



Eosinophilic vs. Neutrophilic Asthma

Sara M. Assaf¹ · Nicola A. Hanania¹

© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Purpose of Review Understanding the molecular mechanisms and heterogeneity of asthma has allowed the discovery of two distinct endotypes based on the mechanisms driving the underlying airway inflammation: eosinophilic asthma, a subtype of T2-high asthma, and neutrophilic asthma, a subtype of non-T2 asthma or T2-low asthma. In this review, we highlight the current knowledge about the immunopathology of these distinct subtypes and their clinical and therapeutic implications.

Recent Findings The intricate interplay of immune pathways has been recently evaluated in both eosinophilic and neutrophilic asthma. The delineation of signaling molecules and cytokines in the eosinophilic pathway has led to the identification of biomarkers that can guide in diagnosing and prognosticating patients and the advent of several targeted biologic therapies. However, the mechanisms of neutrophilic asthma are still not well understood and constitute an unmet need and a therapeutic challenge especially that patients with this type of asthma are often characterized by severe and refractory disease.

Summary The understanding of the heterogeneity of asthma profiles and the fundamental inflammatory pathways driving airway inflammation helped in stratifying the disease into distinct endotypes and phenotypes. Recognizing the diverseness of the disease helped in understanding the varying response to treatment options and accounting for the shift in treatment paradigms from a “one size fits all” approach to targeted personalized medicine mostly in eosinophilic asthma. Knowledge gaps exist in the understanding of the pathophysiology of neutrophilic asthma with further studies needed to elucidate its pathogenesis and to develop more effective therapy to target this subgroup of patients with more resistant disease.

Keywords Endotypes · Phenotypes · Eosinophilic asthma · Neutrophilic asthma · Biomarkers · Targeted therapies

Introduction

Asthma is a heterogenous syndrome driven by chronic airway inflammation, airway hyperresponsiveness, and airway obstruction. With emerging recognition of the diversity of the disease, the existing paradigms of treatment of asthma have shifted over the last few years as it became apparent that this is a no longer “one size fits all” disease, and to achieve an optimal outcome, existing treatment strategies have to be more personalized [1]. Indeed, the traditional model of asthma as a single-entity disease with simplistic classification into atopic or “extrinsic” asthma and non-atopic or “intrinsic asthma” has

now been refuted. With better understanding of the molecular pathways driving the disease, asthma is now regarded as an umbrella diagnosis highlighting the heterogeneity of the disease. The new approach to delineate the pathophysiological characteristics of the disease led to the emergence of the concept of phenotypes and endotypes [2]. Asthma endotypes describe distinct inflammatory pathways at a molecular and cellular level that lead to the observable clinical characteristics of the disease or the so-called phenotypes. Therefore, despite similar clinical symptomatology, patients with asthma have distinct and at times interrelating endotypes that dictate the variable response to treatment strategies. Severe asthma accounts for about 5–10% of all patients but has the highest share of morbidity, mortality, and healthcare-related expenses. Understanding the underlying phenotypes and endotypes of the disease is particularly relevant in severe asthma which often presents with refractory symptoms despite optimized controller therapies and has allowed for the development of treatments targeted at patients based on their underlying phenotypes and endotypes [2]. Stratification of molecular data

This article is part of the Topical Collection on *Lung Transplant*

✉ Nicola A. Hanania
hanania@bcm.edu

¹ Section of Pulmonary, Critical Care and Sleep Medicine, Baylor College of Medicine, 1504 Taub Loop, Houston, TX 77030, USA

helped in the recent identification of two distinct inflammatory types: type 2-high and the non-type 2 (type 2-low) asthma. A major component of type 2-high asthma includes the eosinophilic asthma and a major component of non-type 2 asthma includes the neutrophilic asthma [2]. We herein provide an overview of current knowledge of these two large but distinct subtypes of asthma and highlight differences between them and the clinical and therapeutic implications of these differences.

Pathobiology of Asthma

In T2-high asthma, cytokines produced by the antigen-presenting cells (dendritic cells) of the airway lead to differentiation of T cells into Th2 cells subsequently driving eosinophilic airway inflammation and the release of effector cytokines including IL-5 and IL-13 [3]. However, this type 2 immune response is not solely driven by the adaptive immune response and Th2 cells. Recent evidence suggests an equal contributory role for the innate immune system driven by non-allergic mechanisms and by the activation of the ILC2 cells (type 2 innate lymphoid cells) by triggers other than allergens in response to epithelial-derived cytokines or alarmins including TSLP (thymic stromal lymphopoietin), IL-25, and IL-33. ILC2 cells in turn stimulate T2 airway inflammatory pathway and the

production of similar cytokine like IL-5 and IL-13, independent of effector T cells [4] (Fig. 1).

While the molecular pathway underlying T2 high asthma is well studied and understood, the mechanisms of non-T2 asthma appears more heterogenous, and airway inflammation may not be present in all the patients (Fig. 1). However, in those patients with airway inflammation, the inflammatory drivers (cells and mediators) are quite distinct including the Th17, neutrophils, and cytokines including IL-17, IL-8, TNF- α , and LTB4. Constituting about 50% of airway inflammation in asthma patients and 37% of severe asthma, non-T2 asthma represents a large unmet need [5].

Eosinophilic Asthma

According to different studies, presence of sputum eosinophilia of more than 2–3% in patients with asthma is diagnostic of eosinophilic asthma. As mentioned above, this type of asthma falls under the umbrella of T2-high asthma and is propagated by either the innate or adaptive immune pathways leading to the production of type 2 cytokines and the perpetuation of type 2 airway inflammation where eosinophils play a major role.

Antigen-presenting cells of the airway including dendritic cells induce the differentiation of T lymphocytes into Th2 cells, which in turn produce cytokines like IL-4, IL-5, and IL-13 involved in type 2 inflammation. IL-4 and IL-13 share

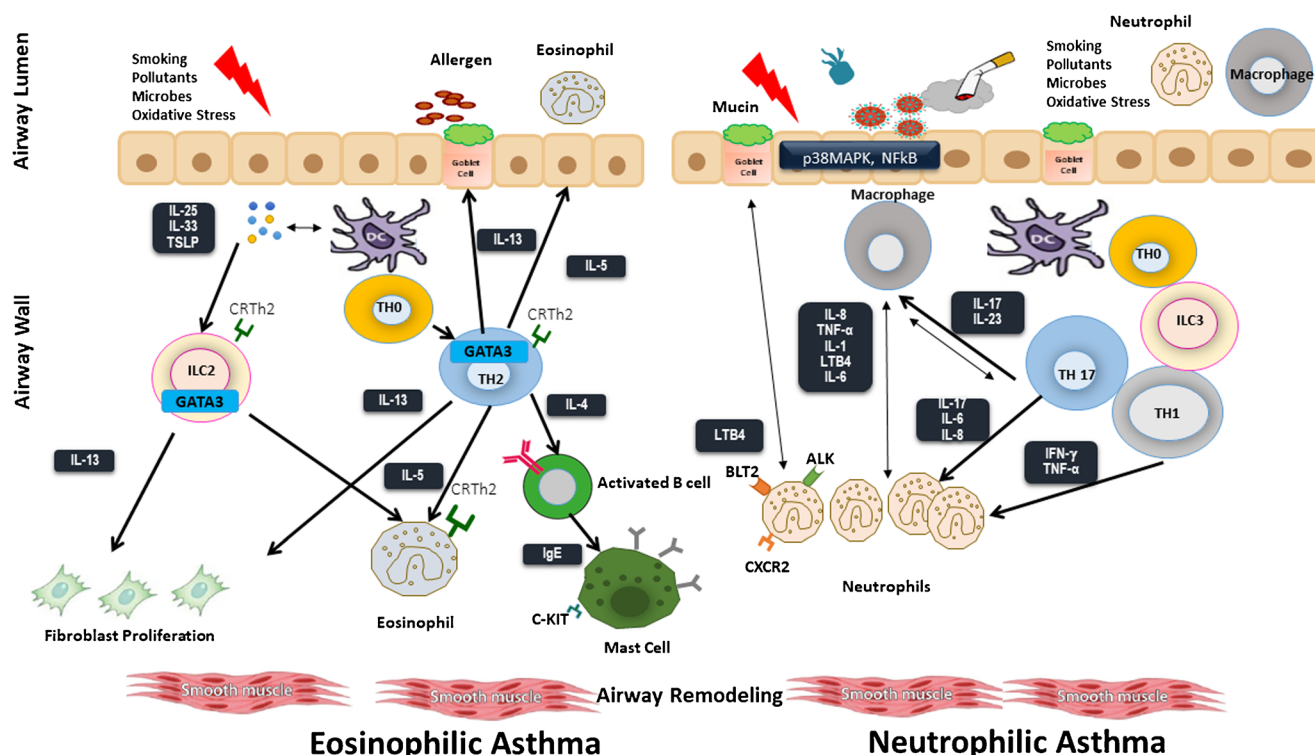


Fig. 1 The immunopathology of eosinophilic and neutrophilic asthma. Th, T helper cells (0, 1, 2, 17); CRTH2, chemoattractant receptor homologous molecule expressed on Th2 cells; GATA3, GATA

transcription factor; ILC2, group 2 innate lymphoid cells; ILC3, group 3 innate lymphoid cells; TSLP, thymic stromal lymphopoietin; IL, interleukin; LTB4, leukotriene B4

a common functional receptor (IL-4R α /IL-13R α) and initiate downstream signaling through phosphorylation of transcription factors like STAT6 [6]. By binding to T cells, IL-4 helps in the differentiation of Th2 cells and subsequent production of IL-5 and IL-13 which leads to eosinophilic inflammation as well as IgE production by promoting B cell activation and switching into the IgE isotype. IL-13 is a pleiotropic cytokine which has been associated with airway remodeling, mucus production, and goblet cell hyperplasia and has direct effects on airway smooth muscles leading to airway hyperresponsiveness. IL-5 is another pivotal cytokine in type 2 inflammatory pathway; it is primarily involved in the maturation of eosinophil progenitor cells in the bone marrow and in their recruitment, mobilization, and differentiation. In the site of inflammation, degranulation of eosinophils leads to the release of several cytokines (IL-5 and IL-13), chemokines like eotaxins, and cytotoxic proteins [7, 8]. These products of degranulation correlate better with the activity status of eosinophilia rather than just absolute peripheral eosinophilic counts. An example of the inflammatory mediators released by eosinophils is bronchoconstrictors like cysteinyl leukotrienes (CysLTs) which along with IL-33 stimulate the innate pathway and lead to the production of type 2 inflammatory cytokines from ILC2 cells [8]. Profibrotic factors released by eosinophils in turn lead to the thickening of the airway membrane and contribute to the overall airway remodeling.

Another potentiator of airway remodeling in eosinophilic asthma is IgE. Its high-affinity receptor (Fc ϵ RI) is implicated in mediating an allergen-specific immediate hypersensitivity response through mast cell degranulation. Upon activation, mast cells release mediators like protease, tryptase, and prostaglandin D2 (PGD2). The latter contributes to increased vascular permeability and vasodilation. In fact, a subtype of mast cells with increased propensity to generate PGD2 (known as PGD2—high mast cells) was associated with poorly controlled T2-high asthma. Patients with severe asthma have an increased expression of PGD2 receptors (D-prostanoid DP2 receptor and CRTH2 receptor) on Th2 cells and eosinophils. The expression of these receptors in bronchial biopsy samples was a predictor of the severity of asthma and poor control of the disease [9, 10].

Other propagators of eosinophilic asthma are the alarmins which are epithelial-derived mediators. They include the thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 which can serve to activate lineage negative ILC2 cells and lead to the augmentation of T2 response through the downstream production of cytokines like IL-5 and IL-13 [4].

Eosinophilic/T2-High Phenotypes

Common T2-high asthma phenotypes include early-onset asthma, late-onset eosinophilic asthma, and aspirin-exacerbated respiratory disease (AERD) and are discussed below.

Early-Onset Atopic Asthma Previously known as extrinsic asthma, this phenotype of T2-high asthma is the most common and presents during childhood and is most of the time associated with atopic diathesis. This type of asthma is also often called allergic asthma. It is characterized by the presence of elevated total and allergen-specific IgE as well as positive allergy skin testing. Peripheral eosinophilia and airway eosinophilia are common in this type of asthma although they are not always present [11].

Late-Onset Eosinophilic Asthma This type of asthma includes adult patients who often have severe disease often refractory to inhaled and oral steroids and is on many occasions associated with fixed airway obstruction. This distinct eosinophilic phenotype is usually driven by ILC2 production of IL-5 and IL-13 and rarely driven by aeroallergen sensitization. Patients are characterized by high sputum and blood eosinophilia. Chronic rhinosinusitis with polyposis (CRSwNP) has been often linked to this phenotype and can precede its onset. In a recent cluster analysis, a subgroup of patients with CRSwNP had an expression of *Staphylococcus aureus* enterotoxin-specific IgE and had high levels of IL-5 and fraction of exhaled nitric oxide (FeNO) suggesting that allergic mechanisms may also be implicated in some of these patients [12, 13]. As this subset tends to have more severe resistant disease, early recognition is important as it will allow for earlier institution and escalation of therapy [13].

Aspirin-Exacerbated Respiratory Disease Another subgroup of late-onset asthma is AERD. It is characterized by late-onset asthma, COX-1 inhibitor–induced respiratory symptoms, and chronic rhinosinusitis with polyposis. Aspirin is a potent COX inhibitor that shifts arachidonic acid metabolism from COX pathway to 5-lipoxygenase (5-LOX) pathway. This in turn will lead to the overproduction of CysLT including LTC4, LTD4, and urinary leukotriene E4 (LTE4) that act as bronchoconstrictors. The latter will lead to the upregulation of tissue and blood eosinophilia by upregulating the ILC2/alarmin pathway [14, 15]. AERD constitutes about 10% of adult-onset asthma, is usually refractory to corticosteroids, and represents a non-allergic hypersensitivity reaction to NSAID. Patients present with eosinophilic rhinosinusitis, nasal polyposis, and asthma exacerbations. Clinical manifestations can include nasal congestion, nasal obstruction, and asthma attacks when exposed to NSAID. Facial flushing, conjunctival redness, skin rashes, and GI symptoms can also be observed and are attributable to histamine overproduction.

Biomarkers of Eosinophilic Asthma

Sputum Eosinophils As previously described, a sputum eosinophilia of more than 2–3% suggests eosinophilic asthma and airway inflammation. Increased sputum eosinophilia has been

associated with an increased risk of exacerbations and an increased response to inhaled corticosteroids [16]. Despite its benefit in classifying asthma phenotypes, inducing sputum remains limited and cumbersome, and its clinical utility is limited to specialized centers. Other point-of-care biomarkers that correlate with eosinophilic inflammation are being investigated. When used together, exhaled nitric oxide (FeNO) and blood eosinophil counts can predict with accuracy underlying sputum eosinophilia and thus serve as surrogate markers in most clinical settings [17••].

Peripheral Blood Eosinophils The utility of absolute blood eosinophilic counts (AEC) as a biomarker to reflect eosinophilic airway inflammation has been inconsistent across studies. Conversely, the prognostic value of peripheral eosinophils and risk of asthma exacerbation have been replicated. In fact, many randomized controlled trials of targeted therapies against IL-5 and IL-4/13 have used blood eosinophilia (> 150–400 cells/UL) as an inclusion criterion and showed that response to such treatments (reduction of asthma exacerbation) was more pronounced in patients with higher baseline blood eosinophilia [18, 19]. While no cutoff of blood eosinophils is yet agreed on, multiple measurements (at least 3) are needed to overcome the caveat of day-to-day variability in AEC.

Fraction of Exhaled Nitric Oxide T2-high airway inflammation drives the production of nitric oxide by airway epithelial cells through the inducible nitric oxide synthetase (NOS) transcription. This mechanism is upregulated by cytokines like IL-4 and IL-13. FeNO > 25 ppb is predictive of eosinophilic airway inflammation and responsiveness to corticosteroids. Furthermore, novel therapy targeting the IL-4/13 pathway elucidated the predictive and prognostic roles of FeNO. Randomized controlled trials have shown that the efficacy of the IL-4/13 inhibitor, dupilumab, was more pronounced in subjects with higher baseline FeNO (> 25 ppb) [20, 21]. FeNO levels were also reduced with therapy reflecting pharmacodynamic properties of FeNO in this situation.

Serum Immunoglobulin E IgE is a central mediator in the pathogenesis of allergic/atopic asthma. When exposed to allergens in susceptible individuals, IgE binds to mast cells and leads to cellular degranulation and the release of pro-inflammatory cytokines. Increased IgE levels were also associated with the presence of eosinophilic airway inflammation and sputum eosinophilia [22]. IgE levels are used to identify candidates for omalizumab therapy, an anti-IgE antibody blocking the interaction of IgE with its FcεRI receptors on mast cells, basophils, and dendritic cells. Conversely, IgE levels are not helpful in monitoring and predicting response to omalizumab [23].

Urinary Leukotriene E4 A product of cysteinyl leukotriene metabolism, urinary LTE4 may be a predictive of aspirin sensitivity in patients with asthma and nasal polyposis. While its specificity is around 89%, its high negative predictive value can be used to discriminate AERD. Higher levels were also associated with greater response to leukotriene receptor antagonists [24].

Serum Periostin Periostin is an extracellular protein secreted from bronchial cells consequent to the activity of IL-4 and IL-13. Serum periostin levels were shown to be a surrogate of the IL-4/13 pathway activity [25]. Its levels decreased after the institution of targeted biologic therapy against IL-4 and IL-13. Furthermore, serum periostin levels and its expression in bronchial cells were correlated to persistent eosinophilic airway inflammation despite the use of corticosteroids and to increased risk of exacerbations [26]. However, the lack of specificity restricts the utility of serum periostin as an asthma alone biomarker and limits its clinical use to investigational at this point.

Neutrophilic Asthma

While T2 airway inflammation and eosinophilic asthma represent the majority of the pathomechanisms underlying severe asthma, little is known about the T2-low disease which includes neutrophilic asthma [27]. Furthermore, there still is no universally accepted definition of T2-low asthma. It can be characterized by sputum neutrophilia with no clear cutoff (> 40–60%) or be paucigranulocytic with the absence of either airway neutrophilia or eosinophilia. In most cases, however, it is characterized by the absence of T2-high biomarkers, refractoriness to corticosteroid therapy, more severe disease, and reduced pulmonary function often represented by fixed airway obstruction. The underpinnings of the neutrophilic airway inflammation are yet to be fully elucidated, and the role of neutrophilia is debatable as it could represent the consequence of high-dose steroid therapy. A putative role of Th1 and Th17 pathways is suggested; however, the full mechanism behind T2-low asthma is still poorly understood and represents an unmet need [28••].

IL-17-driven inflammatory pathway is generally characterized by lack of response to corticosteroid therapy and increased airway hyperresponsiveness. Increased levels of IL-17 A and F have been found in bronchial biopsies of patients with severe asthma and neutrophilic airway inflammation. When exposed to stimuli including bacterial/viral infections, smoking, and air pollutants, airway epithelial cells inflict the differentiation of naïve T cell to pro-neutrophilic subset of helper cells which lead to the expression of a Th17 milieu in the airways and the subsequent release of neutrophilic cytokines. Indeed, activated Th17 cells and ILC3 release IL-17

and IL-22 which increase smooth muscle cell proliferation and collagen deposition [13, 29]. Moreover, these cytokines stimulate the expression of IL-8 from bronchial epithelial cells, further accentuating the neutrophilic inflammation through an IL-8-driven proliferation, recruitment, and chemotaxis of neutrophils [30]. Th-1 pathway has also been implicated in the pathogenesis of T2-low asthma through the production of IFN- γ . The latter is thought to be correlated with increased airway hyperresponsiveness and steroid refractoriness through the downregulation of secretory leukocyte protease inhibitor (SLPI) [31].

Neutrophilic/Non-T2 Phenotypes

The categorization of neutrophilic/non-T2 phenotypes include obesity-associated asthma, smoking-associated asthma, and very late-onset asthma often seen in older adults with asthma.

Obesity-Associated Asthma This phenotype is mostly seen in middle-aged, obese females with no atopic features and relatively preserved lung function and resistance to steroid therapy. The Th1 pathway has been implicated as a potential driver of obesity-associated asthma. In addition, innate immune response through ILC3 has a key role in the neutrophilic airway inflammation in obese patients through the expression of both IL-17 and IL-22. Inflammation potentiated through IL-6 has also been uniquely described in a subset of obese patients with severe asthma, which might be clinically relevant in identifying patients with more severe disease and identify future targets of therapy [32–35].

Smoking-Associated Asthma It has been postulated that a T2-low neutrophilic airway inflammation drives smoking-associated asthma through oxidative stress and epigenetic modifications ultimately leading to neutrophilic recruitment and activation. Moreover, smoking has been linked to increased allergen sensitization and increased levels of IgE which can potentially explain the overlap between COPD and asthma, as seen in asthma-COPD overlap (ACO) [36].

Elderly Asthma Asthma in the elderly is often characterized by late-onset or long-standing disease in patients > 65 years of age. It is often underdiagnosed and undertreated and can present with different symptomatology. Proposed mechanisms include alteration in airway inflammation with higher neutrophilic counts. In fact, it has been postulated that “inflammaging” occurs in elderly with asthma. It is characterized by an increased basal inflammatory status and airway inflammation with increased expression of IL-6, IL-8, and TNF- α . Another potential mechanism is “immunosenescence,” where the innate and adaptive responses have a blunted immune response or have an altered one with decreased capacity [37–40].

Biomarkers of Neutrophilic Asthma

Thus far, little is known on potential predictive and prognostic biomarkers for neutrophilic airway inflammation. Whereas sputum neutrophilia > 40–60% has been proposed as a biomarker of neutrophilic asthma, blood neutrophilia remains an unreliable biomarker as its levels can fluctuate secondary to other inciting events like corticosteroid use or concomitant bacterial infection.

Table 1 Asthma classification into eosinophilic and neutrophilic with associated clinical phenotypes, underlying pathobiology, and potential biomarkers

Severe asthma		
	Eosinophilic	Neutrophilic
Immune profile	Innate and adaptive mechanisms Th2 cells, mast cells, and ILC2 IgE, IL-4, IL-5, IL-9, IL-13	Innate and adaptive mechanisms Th1 cells, Th17 cells, and ILC3 IL-17, IL-6, TNF- α , LTB-4
Phenotypes	- Early-onset allergic - Late-onset eosinophilic - Aspirin exacerbated respiratory disease (AERD)	- Obesity-associated asthma - Smoking-associated asthma - Very late-onset asthma - Asthma in elderly
Triggers/associated conditions	Allergens, aspirin exacerbated, exercise, occupational exposure	Smoking, obesity, air pollutants/irritants, aging
Comorbidities	Chronic rhinosinusitis, nasal polyposis, atopic dermatitis	Obesity, smoking, recurrent infections
Age of onset	Early and late onset	Late onset
Biomarkers	Sputum eosinophilia > 2–3% Blood eosinophils 300 cells/UL, FeNO > 25 ppb, allergen-specific IgE (others: serum periostin, urinary LTE4)	Sputum eosinophilia < 3% Sputum neutrophilia > 40–60% VOCs, IL-6, IL-17
Clinical and therapeutic implications	Responsive to corticosteroids and T2-targeted biologic therapy	Poor response to corticosteroids, no available targeted biologic therapy

Th2, T helper 2 cells; *ILC2*, type 2 innate lymphoid cells; *Th1*, T helper 1 cells; *Th17*, T helper 17 cells; *ILC3*, type 3 innate lymphoid cells; *AEC*, absolute eosinophilic count; *FeNO*, fraction excretion of nitric oxide; *Urinary LTE4*, urinary leukotriene E4; *VOC*, volatile organic compounds; *IL-6*, interleukin 6; *IL-17*, interleukin 17

As mentioned above, IL-17 has been associated with neutrophilic airway inflammation, and studies have shown a correlation between IL-17 mRNA levels in sputum and neutrophilic counts [41]. IL-6 has also been recently studied in a subset of obese patients with severe asthma, and as aforementioned, it could be considered a putative biomarker to identify a subgroup of obese patients with more severe and refractory disease. However, IL-6 levels can also be elevated in the setting of viral infection [35].

Other inflammatory markers like CXCR1 and CXCR2 have been shown to be increased in patients with neutrophilic asthma and can be a potential diagnostic biomarker of this type of asthma. Investigational biomarkers identifying airway remodeling have been suggested and include non-invasive sputa levels of matrix metalloproteinase-1 (MMP-1), fibroblast growth factor-2 (FGF-2), and galectin-3 [42]. More recently, a study highlighted the potential role of volatile organic compounds (VOCs) in characterizing asthma subphenotypes and suggested that their use may differentiate between eosinophilic and neutrophilic phenotypes. VOCs are measured in exhaled breaths through gas chromatography and mass spectrometry. Compounds like nonanal, 1-propranolol, and hexane were found in higher levels in patients with neutrophilic asthma as opposed to the combination of hexane and 2-hexanone that was highly predictive of eosinophilic asthma [43, 44].

Therapeutic Implications

Over the last decade, our improved understanding of the heterogeneity of asthma and the pathobiology driving its airway inflammation has led to a paradigm shift in the approach to its treatment and the emergence of targeted biologic therapies. However, this progress has been, unfortunately, mostly linked to the eosinophilic asthma. A huge unmet need still exists for the diagnosis and treatment of the neutrophilic asthma which is more resistant to conventional controller therapy (corticosteroids) and is associated with more severe phenotypes. In fact, whereas corticosteroids constitute the cornerstone of treatment in eosinophilic asthma, to maintain control of disease and reduce the rate of future exacerbations, their effect in neutrophilic asthma is debatable (Table 1).

Multiple biologic therapies targeting the T2 inflammatory pathway in allergic and eosinophilic asthma have now been approved. Monoclonal antibodies targeting IgE, IL-5, and IL-4/13 have shown improved outcomes in subsets of patients. Other biologics targeting alarmins are under development. Furthermore, small-molecule antagonists such as DP2 antagonists are also being evaluated in different stages of development for eosinophilic asthma [45].

To date, no targeted therapies have proven benefit in neutrophilic asthma. CXC motif chemokine receptor 2 (CXCR-2) antagonist involved in neutrophilic chemotaxis by binding IL-8 have been studied and showed no significant benefit on

exacerbation rate reduction or lung function improvement. TNF- α inhibitors, anti-IL17, and anti-IL1 also failed to show clinically significant benefit in neutrophilic asthma [42].

The chronic use of the macrolide, azithromycin, when used three times weekly, has been studied in neutrophilic asthma and has been shown to decrease the rate of exacerbations in both eosinophilic and non-eosinophilic asthma [46, 47]. Its long-term immunomodulatory effect is to be further elucidated. Non-pharmacologic therapies including smoking cessation, weight reduction, low-fat diets, and bronchial thermoplasty are currently incorporated in the clinical management of patients with neutrophilic asthma with further studies needed to implicate clinical benefit [42].

Future Directions

While an improved understanding of the molecular mechanisms of asthma has allowed the recognition of both eosinophilic and neutrophilic diseases, several questions remain unanswered and require further exploration. Available biomarkers to distinguish between these two common subtypes of asthma are limited to only few reflecting eosinophilic disease, and most are not point of care and their levels are affected by several confounders. No biomarkers exist to identify neutrophilic disease; as such, this remains as a diagnosis of exclusion if eosinophilic disease is absent. A better understanding on what drives neutrophilic asthma is of major importance to employ appropriate preventative measures and treatments. The natural history of both eosinophilic and neutrophilic asthma has not been fully evaluated, and whether one may transition to the other with time or in response to targeted therapies remains unknown.

Compliance with Ethical Standards

Conflict of Interest Sara M. Assaf and Nicola A. Hanania declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J*. 2016. <https://doi.org/10.1183/13993003.01359-2015> **An important paper describing the importance of the concept of personalized medicine and the emergence of endotypes and phenotypes in asthma.**

2. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med*. 1999. <https://doi.org/10.1164/ajrccm.160.3.9812110>.
3. Assaf SM, Hanania NA. Biological treatments for severe asthma. *Curr Opin Allergy Clin Immunol*. 2019. <https://doi.org/10.1097/ACI.0000000000000549>.
4. Camelo A, Rosignoli G, Ohne Y, Stewart RA, Overed-Sayer C, Sleeman MA, et al. IL-33, IL-25, and TSLP induce a distinct phenotypic and activation profile in human type 2 innate lymphoid cells. *Blood Adv*. 2017. <https://doi.org/10.1182/bloodadvances.2016002352>.
5. Borish L. The immunology of asthma: asthma phenotypes and their implications for personalized treatment. *Ann Allergy Asthma Immunol*. 2016. <https://doi.org/10.1016/j.anai.2016.04.022>.
6. Paul WE. What determines Th2 differentiation, in vitro and in vivo? *Immunol Cell Biol*. 2010. <https://doi.org/10.1038/icb.2010.2>.
7. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol*. 2010. <https://doi.org/10.1016/j.jaci.2009.11.017>.
8. Persson C. Lysis of primed eosinophils in severe asthma. *J Allergy Clin Immunol*. 2013. <https://doi.org/10.1016/j.jaci.2013.09.036>.
9. Balzar S, Fajt ML, Comhair SAA, et al. Mast cell phenotype, location, and activation in severe asthma. *Am J Respir Crit Care Med*. 2011. <https://doi.org/10.1164/rccm.201002-0295oc>.
10. Fajt ML, Gelhaus SL, Freeman B, Uvalle CE, Trudeau JB, Holguin F, et al. Prostaglandin D2 pathway upregulation: relation to asthma severity, control, and TH2 inflammation. *J Allergy Clin Immunol*. 2013. <https://doi.org/10.1016/j.jaci.2013.01.035>.
11. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol*. 2004. <https://doi.org/10.1016/j.jaci.2003.10.041>.
12. Peters MC, Kerr S, Dunican EM, et al. Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol*. 2019. <https://doi.org/10.1016/j.jaci.2017.12.1009>.
13. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016. <https://doi.org/10.1016/j.jaci.2015.12.1324>.
14. Liu T, Kanaoka Y, Barrett NA, et al. Aspirin-exacerbated respiratory disease involves a cysteinyl leukotriene-driven IL-33-mediated mast cell activation pathway. *J Immunol*. 2015. <https://doi.org/10.4049/jimmunol.1500905>.
15. Buchheit KM, Cahill KN, Katz HR, et al. Thymic stromal lymphopoietin controls prostaglandin D2 generation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2016. <https://doi.org/10.1016/j.jaci.2015.10.020>.
16. Walsh CJ, Zaihra T, Benedetti A, Fugère C, Olivenstein R, Lemièrè C, et al. Exacerbation risk in severe asthma is stratified by inflammatory phenotype using longitudinal measures of sputum eosinophils. *Clin Exp Allergy*. 2016. <https://doi.org/10.1111/cea.12762>.
17. Westerhof GA, Korevaar DA, Amelink M, De Nijs SB, De Groot JC, Wang J, et al. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. *Eur Respir J*. 2015. <https://doi.org/10.1183/09031936.00012415> **An important paper investigating the accuracy of surrogate biomarkers of sputum eosinophilia.**
18. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012. [https://doi.org/10.1016/S0140-6736\(12\)60988-X](https://doi.org/10.1016/S0140-6736(12)60988-X).
19. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013. <https://doi.org/10.1056/NEJMoA1304048>.
20. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011. <https://doi.org/10.1164/rccm.9120-11ST>.
21. Hanania NA, Massanari M, Jain N. Measurement of fractional exhaled nitric oxide in real-world clinical practice alters asthma treatment decisions. *Ann Allergy Asthma Immunol*. 2018. <https://doi.org/10.1016/j.anai.2018.01.031>.
22. Schleif F, Demarche S, Louis R. Biomarkers in the management of difficult asthma. *Curr Top Med Chem*. 2016. <https://doi.org/10.2174/1568026616666151015093406>.
23. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014. <https://doi.org/10.1002/14651858.CD003559.pub4>.
24. Divekar R, Hagan J, Rank M, Park M, Volcheck G, O'Brien E, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. *J Allergy Clin Immunol Pract*. 2016. <https://doi.org/10.1016/j.jaip.2016.03.004>.
25. Izuhara K, Conway SJ, Moore BB, Matsumoto H, Holweg CTJ, Matthews JG, et al. Roles of periostin in respiratory disorders. *Am J Respir Crit Care Med*. 2016. <https://doi.org/10.1164/rccm.201510-2032PP>.
26. Jia X, Li S, Xu TT, Ji N, Huang M. Diagnostic accuracy of periostin in predicting asthma: a systematic review and meta-analysis. *J Asthma*. 2019. <https://doi.org/10.1080/02770903.2019.1684518>.
27. Kuo CHS, Pavlidis S, Loza M, et al. A transcriptome-driven analysis of epithelial brushings and bronchial biopsies to define asthma phenotypes in U-BIOPRED. *Am J Respir Crit Care Med*. 2017. <https://doi.org/10.1164/rccm.201512-2452OC>.
28. Chang HS, Lee TH, Jun JA, Baek AR, Park JS, Koo SM, et al. Neutrophilic inflammation in asthma: mechanisms and therapeutic considerations. *Expert Rev Respir Med*. 2017. <https://doi.org/10.1080/17476348.2017.1268919> **A review discussing the pathomechanisms and clinical implications of neutrophilic asthma.**
29. Al-Ramli W, Préfontaine D, Chouiali F, Martin JG, Olivenstein R, Lemièrè C, et al. T H 17-associated cytokines (IL-17A and IL-17F) in severe asthma. *J Allergy Clin Immunol*. 2009. <https://doi.org/10.1016/j.jaci.2009.02.024>.
30. Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The neutrophilic inflammatory phenotype is associated with systemic inflammation in asthma. *Chest*. 2012. <https://doi.org/10.1378/chest.11-1838>.
31. Raundhal M, Morse C, Khare A, et al. High IFN- γ and low SLPI mark severe asthma in mice and humans. *J Clin Invest*. 2015. <https://doi.org/10.1172/JCI80911>.
32. Maniscalco M, Paris D, Melck DJ, D'Amato M, Zedda A, Sofia M, et al. Coexistence of obesity and asthma determines a distinct respiratory metabolic phenotype. *J Allergy Clin Immunol*. 2017. <https://doi.org/10.1016/j.jaci.2016.08.038>.
33. Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, et al. Cluster analysis of obesity and asthma phenotypes. *PLoS One*. 2012. <https://doi.org/10.1371/journal.pone.0036631>.
34. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol*. 2018. <https://doi.org/10.1016/j.jaci.2018.02.004>.
35. Peters MC, McGrath KW, Hawkins GA, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med*. 2016. [https://doi.org/10.1016/S2213-2600\(16\)30048-0](https://doi.org/10.1016/S2213-2600(16)30048-0).
36. Takahashi K, Pavlidis S, Ng Kee Kwong F, et al. Sputum proteomics and airway cell transcripts of current and ex-smokers with severe asthma in U-BIOPRED: an exploratory analysis. *Eur Respir J*. 2018. <https://doi.org/10.1183/13993003.02173-2017>.
37. Hanania NA, King MJ, Braman SS, et al. Asthma in the elderly: current understanding and future research needs - a report of a

- National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol*. 2011. <https://doi.org/10.1016/j.jaci.2011.06.048>.
38. Dunn RM, Busse PJ, Wechsler ME. Asthma in the elderly and late-onset adult asthma. *Allergy Eur J Allergy Clin Immunol*. 2018. <https://doi.org/10.1111/all.13258>.
 39. Mathur SK. Allergy and asthma in the elderly. *Semin Respir Crit Care Med*. 2010. <https://doi.org/10.1055/s-0030-1265899>.
 40. Baptist AP, Busse PJ. Asthma over the age of 65: all's well that ends well. *J Allergy Clin Immunol Pract*. 2018. <https://doi.org/10.1016/j.jaip.2018.02.007>.
 41. Maes T, Cobos FA, Schleich F, et al. Asthma inflammatory phenotypes show differential microRNA expression in sputum. *J Allergy Clin Immunol*. 2016. <https://doi.org/10.1016/j.jaci.2016.02.018>.
 42. Nair P, Aziz-Ur-rehman A, Radford K (2015) Therapeutic implications of "neutrophilic asthma." *Curr Opin Pulm Med* <https://doi.org/10.1097/MCP.0000000000000120>.
 43. Cavaleiro Rufo J, Madureira J, Oliveira Fernandes E, Moreira A. Volatile organic compounds in asthma diagnosis: a systematic review and meta-analysis. *Allergy Eur J Allergy Clin Immunol*. 2016. <https://doi.org/10.1111/all.12793>.
 44. Schleich FN, Zanella D, Stefanuto PH, et al. Exhaled volatile organic compounds are able to discriminate between neutrophilic and eosinophilic asthma. *Am J Respir Crit Care Med*. 2019. <https://doi.org/10.1164/rccm.201811-2210OC>.
 45. Murillo JC, Dimov V, Gonzalez-Estrada A. An evaluation of fevipiprant for the treatment of asthma: a promising new therapy? *Expert Opin Pharmacother*. 2018. <https://doi.org/10.1080/14656566.2018.1540589>.
 46. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017. [https://doi.org/10.1016/S0140-6736\(17\)31281-3](https://doi.org/10.1016/S0140-6736(17)31281-3).
 47. Brusselle GG, VanderStichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax*. 2013. <https://doi.org/10.1136/thoraxjnl-2012-202698>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.