Asthma: definitions and pathophysiology

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Background: **Asthma is a common condition due to chronic inflammation of the lower respiratory tract. Chronic lower airway inflammation is known to be more common in individuals that also have inflammatory disorders of the upper airway. The scientific understanding of asthma continues to improve and it is important for providers who treat upper or lower airway inflammation to be familiar with asthma's definition and pathophysiology.**

Methods: **Articles were selected based on literature reviews through PubMed and personal knowledge of the author. The search selection was not standardized.**

Results: **Asthma is a heterogenic condition that is underdiagnosed and undertreated despite that the skills needed to diagnose it are readily attainable and effective treatments are available. Providers need a working understanding of asthma in order to be proficient at managing their patients with chronic nasal or sinus inflammation. This article provides a primer focusing on the current conception asthma in terms of definition, possible etiologies, inflammatory profile, pathophysiology, subtypes, and overlapping conditions.**

Conclusion: **Asthma is a chronic inflammatory disorder arising from not fully understood heterogenic gene-environment interactions. It features variable airway obstruction and bronchial hyperresponsiveness. Clinically, asthmatics exhibit recurrent episodes of wheeze, cough, chest tightness, and shortness of breath.** © 2015 ARS-AAOA, LLC.

Key Words:
asthma; pathophysiology; genetics; epigenetics; phenotypes; definitions

***How to Cite this Article*:**
Mims JW. Asthma: definitions and pathophysiology. *Int Forum Allergy Rhinol*. 2015;5:S2–S6.

What is asthma? Chronic upper airway inflammation, such as chronic otitis media, chronic rhinitis, chronic sinusitis, chronic pharyngitis, and chronic laryngitis, encompass a wide array of potential causes and conditions. However, "asthma" is more specific than chronic inflammation of the lower respiratory tract but still represents a heterogeneous set of clinical conditions that vary in severity, onset, risk factors, triggers, response to treatment, genetics, and natural history.[1] Moreover, the differences and overlap between asthma and other labels such as reactive airway disease and bronchiolitis are often unclear. This article attempts to help providers understand the core features of asthma that separate it from other conditions, and the underpinnings of the wide heterogeneity of clinical expressions encountered within the asthma diagnosis.

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Potential conflict of interest: None provided.
Received: 19 April 2015; Revised: 22 May 2015; Accepted: 26 June 2015

DOI: 10.1002/alr.21609
View this article online at wileyonlinelibrary.com.

Asthma definition

The 1991, 1997, and 2007 National Institute of Health Guidelines on Asthma (NIH Guidelines) define asthma as follows: "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma."[1] This definition, similar to chronic sinusitis, places the emphasis on the presence of inflammation and resulting symptoms without reference to cause, which is not fully known, or natural history, which is variable.

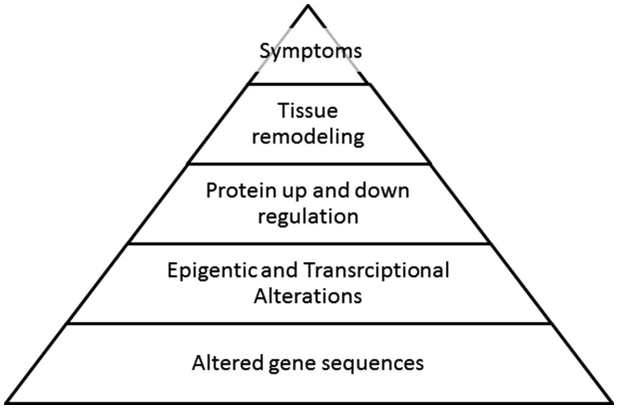

FIGURE 1. Asthma is a complex and heterogenic condition with broad variability at the genetic level and multiple opportunities for altering how the genetic diversity is expressed. There is a confluence of histopathological changes seen from the gene-environment interactions resulting in a relatively few symptoms, but with variations in severity, natural history, and response to therapy.

Asthma etiology

The cause of asthma is not known, but risk factors have been identified and gene-environment interactions are important. Genetics are known to play a role, with asthma with heritability ranging between 35% and 95%.[2] Large genetic studies have identified hundreds of genetic variants associated with an increased risk of asthma.[3] Epigenetic variations in how the genetic code is translated have also been shown to have a role in the development of asthma.[4] Respiratory infections, especially viral infections early in life, increase the risk of developing asthma, particularly if the symptoms are severe.[5] Airborne environmental exposures increase the risk of asthma, including tobacco smoke, pollutants, and ozone. Atopic conditions and sensitization to inhalant allergens are also associated with developing asthma.[1] Other factors have been theorized to play a role in asthma development, including effects of the microbiome,[6] vitamin D,[7] chemical exposure,[8] dietary changes,[9] stress,[10] and metabolites.[6] Current asthma understanding entails a broad amount of genetic diversity, which is variably translated and environmentally influenced via epigenetic and transcriptional factors, leading to less diverse histopathological features with resulting cardinal asthmatic symptoms (Fig. 1).

Genetics

It has long been recognized that asthma has a genetic component. Several studies have shown that offspring of asthmatic parents are at increased risk of developing asthma, and maternal asthma is a greater risk than paternal asthma.[2,11] Genetics do not entirely explain asthma, as exhibited by discordance of asthma in identical twins.[12] Genetic studies have described broad genetic heterogeneity in asthma, which is influenced by hundreds of genes (Table 1).[3] Genomewide association studies that look for genetic differences between populations of those with and without asthma across the human genome have most consistently identified the 17q21 locus. Changes in 4 genes (ORMDL3, GSDMB, ZPBP2, and IKZF3) in this locus reduce protein folding in the endoplasmic reticulum, resulting in a proinflammatory effect.[6] Much of the genetic risk for asthma is not yet explained.[6]

TABLE 1. Major gene alterations identified in various asthma studies*

Possible functional groups	Genes
Protein folding in endoplasmic reticulum	ORMDL3, GSDMB, ZPBPW, IKZFE
Atopy	HLAG, FCR1A, CD23, OPN3/CHML, CYF1P2, IL4, IL4RA, IL12, IL13, GATA3, STAT5, STAT6, TBX21, PHF11, IRAKM
Epithelium	IRAKIM, TLR2, TLR4, CD14, GSTP1, GSTMI1,3,5, GSTT
Eosinophils	MYB, WDR36, ILR1RL1, IL33
Tissue response	ADAM33, UPAR, NPSR1, IRAKM, IL13, COL29A1, TNC
Barrier function	FLG, SPINK5, CTNNA3, C11orf30, COL29A1, PNEDRIN, IL13

*Hundreds of gene alterations have been identified more commonly in asthmatics than nonasthmatics, although reproducibility between asthmatic populations has been problematic. This table shows the extent of heterogeneity among some of the most commonly identified genes.[3,6]

Epigenetics

Epigenetics refers to DNA characteristics that modify gene expression but are independent of the nucleotide sequence. Examples include DNA methylation, DNA hydroxylmethylation, histone modifications, and mitochondrial RNA modifications generally resulting in dysregulation of inflammation.[13] Maternal atopic risk may also be related to epigenetic DNA methylation.[14] Examples are listed in Table 2.

Transcription

Multiple studies have compared RNA transcription differences in and within asthma largely using oligonucleotide microarrays for transcriptome profiling.[6] Differences in gene expression between asthmatics and nonasthmatics[15] or between asthmatics before and after steroids[16] have again implicated hundreds of genes. This represents another level where environmental exposures and physiologic heterogeneity can alter the clinical expression of asthma.

Microbiome

The advent of RNA sequencing specific to bacteria (16S rRNA) has changed the conception of healthy bronchial airways from sterile to that of a healthy epithelium hosting of thousands of bacterial genomes per square centimeter.[17]

TABLE 2. Major gene alterations identified in various asthma studies*

Epigenetic mechanisms	Possible examples in asthma
DNA methylation	Downregulation of inflammatory regulators, increased methylation with tobacco smoke exposure. Maternal inheritance
Histone modifications	Modification in T cell profiles
Mitochondrial gene silencing	Not known

*Epigenetic alterations in expression or transcription of DNA are independent of gene sequence and likely mitigate some gene-environment interactions.[4,6]

Although Bacteroidetes predominate healthy airways, Proteobacteria and increased bacterial diversity have been associated with asthma.[18] Lower gut microbiome diversity in infancy has been associated with asthma at age 7 years.[19] Whether these relationships play a causal role in asthma has yet to be determined, but the role of commensal bacteria has generated interest.[20]

Pathophysiology

Cellular inflammation

Inflammation in the lower airway most likely arises from a combination of genetic predisposition, environmental exposures, and possibly alterations in the microbiome and metabolite (low molecular weight molecules in biologic systems).[6] Most asthmatics have type 2 inflammation, named for the type 2 T helper cell lymphocyte. Type 2 inflammation is associated with certain cytokine profiles (interleukin [IL]-4, IL-5, and IL-14) and inflammatory cells (eosinophils, mast cells, basophils, type 2 T helper lymphocytes, and immunoglobulin E [IgE]-producing plasma cells).[21] Type 2 inflammation is commonly seen in allergic diseases, eosinophilic disorders, and parasite infections. Airway epithelial cells have also been identified to play a large role regulating type 2 inflammation via cytokines (IL-25, IL-33, and thymic stromal lymphopoietin).[21] Asthmatics without a strong bias toward type 2 inflammation often exhibit poor response to corticosteroids and can be difficult to manage. Common features of cellular inflammation are summarized in Table 3.

Tissue remodeling

A plethora of pathological alterations occur in the lower airways; these alterations are collectively referred to as tissue remodeling. These primarily occur in the mucosa and submucosa. Pathological changes in the mucosa include epithelial hyperplasia and metaplasia of goblet cells with increased mucus production. Submucosally, smooth muscle hypertrophy, collagen deposition, and larger mucous glands dominate the changes seen, leading to narrower airways and increased mucous production during asthma episodes.[21] Table 4 highlights features of tissue remodeling observed in asthma.

TABLE 3. Type 2 inflammatory changes commonly identified in asthma (partial list)*

Airway cell type	Inflammatory changes
Epithelial cells	Increased IL-33, thymic stromal lymphopoietin
Dendritic cells	Increased OX40L expression, lymph node migration affecting lymphocyte maturation
Goblet cell	Metaplasia, increased mucin stores
Lymphocytes	Increased TH2 bias with downregulation of Treg cells. Increased IL-4, IL-5, and IL-13. Increased IgE-producing plasma cells
Eosinophils	IL-5–mediated accumulation
Mast cells and basophils	Increased IgE binding and mediator storage

*Most asthma features type 2 inflammation with a myriad of inflammatory changes leading to hyperreactivity and tissue remodeling.[21]
IgE = immunoglobulin E; IL = interleukin; TH2 = T helper 2; Treg = T regulatory.

TABLE 4. Tissue remodeling in asthma*

Histopathological changes in asthma
Smooth muscle hypertrophy and hyperplasia
Goblet cell hyperplasia
Hypertrophy of submucosal mucus glands
Subepithelial fibrosis and collagen deposition
Increased blood vessels in submucosa
Inflammatory cell infiltrate and submucosal edema

*Airway obstruction is caused by smooth muscle constriction and swelling reducing the airway diameter and increased mucus within the lumen.[21]

Clinical features

Symptoms

The inflammation underlying asthma is thought to be chronically present in most cases; however, asthma often presents clinically in attacks or episodes. The underlying inflammation may be present with an absence of symptoms, and control of the inflammation is central in the management of asthma. The disconnect between the inflammation and symptoms can allow for poor self-awareness of asthma, which can foster poor recognition and noncompliance with treatments.[1] The inflammation and associated

TABLE 5. Cardinal symptoms of asthma*

Four cardinal symptoms of asthma
Wheezing
Shortness of breath
Coughing
Chest tightness

*Asthmatics can display only 1 symptom or any combination of all 4 symptoms. Symptoms can be episodic or persistent.[1]

pathologic tissue changes cause a constellation of symptoms listed in Table 5.[1] The obstruction is dominantly bronchial and due to mucus production, tissue edema, and smooth muscle constriction. Smooth muscle constriction in the bronchi usually responds to inhaled $\beta 2$ agonists, creating a reversible component to asthma episodes. Testing for asthma is not the focus of this article, but assessment for reversible airflow obstruction representing the bronchial hyperresponsiveness is fundamental to diagnosing asthma in most cases. Asthma symptoms tend to be worse at night, which is concordant with the cycle of endogenous cortisol levels.

Asthma episodes (attacks, exacerbations)

Asthma episodes are the result of airway narrowing that occurs through 3 main mechanisms: swelling, secretions, and muscle constriction of the bronchi. Asthma episodes are more common in asthmatics under 18 years of age, females, and blacks (compared to whites).[1] Roughly one-half of those with asthma have an episode each year. Asthma episodes are more common after a recent asthma episode and at night or early morning.[1] Asthma episodes range broadly in severity. Many episodes resolve spontaneously or with minimal treatment whereas others can lead to emergency room visits, hospitalizations, or death. There is not an accepted classification of asthma episodes.[22]

Asthma triggers

Asthma episodes and worsening of inflammation can be initiated by triggers that can vary over time and between asthmatics. Common triggers include upper or lower respiratory tract viral infections, tobacco smoke, allergens, particulate pollution, ozone, change in temperature (usually cold), excitement, stress, nonsteroidal inflammatory medicines, or exercise.[1,22] Upper respiratory viral infection, especially rhinovirus, is the most common asthma trigger.[23]

Types of asthma (genotypes, phenotypes, endotypes)

Asthma is heterogenic and the literature is replete with papers separating asthma into different subtypes to guide prognosis or treatment responses; however, there is little consensus on the best method. Asthma is generally discussed in terms of endotypes (subtype by functional or biological mechanism) because there are so many genes and epigenetic influences. The advent of new therapies directed at specific inflammatory mediators such as IL-4 or IL-5 may increase the importance of subtyping asthma.[24] Computer models have been used in phenotyping and endotyping but vary between publications. Common "types" of asthma include: cough-variant asthma, exercise-induced asthma, allergic asthma, eosinophilic (type 2 inflammation) asthma, pediatric asthma, adult-onset asthma, steroid-resistant asthma, aspirin-induced asthma, and obesity-related asthma. In-depth discussion of clusters, phenotypes, and endotypes is beyond the scope of this primer, but reviews are available in the literature.[24,25]

Conditions similar to asthma

Reactive airway disease

Asthma is a reactive airway disease, and these terms are sometimes used interchangeably. However, asthma is difficult to diagnose in young children and often a diagnosis of reactive airway disease is preferred before the diagnosis of asthma can be made. Wheezing in young children (less than 3 years of age) is much more common than asthma at the age of 6 years,[26] which often leads to the "reactive airway" description.

Bronchopulmonary dysplasia

Prematurely born children who often have immature and smaller airways frequently exhibit episodic wheezing in childhood and can have persistent obstructive lung disease that resembles asthma and "asthma chronic obstructive pulmonary disease [COPD] overlap" syndrome. Most of these children had neonatal respiratory distress syndrome. Generally, these survivors tend to have less bronchial reversibility than those with asthma, although there is substantial clinical variability in bronchopulmonary dysplasia, which complicates matters.[27]

Bronchiolitis

Viral infection of the lower airway frequently causes bronchiole inflammation with resultant obstructive airway symptoms including wheezing. This is more common in early childhood, with respiratory syncytial virus being an archetypal example.[28] There is evidence that young children with severe symptoms during bronchiolitis are at increased risk of asthma,[5] but bronchiolitis and asthma are generally considered distinct entities.

COPD

COPD and adult-onset asthma have different profiles but can have overlap in almost any single feature. COPD tends to be type 1 neutrophilic inflammation of small airways associated with years of tobacco smoke (the primary risk factor). The tissue hallmarks include destruction of parenchymal lung tissue, loss of elasticity, and obstruction of the small airways. Asthma symptoms and episodes are

commonly reversible with β2 agonists, whereas reversibility is rare in COPD.[29]

Conclusion

Asthma is a heterogenic and complex disease originating from a variety of gene-environment interactions. Most asthma exhibits type 2 inflammation, which is often seen in allergic conditions and also as an immune response to parasites. Type 2 inflammation is mediated by respiratory epithelium and type 2 T-helper lymphocytes. Inflammation of the bronchi leads to increased mucus production, increased bronchoconstriction, and collagen deposition narrowing the airways. Asthma is often episodic, with a variety of environmental triggers that vary among asthmatics. Triggers include viruses, allergens, irritants (smoke), exercise, and temperature changes. The inflammation causes obstruction primarily of the bronchial airways with symptoms of shortness of breath, wheezing, chest tightness, and cough. The bronchoconstriction in asthma is often reversible with an inhaled β2 agonist. Reversibility often helps differentiate asthma from other pulmonary conditions. There are proven methods to diagnose and treat most asthmatics, making knowledge of asthma important for physicians who treat inflammatory disorders of the upper or lower airways.

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