosal inflammation which, in turn, produces chronic sinusitis with the development of nasal polyps and eventually, asthma symptoms [119–121].

Drug Reaction with Eosinophilia and Systemic Symptoms

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, life-threatening medication-induced hypersensitivity reaction. DRESS, also known as drug-induced delayed multi-organ hypersensitivity syndrome (DIDM-OHS), was first described by Saltzstein and Ackerman in 1959 [122]. It is a severe cutaneous hypersensitivity reaction similar to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [123]. According to Bocquet et al., DRESS includes two patterns of clinical presentation. The first is a hypersensitivity syndrome occurring within 2 months of introduction of a new drug. Symptoms include fever, cutaneous involvement with characteristic findings (edema of the face and papular rash containing lymphocytic infiltrate or a desquamative dermatitis), lymphadenopathy, and inflammatory multiorgan involvement including carditis, hepatitis, interstitial nephritis, or pneumonitis. Another presentation of DRESS involves a lack of constitutional symptoms and the appearance of cutaneous findings similar to those previously described. Histology of both presentations mimics a cutaneous pseudolymphoma pattern. Associated lab abnormalities include hypereosinophilia, lymphocytopenia, and atypical lymphocytosis [123–125]. The lungs are less commonly involved than the liver or kidneys, but eosinophilic pneumonitis can occur, as described in a retrospective review of 216 DRESS cases by Peyriere et al. Eosinophilic pneumopathy was identified in 33 % of cases related to the drug minocycline, and abacavir was found to lead to cough, tachypnea, and pharyngitis in 10 % of patients [126]. A 2007 case report by Favrolt et al. also described a patient with acute respiratory distress requiring mechanical ventilation related to minocycline [127]. Diagnosis of DRESS can often be difficult due to the delayed and variable appearance of symptoms. The average onset of symptoms is approximately 4 weeks after exposure to the culprit drug, though by definition, onset of symptoms can range from 2 weeks to 3 months [124, 125, 128, 129]. Peyriere et al. summarized a list of medications and corresponding median time until adverse reaction, with the range being 11–47 days [126]. Pulmonary imaging studies may show various nonspecific abnormalities. In the case report by Favrolt et al., the patient with DRESS was found to have alveolar opacities in bilateral lung fields on CXR [127]. It is speculated that reactivation of a dormant herpesvirus contributes to severity and duration of symptoms [130]. Therapy is typically targeted at immunosuppression with corticosteroids, in addition to discontinuation of the culprit drug. Complete resolution occurs in a majority of patients with cure rates up to 90 %, though relapses may occur [123, 124].

Heiner Syndrome

Allergic triggers of eosinophilic pulmonary disorders have been previously discussed within the context of more common disease processes such as asthma. Heiner syndrome (HS), or food-induced pulmonary hemosiderosis, is a rare form of hypersensitivity lung disease resulting from allergen exposure. HS was first identified by Heiner et al. in 1962 as a respiratory disease triggered by ingestion of cow's milk. Since that time, case reports have described other potential culprit foods, including soy, egg, and pork, though cow's milk remains the most common. The syndrome primarily affects infants. Clinical manifestations include hemoptysis, wheezing, pulmonary hemosiderosis, fever, iron deficiency anemia, and poor growth. Laboratory studies typically reveal peripheral eosinophilia and precipitating antibodies to cow's milk proteins, while imaging studies show pulmonary infiltrates [131, 132].

Occupational Asthma

Immunologic occupational asthma (OA) may develop after repeated exposure to a wide variety of environmental elements which can be divided into two categories: low- and high-molecular-weight compounds. Common high-molecular-weight agents known to cause OA are animal proteins, flour, and enzymes, while common low-molecular-weight causative agents include isocyanates, wood dust, and cleaning products [133]. Eosinophilic inflammation is typically seen in OA and about 90 % of cases are IgE-mediated [134, 135]. Due to the latency period between exposure and symptom onset, a high index of suspicion is needed for the diagnosis of OA. For example, as noted in a case report by Enriquez et al., a 30-year-old male smoker was found to exhibit symptoms of occupational asthma after 9 years of exposure to an industrial fiber made of grass. He presented with a 3-year history of cough, dyspnea, and wheezing immediately after exposure to the offending agent, with symptoms continuing for several hours after exposure. Symptoms resolved when the patient was not at work, and there was no history of fever or other systemic symptoms suggestive of HP. His laboratory findings were significant for peripheral blood eosinophilia and positive skin prick testing to the trigger, esparto fibers contaminated with *Mucor* species. He had normal chest radiograph and spirometry. Methacholine and specific bronchoprovocation challenges were positive and peak expiratory flow (PEF) measurements were notably decreased at work as compared to outside of work [136]. OA responds to asthma medications; however, resolution only occurs with avoidance of the offending agent.

Infection

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is an inflammatory disorder of the airways secondary to fungal colonization with *Aspergillus* species. Sensitization to *Aspergillus fumigatus* produces the most commonly recognized form of ABPA, though colonization by other species can also lead to the disease. ABPA is most often seen in individuals with chronic asthma or cystic fibrosis, though it is uncommon even in these populations. The incidence of ABPA is estimated to be approximately 1–2 % in patients with asthma, with up to a sevenfold increase in patients with cystic fibrosis (1–15 %). These two patient populations are predisposed to colonization by fungi due to the chronic nature of their airway disease and poor mucociliary clearance. While many healthy individuals have a history of contact with *Aspergillus* species without adverse effect, individuals with chronic underlying pulmonary complications tend to have worse outcomes with aspergillus exposure. Clinical features of ABPA include peripheral blood eosinophilia, elevated serum total IgE, mucus plugging, and bronchiectasis. Patients may have fever, malaise, cough, and wheeze. The pathophysiology of the disease involves an immune response to the fungal antigen and fungal proteases, including T cell activation, cytokine response to IL-5, and influx of eosinophils and IgE. Fungal antigens are processed by antigen-presenting cells and subsequently activate a Th2 CD4+ cellular response, ultimately releasing cytokines IL-4, IL-5, and IL-13. These cytokines promote enhanced production of IgE and also recruit eosinophils to the affected area. Eosinophils promote inflammation by release of preformed granules. Neutrophil migration occurs as well, likely as a result of IL-8. Subsequent damage to the airway due to chronic inflammation and consequent remodeling produces pulmonary infiltrates. Diagnosis is established using criteria as outlined in Table 5. Using the Agarwal criteria, a diagnosis of ABPA should be considered for patients with asthma if they have high serum-specific IgE to *Aspergillus fumigatus* and total IgE levels >1000 ng/ml, as well as any two of the following: opacities on radiographic lung visualization, AEC >1000 cells/μL, central bronchiectasis visualized on chest CT, and/or precipitating antibodies to *A. fumigatus* [137]. Treatment involves targeting and treating symptoms of the disease in order to limit progression of lung injury by decreasing inflammation and reducing exacerbations. Combination therapy targets the fungus while helping to control asthma and bronchiectasis. One mainstay of therapy includes corticosteroids, primarily systemic but also inhaled, to suppress the overactive immune response against fungal antigens and reduce inflammation. Additionally, antifungals, such as amphotericin B, or azole drugs such as itraconazole, may be utilized to eliminate fungal colonization and diminish

Table 5 Diagnostic criteria for Allergic bronchopulmonary aspergillosis

Patients with cystic fibrosis	Patients with asthma
I. Chronic cough	I. Worsening of asthma symptoms
II. Worsening of symptoms in an acute or subacute manner without other causation	a. Cough, wheeze
III. Peripheral blood eosinophilia (>500 cells/μL)	II. Peripheral blood eosinophilia (>1000 cells/μL)
IV. Bronchopulmonary manifestations	III. Bronchopulmonary manifestations
a. Lung infiltrates on chest X-ray or CT with no improvement after therapy	a. Central bronchiectasis
V. Elevated total serum IgE >1200 ng/ml[a]	IV. Elevated total serum IgE >1000 ng/ml
VI. Elevated serum-specific IgE and/or IgG to *Aspergillus*	V. Elevated serum-specific IgE and/or IgG to *Aspergillus*
VII. Hypersensitivity to *A. fumigatus* via skin prick test or intradermal test	VI. Hypersensitivity to *A. fumigatus* via skin prick test or intradermal test
VIII. Precipitating serum antibodies to *A. fumigatus*	VII. Precipitating serum antibodies to *A. fumigatus*

Source: [3, 137, 155]

[a] In cystic fibrosis, the classic findings are a total IgE >1000 IU/ml (>2400 ng/mL) with a minimum total serum IgE >500 IU/mL (>1200 ng/mL); if total IgE is 200 to 500 IU/mL [480 to 1200 ng/mL], re-test in 1 to 3 months; if the patient is taking steroids, repeat when patient is no longer receiving steroid therapy [155]

eosinophils. Itraconazole has been found to decrease activation of the immune system, thereby reducing IgE and IgG production and lessening eosinophil recruitment [3, 138, 139]. Lastly, omalizumab has been reported to have therapeutic benefit, particularly in patients with cystic fibrosis. As a monoclonal antibody, omalizumab binds to specific receptors to inhibit the inflammatory cascade. This management option is particularly beneficial as it decreases lung injury while reducing the need for steroids [140, 141]. While treatment has been shown to decrease the AEC in patients with ABPA, the AEC alone is not helpful for monitoring response to medications. Conversely, IgE levels do respond to treatment and may be useful as a means of assessing efficacy of therapy [138, 142].

There is thought to be a subgroup of asthmatics who develop severe asthma symptoms and are found to be sensitized to fungi, though they do not fit criteria for ABPA [143]. A study completed by Denning et al. showed that a large majority of this patient subgroup responded well to antifungal therapy, such as itraconazole [144].

Helminth-Induced Eosinophilic Lung Disease

Another cause of eosinophilic lung disease includes parasitic infection, which may be induced by either unicellular organisms, such as protozoa, or multicellular organisms, such as helminths. Helminths are worms that are introduced into the host's body by ingestion or penetration of the epidermal barrier and subsequent relocation to the area of infection. An infection via helminth can be complex and difficult to treat due to the various life cycle stages of the parasite and migration to different areas of the body. With each change, the body must adapt and mount a separate immune response to fight the current phase of the pathogen [145]. Interestingly, select helminths migrate to the lung for different reasons, including a necessary developmental stage in the life cycle or as a result of an excessive parasite load. Pulmonary damage in parasitic infection occurs as a result of the immune response and physical injury from the organism itself [146]. Systemic and localized symptoms are common in helminth infection of the lungs, and include fever, cough, hemoptysis, wheeze, shortness of breath and even acute respiratory failure in severe cases [147]. Infection from parasites, most commonly helminths, produces a Th2 cellular immune response, leading to pulmonary and peripheral eosinophilia, as well as increased IgE antibody production [148]. Local inflammation then occurs with participation of both eosinophils and mast cells. This immune response is hypothesized to aid in the defeat and removal of the parasite by the generation of antibodies, complement proteins, cytotoxic components (e.g., leukotrienes, platelet-activating factor, and lysosomal hydrolases) and/or toxic granule proteins. Eosinophil release is prompt and lacking in specificity; thus accumulation of these cells can also lead to a physical barrier against helminth attack. The inflammatory response, however, has its drawbacks as additional host tissue damage can occur as a result. In contrast, eosinophils are important in the natural immune response to destroy the parasite and are also crucial in the defense of the body from more severe infection. The role of the eosinophil in infectious helminth infections is thus contradictory and can both help and harm the individual [145, 148].

Neoplastic Disorders

Neoplasms may lead to secondary pulmonary eosinophilic disease through a variety of mechanisms. Eosinophilia may

occur as a result of opportunistic infections, side effects of therapies, or an immune response to the neoplastic process itself [39]. Respiratory eosinophilic disorders can occur with a multitude of cancers, including lymphoma, leukemia, myelodysplasia, and solid organ cancer [149–151]. One example is eosinophilic pneumonia related to treatment complications for leukemia and lymphoma, as noted in case reports by Furuta et al. and Trojan et al., respectively [152, 153]. Hypereosinophilia as a paraneoplastic process has also been documented in the literature. Case reports by Verstraeten et al. and Pandit et al. described two patients presenting with peripheral blood eosinophilia and respiratory compromise. Both patients were later discovered to have non-small cell carcinoma of the lung (NSCLC) and a subsequent paraneoplastic syndrome of hypereosinophilia [149, 154]. It is likely that elevated eosinophils were a by-product of the cancerous process in these cases, as the tumor secretes IL-5 and, thus, promotes eosinophilia [149].

Conclusion

In summary, eosinophils in the respiratory system can produce a wide array of symptoms, leading to many common as well as some more rare disease processes. While eosinophils can affect many different organ systems, eosinophil pathology in the respiratory system is a commonly encountered issue affecting both pediatric and adult populations. From noncomplex diagnoses such as intermittent asthma to more serious diseases such as DRESS, pulmonary eosinophilia can occur with varying degrees of significance.

Most diseases require corticosteroid therapy, both systemic and those targeted at specific tissues, with inconsistent results and cure rates. New therapies to target the inflammatory cascade remain at the forefront of research in eosinophilic disease processes. Studies involving anti-IL-5 have shown much promise in targeting reduction of eosinophilic concentration, thereby improving morbidity and mortality, specifically in eosinophilic asthma. Human trials are continuing for mepolizumab and benralizumab to determine appropriate dosages for optimal results. With encouraging outcomes thus far, additional research will likely be dedicated toward innovative approaches to pulmonary eosinophilic pathology.

With its overarching reach and relevancy to many patient populations, eosinophils in the respiratory system will remain an important topic for many years to come.

Compliance with ethical standards

Conflict of Interest Drs. Eng and DeFelice have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product or device.

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