SIXTH EDITION

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PULMONARY DISEASES AND DISORDERS

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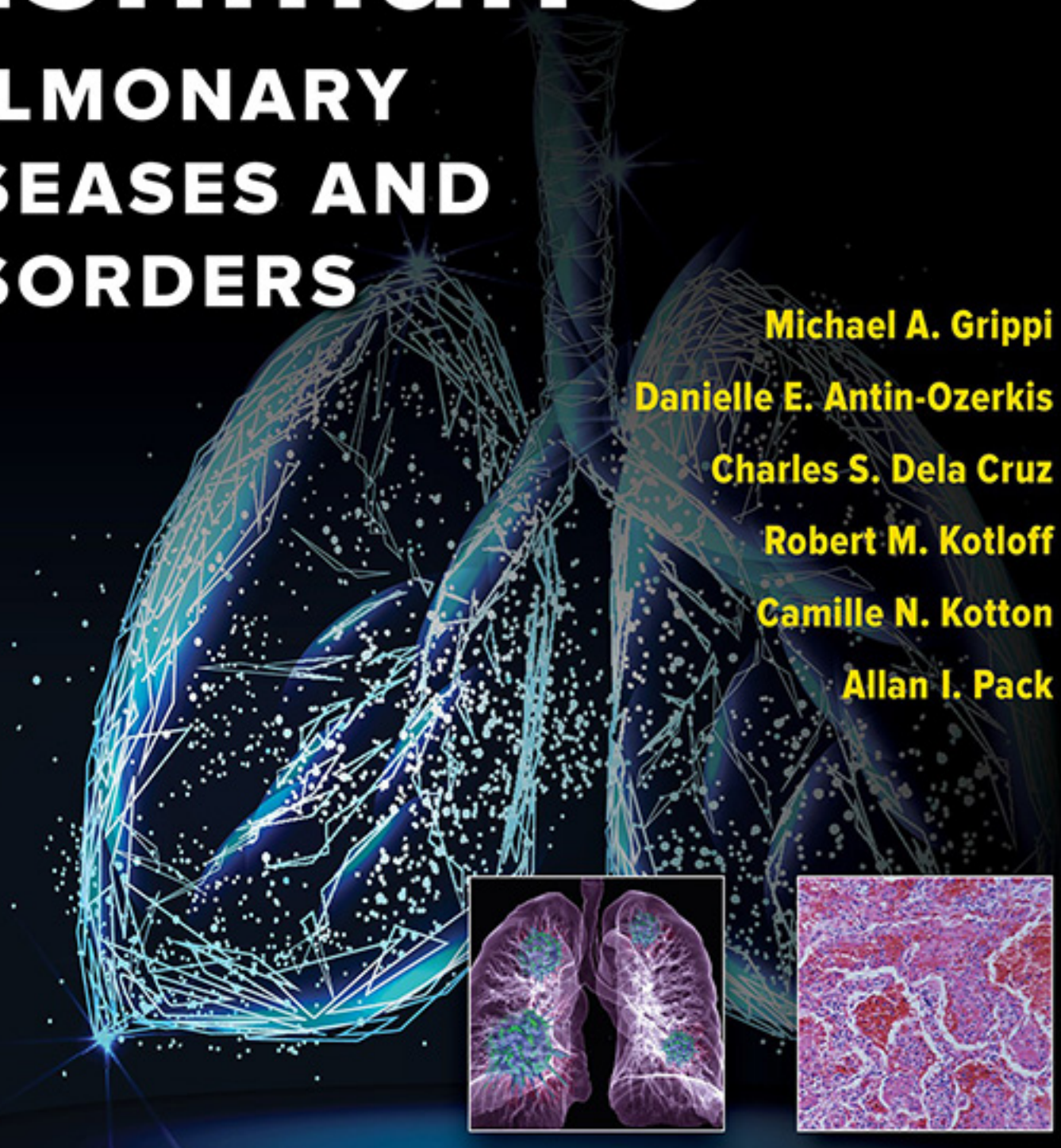

Mc Graw Hill

Fishman's Pulmonary Diseases and Disorders

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Volume 1

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New York Chicago San Francisco Lisbon London Madrid Mexico City
Milan New Delhi San Juan Seoul Singapore Sydney Toronto

ISBN: 978-1-26-047406-0
MHID: 1-26-047406-2

The material in this eBook also appears in the print version of this title: ISBN: 978-1-26-047398-8,
MHID: 1-26-047398-8.

eBook conversion by codeMantra
Version 1.0

Library of Congress Cataloging-in-Publication Data

Names: Grippi, Michael A., editor.
Title: Fishman's pulmonary diseases and disorders / editor-in-chief, Michael A. Grippi ; co-editors, Danielle E. Antin-Ozerkis, Charles S. Dela Cruz, Robert M. Kotloff, Camille N. Kotton,
Allan I. Pack
Other titles: Pulmonary diseases and disorders
Description: Sixth edition. | New York : McGraw-Hill Education, [2023] | Includes bibliographical references and index. | Summary: "A presentation of pulmonary and critical care medicine with the underlying basic and applied science upon which the clinical material is based. The book includes relevant respiratory biology and underlying cellular and molecular mechanisms, and incorporates of a number of videos designed to complement and, at times, accentuate information contained within the text"– Provided by publisher.
Identifiers: LCCN 2021052087 | ISBN 9781260473988 (hardcover ; set ; alk. paper) | ISBN 9781260474060 (ebook)
Subjects: MESH: Lung Diseases
Classification: LCC RC756 | NLM WF 600 | DDC 616.2/4–dc23/eng/20220510
LC record available at https://lccn.loc.gov/2021052087

CHAPTER 43

The Biology of Asthma

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INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by persistent variable symptoms that include shortness of breath, cough, and wheezing.[1] It is the most common chronic lung disease and one of the most prevalent diseases in the United States, affecting more than 20 million adults and 7 million children.[2] Attempts to elucidate the cellular and molecular effector pathways that contribute to asthma have led to the realization that it is a protean disease driven by many cell types and mechanisms. This degree of mechanistic variation explains the numerous clinical phenotypes that are now recognized, as well as differences in response to treatment with inhaled therapies and the targeted biologic treatments that have entered the clinic over the last decade.

Core to the pathogenesis of asthma is bronchoconstriction and variable airflow obstruction, airway hyperresponsiveness, and chronic airway inflammation.[3] It is, however, the complex interplay between these factors that eventually defines the clinical expression of disease in individual patients. Here, a close examination of the cellular and molecular mediators involved in each of these components will be presented to allow for a more comprehensive understanding of this complex disease.

ADAPTIVE AND INNATE INFLAMMATORY RESPONSES IN ASTHMA

The inflammatory response in the airways of patients with asthma is complex, heterogenous, and evolves over time, but the prototypical events seen in most patients with asthma (65%–80%) are type 2 (T2) inflammatory responses (Fig. 43-1). T2 inflammation is currently thought of as being driven by both innate and adaptive mechanisms to varying degrees in each individual with asthma, which explains much of the heterogeneity in clinical presentation, biomarkers, and treatment response. The most well-understood T2 pathway is the

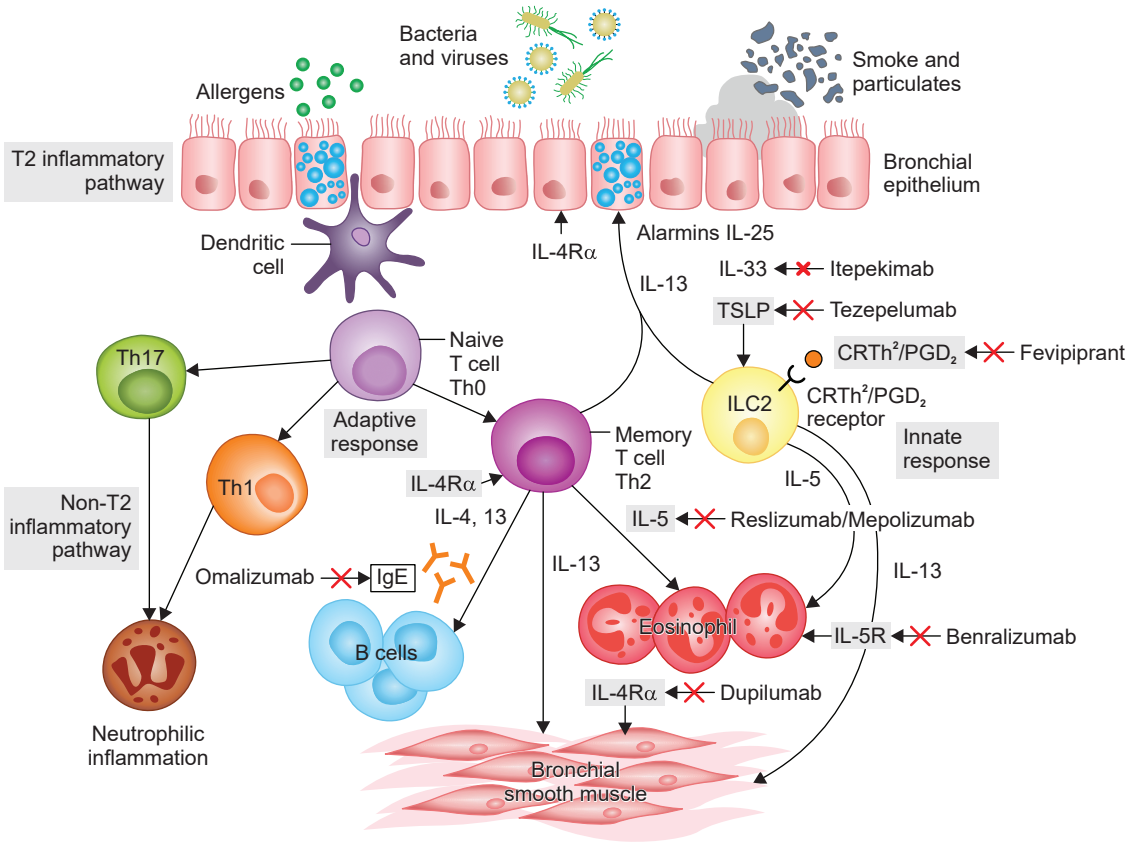


Figure 43-1 Inflammatory pathways in asthma. The T2 inflammatory pathway with contributions from the adaptive and innate immune response leads to production of T2 cytokines IL-4, IL-5, and IL-13. The non-T2 pathway with activation of T_H1 and T_H17 cells leads to neutrophil activation. Both inflammatory pathways can lead to asthma symptoms and airway remodeling. TSLP is the target of tezepelumab; IL-5 is the target of reslizumab and mepolizumab; IgE is the target of omalizumab; CRTH2/PGD2 is the target of fevipiprant; IL-4Rα is the target of dupilumab; IL5R is the target of benralizumab. FTH, follicular T helper; ILC2, innate lymphoid cell 2; NKT, natural killer cell; TCR, T cell receptor; TSLP, thymic stromal lymphopoietin; TSLPR, TSKP receptor.

allergic inflammatory response that is, largely, an adaptive immune response to initial and subsequent exposures to inhaled allergens. While the key cellular and molecular mediators will be described in greater detail later in the chapter, we now describe the evolution of the allergic response. This is the foundation upon which other concepts have been constructed and illustrates the basis for chronic variable changes that occur in the airway in asthma and in the clinical expression of disease.

The adaptive response begins when a novel antigen (allergen) enters the airway of an individual at risk, where it becomes trapped in the mucus layer lining the airway. Here it is endocytosed by professional antigen-presenting dendritic cells. During this process it encounters tentacle-like projections or "dendrites" of the dendritic cells that are intercalated amongst bronchial epithelial cells throughout the airways.[4,5] After the uptake and processing of the antigen, the dendritic cells migrate to local lymph nodes in the lung and mediastinum, where the antigen is presented to naïve $CD4^+$ T cells via the T cell receptor (TCR).[5] Additional signals derived from the dendritic cell determine which type of $CD4^+$ memory T cell the naïve T cell will become (i.e., Th1, Th2, Th17, Treg)—which determines what repertoire of cytokines the memory T cell will produce. Prior to this event, the dendritic cell is influenced by a complex network of molecular signals that are derived from airway epithelial cells and other local cell types. For example, the production of epithelial cytokines or alarmins—such as thymic stromal lymphopoietin (TSLP), interleukins (IL)-33 and -25, and granulocyte-monocyte colony-stimulating factor (GM-CSF)—creates a milieu for dendritic cells to promote naïve $CD4^+$ T cell polarization into T_H2 that creates an environment favorable for the persistence of allergic inflammation.[5] Other cell types also are activated including B cells, which, in the presence of IL-4 and IL-13, are influenced to produce antigen-specific IgE that binds to high-affinity IgE receptors (FcεRI) on mast cells and basophils. Upon rechallenge with the sensitizing antigen, the sensitized T_H2-differentiated $CD4^+$ T cells are recruited back to the airway by other signals, such as chemokines CCL17 and CCL22 secreted by dendritic cells.[6] Upon arrival to the airway, the $CD4^+$ T_H2 cells become key sources of the T_H2 cytokines IL-4, IL-5, and IL-13, which serve as the molecular catalysts that drive the T_H2 inflammatory response.[6]

Upon subsequent exposure to the antigen, the local environment of the airways is now primed to respond to the antigen in the future, rich with T_H2 cytokines and antigen-specific IgE, which act on other cell types, either present or recruited to the airway, to amplify the allergic inflammatory response. When inhaled antigen cross-links membrane-bound IgE on mast cells and basophils, a variety of preformed and synthesized meditators are released and cause bronchoconstriction, airway wall edema, and local tissue damage.[7] Mast cells release chemoattractants such as leukotrienes and chemokines that recruit additional inflammatory cells including eosinophils, basophils, neutrophils, and lymphocytes to establish a late-phase inflammatory response.[7] The eosinophil appears to be, in most cases, the most important and abundant inflammatory cell associated with the late-phase response and the primary cell contributing to inflammation, tissue damage, and airflow obstruction through a vast number of mediators that are reviewed below.[8] Eosinophil products can cause local tissue damage, mucus hypersecretion, increased vascular permeability, and smooth muscle contraction, and they sustain the inflammatory response by recruiting other cell types that perpetuate the inflammation.[7,8] The roles of macrophages, neutrophils, and basophils in the pathogenesis of the acute- and late-phase allergic inflammatory responses are less well defined but are likely important in other subtypes of disease and clinical settings as outlined below.

While the acute allergic response to allergen illustrates the pattern of inflammation seen in asthma, it should be noted that other forms of inflammation also play important roles in asthma pathogenesis. Viral respiratory infections, especially with human rhinovirus (HRV), are important triggers of asthma exacerbations.[9] The response to HRV is a primarily T_H1-driven response with increased production of IL-8 and IL-1β and the initial appearance of airway neutrophilia, in contrast to the T_H2 response seen after allergen exposure.[9,10] With HRV infections, there is also release of epithelial cell alarmins, with IL-33 in particular activating ILC2 to generate IL-5 and recruit eosinophils to the airway and cause inflammation and airflow obstruction.[11] In asthma, there is evidence that in the milieu of the T2 response there is diminished production of type I and III interferons. Some patients with asthma may be deficient in these critical antiviral cytokines, which leads to increased risk for viral respiratory infections and a greater susceptibility to exacerbations of asthma.[9,10]

The pattern of the acute- and late-phase inflammatory responses to antigen is a central paradigm of asthma that leads to chronic variable symptoms and chronic inflammation associated with the disease. Many of the cell types and inflammatory mediators seen in asthma that were briefly touched upon in the preceding paragraphs will now be discussed in more detail.

CELL TYPES IN ASTHMA

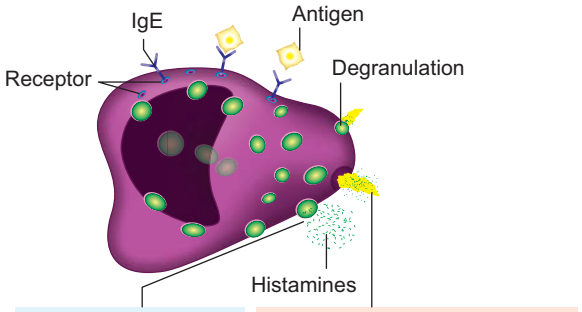
A review of the pathogenesis of any complex disease begins at the cellular level. The importance of cells of the immune system, including mast cells, basophils, $CD4^+$ T cells, eosinophils, neutrophils, macrophages, dendritic cells, and T lymphocytes, as well as their molecular mediators, has long been recognized and appreciated in the development and regulation of inflammation. The contribution of airway smooth muscle cells, especially in relationship to the acute asthmatic response, also has been well documented. More recently, innate immune responses have been increasingly recognized as important drivers of T2 inflammation independent of the adaptive immune response in as many as 50% of patients with severe asthma.[12] In addition, bronchial epithelial cells of the airway have become the focus of intense research and are emerging as critical to both the acute and chronic inflammatory responses in asthma. Their role in airway inflammation and airway remodeling is increasingly cited as a major contributor to the severity of this disease.

Cells of the Immune System in Asthma

Below we consider a variety of cellular components of the immune system in asthma.

Mast Cells

Human mast cells are derived from the same $CD34^{+/}cKit^+$ hematopoietic stem cell population that also gives rises to eosinophils, basophils, neutrophils, and monocytes.[13] They are resident cells in most tissues of the body and are commonly found in association with blood vessels, nerves, and surfaces that have contact with the external environment.[14] Mast cells (MC) exist in two types in humans and are differentiated by their immunohistochemical staining properties.[15] MC_T mast cells contain only the neutral protease tryptase, while MC_{TC} mast cells contain chymase, carboxypeptidase A3, and cathepsin G–like protease in addition to tryptase.[15–17] In normal lung tissue, mast cells are located in the subepithelium of the bronchi, bronchioles, and alveolar walls and are almost exclusively of the MC_T type.[15] This distribution of mast cell types is also seen in mild asthma. However, in severe asthma, mast cells are primarily of the MC_{TC} type and are decreased in number in the submucosa but are increased in the airway epithelium, a finding not seen in normal airways or milder disease.[18] Mast cells also infiltrate airway smooth muscle bundles in asthma, where they likely contribute to inflammation, airway hyperresponsiveness, and bronchoconstriction through the action of their released mediators.[19]



Preformed mediators

- Histamine
- Proteases
  - Tryptase
  - Chymotryptase
  - Carboxypeptidase
  - Kininogenase
- Heparin

Newly synthesized mediators

- Platelet activating factor
- Arachidonic acid metabolites
  - Leukotrienes
    - LTB4, LTC4, LTD4
  - Prostaglandins
    - PGD2
  - Thromboxane A2
- Growth factors
  - GM-CSF, FGF-2, VEGF
- Cytokines
  - TNF-α, IL-4, IL-5, IL-8, IL-13

Figure 43-2 The mast cell and its mediators. FGF-2, fibroblast growth factor 2; GM-CSF, granulocyte-monocyte colony-stimulating factor; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

While the role of mast cells in allergic (IgE-mediated) asthma is well established, these effector cells also appear to be important in nonallergic disease.[20] In allergic responses, antigen-specific IgE molecules bind allergen and cross-link high-affinity IgE receptors (FcεRI) present on the mast cell surface. Mast cells can also be activated by nonallergic stimuli such as heat and bronchospasm. This results in the release of preformed mediators, such as histamine, tryptase, chymase, and heparin, as well as tumor necrosis factor alpha (TNF-α) and vascular endothelial growth factor (VEGF).[21] Upon activation, mast cells generate and release newly synthesized mediators, which contribute to the ongoing inflammatory milieu. These include leukotrienes (predominantly LTC4); prostaglandins (predominantly PGD_2); thromboxane A2; platelet activating factor (PAF); growth factors including GM-CSF, fibroblast growth factor 2, and VEGF; and many other cytokines including but not limited to TNF-α, IL-4, IL-5, IL-8, and IL-13 (Fig. 43-2).[21,22]

The effect of mediators released from mast cells contributes to numerous features of the asthmatic response.[7] Histamine, leukotrienes, and proteases contribute to increased mucus production. Prostaglandins, leukotrienes, thromboxane A2, and histamine cause bronchoconstriction and increase vascular permeability. These proteases produce tissue damage and activation of many protein precursors. This, in turn, contributes to the recruitment, differentiation, and activation of other inflammatory cells, which results in the propagation of the inflammatory response.

Basophils

With the exception that basophils are present primarily in the peripheral circulation, basophils share many similarities with mast cells. These enigmatic cells share a common progenitor cell with mast cells, also express FcεRI on their cell surface, and release both preformed and newly synthesized mediators and cytokines upon cross-linking by IgE-antigen complexes on their surface. Like mast cells, the major preformed mediator released from basophils is histamine. Preformed heparin and tryptase also are released, albeit at lower concentrations than by mast cells.[23] Basophils synthetize and release LTC_4 upon activation, but unlike mast cells, they do not produce PGD_2.[23] Upon activation, basophils produce large quantities of IL-4 and IL-13.[23] Basophils have been shown to contribute to T_H2 differentiation by presenting antigen via major histocompatibility complex (MHC) class II and co-stimulatory molecules,[24] and basophils, along with eosinophils, are a primary target of the alarmin IL-33, a potent promoter of allergic inflammation and T_H2 polarization.[25]

Eosinophils

Eosinophils, like basophils and mast cells, are granulocytes derived from $CD34^+$ hematopoietic stem cells. Early eosinophil production is highly dependent upon the presence of GM-CSF and IL-3.[26] Eosinophil precursors are recruited to the airway in asthma as the result of cytokine and chemokine signaling. This signaling involves IL-5; eotaxins; CCL5/regulated on activation, normal T cell expressed and secreted (RANTES); macrophage inflammatory protein (MIP) 1α; and macrophage chemotactic factors 2, 3, and 4 (MCP-2, -3, and -4).[27] IL-5 is critically important to the terminal differentiation of eosinophils and release from the bone marrow.[26] Blockade of the IL-5 pathway with biologic therapies in patients with asthma results in the near elimination of eosinophils from the blood, highlighting this cytokine's importance to this cell's association and contribution to asthma.[28]

Once in the airway, eosinophils are activated by mechanisms not clearly established to contribute to the inflammatory response by releasing a wide variety of mediators. These include cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, tumor necrosis factor α [TNF-α], and transforming growth factor α and β [TGF-α and TGF-β]), chemokines (MIP-1, MCP-2, RANTES, and eotaxin), and lipid mediators (PGE_1, PGE_2, thromboxane B_2, PAF, and LTC_4) (Fig. 43-3).[29,30] Eosinophils secrete granule proteins, which are recognized as the eosinophil's essential mechanism in defense against parasites.[29,31] Eosinophils contain both primary and secondary granules. The primary granules contain Charcot-Leyden crystal protein, while the secondary granules contain the four principal cationic proteins: MBP (major basic protein), ECP (eosinophil cationic protein), EDN (eosinophil-derived neurotoxin), and EPO (eosinophil peroxidase).[29] These cationic proteins contribute to the pathogenesis of asthma through the induction of mast cell and basophil degranulation (ECP and MBP), increasing airway mucus production (ECP), and formation of reactive oxygen species (EPO).[29] The presence of Charcot-Leyden crystals has proved to be a key factor in the eosinophil's contribution to airway inflammation.[32]

Over the past 30 years, the role of the eosinophil in asthma has undergone considerable re-evaluation. Since the discovery of the eosinophil by Ehrlich in 1879 and the later discovery that Ehrlich's cells were present in the sputum of asthmatic patients, the eosinophil has been viewed as the primary effector cell in asthma.[33] Studies have noted that peripheral blood eosinophilia is a characteristic of asthma, correlated with disease severity, and that eosinophilic infiltrates were in the airways of asthma patients at autopsy, regardless of whether asthma was the primary cause of death.[34,35] Later studies detected increased eosinophils and eosinophil products in bronchoalveolar lavage (BAL) fluid after antigen challenge.[36] This concept of the eosinophil as a principal effector in asthma was largely unvalidated until the new millennium, when monoclonal antibodies against IL-5 (mepolizumab and reslizumab) and the IL-5 receptor (benralizumab) were demonstrated to be potent modulators of eosinophil levels in the blood, asthma exacerbations, and airway obstruction.[28]

Initial studies with monoclonal antibodies against IL-5 in patients with asthma (independent of their level of eosinophilic inflammation) showed a decrease in sputum and peripheral blood eosinophilia, as expected, but failed to demonstrate significant benefit in a wide variety of clinical outcome measures, including symptom score or improved airflow obstruction.[37,38] Although the

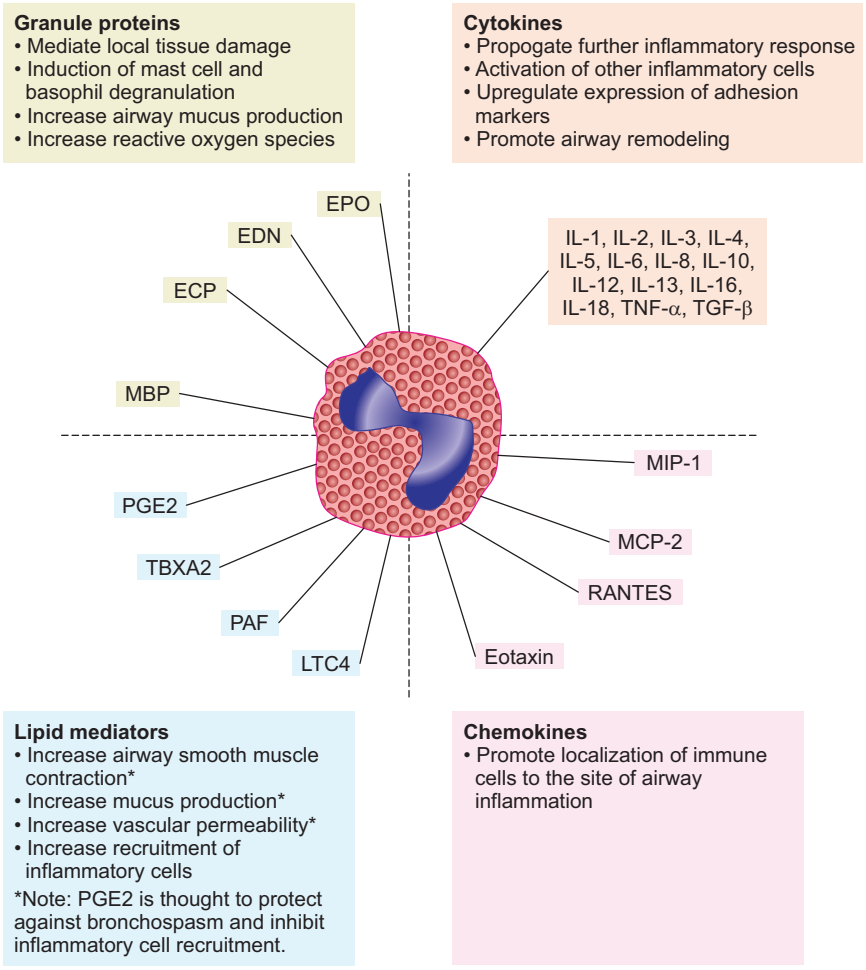


Figure 43-3 Eosinophil products in asthma. ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EPO, eosinophil peroxidase; LTC4, leukotriene C4; MBP, major basic protein; MCP-2, monocyte chemotactic protein 2; MIP-1, macrophage inhibitory protein 1; PAF, platelet activating factor; PGE2, prostaglandin E2; RANTES, regulated upon activation normal T cell expressed and secreted; TBXA2, thromboxane A2; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

lack of effect on these parameters of clinical asthma was a surprise, it contributed to the current understanding of asthma as a highly heterogeneous disease where inflammatory cells like eosinophils can play variable roles in different patients, thus emphasizing the importance of determining the individual phenotype of an asthma patient when judging the likely efficacy of a particular biologic agent.[28] Studies with the anti-IL-5 monoclonal antibodies mepolizumab and reslizumab, and the anti-IL-5 receptor antibody benralizumab, were conducted in patients with uncontrolled asthma. Treatment of patients with a history of multiple exacerbations and persistent eosinophilia in the blood or sputum or high exhaled nitric oxide levels despite treatment with inhaled corticosteroids (ICS) led to a substantial reduction in systemic corticosteroid-requiring exacerbations.[39,40] From these studies emerged the concept that there exists a subtype of patient with asthma in which the eosinophil plays a key role. Eosinophils are also a prime contributor to airway remodeling, mucus hypersecretion, and formation of mucus plugs, discussed later in the chapter.[41]

Neutrophils

Neutrophils are granulocytes also derived from $CD34^+$ hematopoietic stem cells that are normally present in the bloodstream, as well as in various tissues, including the lung. They contain primary (azurophilic) and secondary (specific) granules, which contain antimicrobial enzymes, neutral proteases, and acid hydrolases.[42] Neutrophils are attracted to the airway by numerous cytokines and chemokines including IL-8, IL-17, and granulocyte colony–stimulating factor (G-CSF).[43,44] Airway neutrophilia can be seen in many respiratory conditions, viral respiratory infections, COPD, and asthma.[10,44]

The role of neutrophils in the initial response to a viral respiratory infection is well understood. In response to inoculation with a respiratory virus, such as HRV, dendritic cells and other mononuclear cells produce proinflammatory cytokines and chemokines, which recruit neutrophils to the airway.[10] Neutrophils contribute to the inflammatory milieu by secreting cytokines such as TNF-α, IL-1, IL-8, and IL-18, to attract other inflammatory cells, upregulate cytokine production, produce airway inflammation, and enhance bronchial hyperresponsiveness.[45] Neutrophil products, such as elastase, have direct effects on the airway and contribute to mucus production.[10] Furthermore, HRV activation of neutrophils releases DNA-containing NETs that, in turn, activate T_H2 lymphocytes to release T2 cytokines.[46] In addition, because neutrophils are found in some patients with severe asthma, they have been hypothesized to play a prominent role in this phenotype.[47] Neutrophilic inflammation has been noted in the sputum of patients with severe asthma exacerbations, in BAL fluid from patients with noninfectious status asthmaticus, and in autopsy specimens from the airway in patients with acute, fatal asthma.[48–50] Other studies have demonstrated subgroups of patients with chronic asthma in whom the primary inflammatory cell type in the sputum is neutrophils rather than eosinophils.[51,52] These patients are more often female, obese, difficult to treat, and less responsive to treatment with corticosteroids.[32]

Lymphocytes

Cells of lymphoid lineage are also key mediators of innate and adaptive immune responses in asthma. Among them, T lymphocytes, derived from the common lymphoid progenitor, are a household name in asthma. Numerous subsets of T cells have been identified

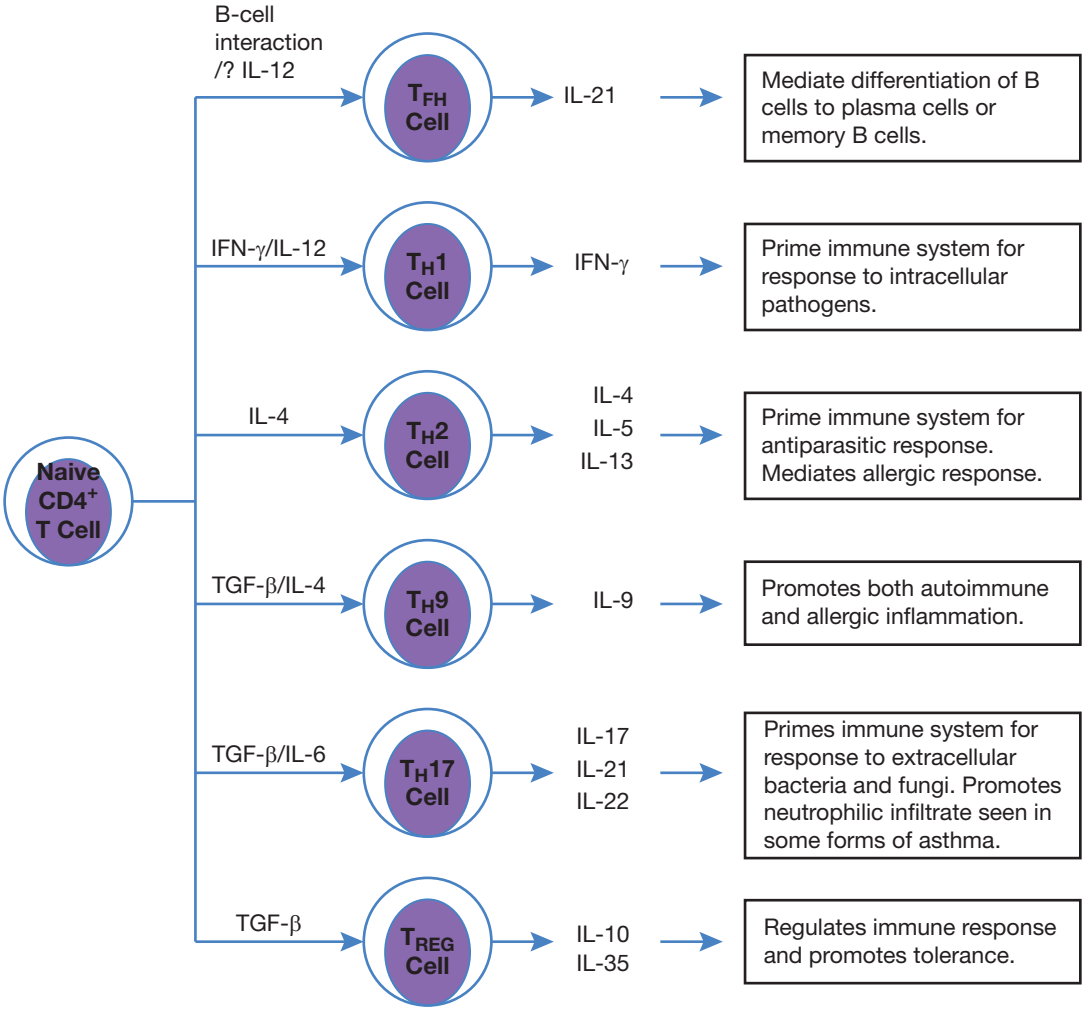


Figure 43-4 $CD4^+$ T lymphocyte subsets. IFN-γ, interferon gamma; TGF-β, transforming growth factor beta.

and are important contributors to asthma, including $CD4^+$ helper T cells and their subsets (T_H1, T_H2, T_H9, and T_H17), $CD8^+$ cytotoxic T cells, and regulatory T cells (T_{Reg}).

$CD4^+$ helper T cells recognize antigens presented to them by antigen-presenting cells (APCs) and, in turn, secrete cytokines to influence the adaptive inflammatory response. In the airway, the dendritic cell is the most important APC (discussed in detail below). A complex series of events involving cytokines and various transcription factors determines whether $CD4^+$ T cells will differentiate into T_H1, T_H2, T_H9, or T_H17 cells (Fig. 43-4).[53]

As outlined above, T_H2 cells are recognized as the primary drivers of inflammation in allergic asthma and other allergic diseases. When T_H2 cells encounter antigen presented by dendritic cells, they produce IL-4, IL-5, and IL-13, all of which play critical roles in the pathogenesis of asthma and pathophysiology in the clinical disease. This has been demonstrated by the detection of increased levels of these cytokines in the BAL fluid of patients with asthma.[54,55] IL-4 increases IgE production by plasma cells, IL-5 is critical to the terminal differentiation and homing of eosinophils to the airway, and IL-13 increases IgE production and drives airway hyperresponsiveness and tissue remodeling.[56]

The role of T_H1 cells in asthma is not as well defined as that of T_H2 cells. Although it has been presumed that T_H1 cells counteract the asthma-inducing effects of T_H2 cells, this is likely an oversimplification as T_H1-associated cytokines have been shown to be increased during asthma exacerbations.[57] Some studies have also suggested that T_H1 cells may play a more prominent role in severe asthma since levels of the canonical T_H1 cytokine, interferon γ (IFN-γ), are increased in the BAL fluid of patients with severe asthma.[58]

T_H9 cells are another adaptive cell type whose primary cytokine is IL-9. T_H9 cells function similarly to T_H2 cells in that they allow persistence of and amplify allergic inflammatory responses. Mast cells are the primary IL-9 receptor–bearing cell, and T_H9 cells are important contributors to the mast cell activation that is notable in asthma.[22] Because mast cells also produce VEGF and fibroblast growth factor (FGF)-2, T_H9 cells likely contribute to airway remodeling as well.[22] The role of targeted therapeutics against the IL-9 pathway in the treatment of asthma remains to be determined.

The last several decades of asthma research and therapeutic development have focused on T2 inflammation, bringing multiple anti-T2 therapeutics to the clinic. As a result, clinicians now have many options to treat allergic and eosinophilic asthma. In contrast, our understanding of non-T2 inflammation in asthma has been hampered by a lack of robust animal models and a consensus on the definition of low-T2 disease. In this regard, the role of T_H17 cells in asthma is an emerging area of intense research. With the identification of a subtype of asthma with primarily neutrophilic inflammation, the role of IL-17 (the primary cytokine produced by T_H17 cells) in asthma has become of an area of considerable interest. Although IL-17 is increased in patients with severe asthma,[59] it is also found in high concentrations in patients with mild asthma (forced expiratory volume in 1 s [FEV_1] >70% predicted) and correlates negatively

with the provocative concentration that causes a 20% reduction in FEV_1 (PC_{20}).[60] Thus, while T_H17 cells most certainly play a role in patients with primarily neutrophilic asthma, they are also important in other forms of disease. Furthermore, treatment of severe asthma with anti-IL-17 monoclonal antibodies has not shown a consistent effect. At present, there are no biomarkers to identify the IL-17/T_H17 phenotype of asthma.[61]

The primary function of $CD8^+$ cytotoxic T cells is the destruction of human cells that are infected with viruses or other intracellular pathogens. $CD8^+$ T cells are also likely to play a role in asthma, although the extent of their contribution has yet to be fully elucidated.[56] IL-4- and IL-5-producing $CD8^+$ T cells are present in the airways of asthmatic patients.[62] IL-5 production by $CD8^+$ T cells is increased in the presence of a viral respiratory infection, and the overall cytokine production by $CD8^+$ T cells correlates with asthma severity.[63,64] Whether $CD8^+$ T cells function as direct contributors or bystanders in the worsening of asthma has yet to be determined.[56]

T_{Reg} cells also appear to play a critical role in asthma development. T_{Reg} cells serve to limit inflammatory responses and promote immune tolerance through the production of IL-10 and TGF-β.[56,65] In patients with asthma and other allergic disorders, T_{Reg} cells appear to be less effective at limiting T_H2 inflammation.[66,67] However, after allergen immunotherapy, for example, T_{Reg} cells increase in the nasal mucosa and may act to promote allergen tolerance.[68] Interestingly, farm exposure early in life is associated with a decreased incidence of allergic disease and asthma, a fact that may be related to increased numbers and function of T_{Reg} cells in infants living in this environment.[69]

Natural killer cells (NK cells) are members of the innate immune system that serve as a first line of defense against infections. Their role in the pathogenesis of asthma has yet to be fully elucidated. They proliferate in response to viral respiratory infections, and their numbers increase during asthma exacerbations.[70] NK cells are capable of producing numerous cytokines including IFN-γ, IL-4, IL-5, and IL-13.[71] NK cells from patients with atopic asthma are skewed toward the production of IL-4 as opposed to IFN-γ upon activation.[71] IFN-γ production by NK cells is also inhibited by prostaglandin D2, a T_H2-promoting lipid mediator produced by mast cells.[72] NK cells may also play a role in "dendritic cell editing" by killing immature dendritic cells, which might influence the development of the type of T_H response.[73]

Macrophages and Dendritic Cells

Macrophages and dendritic cells are descendants of the $CD34^+$ hematopoietic stem cell and arise from a common committed precursor cell.[74] Macrophages arise from circulating monocytes and function primarily to clear debris and microbes from the airway. They may also function as antigen-presenting cells, although this role is likely less important than that of the dendritic cell.[75] Alveolar macrophages may further differentiate into M1 or M2 subsets based on exposure to various cytokines and Toll-like receptor (TLR) agonists.[74] M1 macrophages are "classic" macrophages that clear microbes from the airway. They also produce cytokines, such as IL-12, IL-6, and TNF-α, as well as high levels of nitric oxide (NO).[74] M1 macrophages have traditionally been described as suppressing allergic inflammation, primarily through their secretion of T_H1 cytokines such as IL-12.[74]

Differentiation of monocytes into M2 macrophages is influenced by an environment rich in T_H2 cytokines such as IL-4 and IL-13, indicating they have a role in asthma. When compared with M1 macrophages, M2 macrophages are less effective at clearing intracellular pathogens.[74] They release cytokines such as IL-13 and thus are likely to contribute to the airway hyperresponsiveness in T2 inflammation.[74]

Dendritic cells are the lung's primary presenter of antigen to T cells and are intimately arranged among bronchial epithelial cells in the airway wall. This positions the dendritic cell at a critical junction in determining what type of adaptive T cell response will be directed by the antigen presented by the dendritic cell (e.g., T_H1, T_H2). Dendritic cells in humans exist in two broad categories: the myeloid dendritic cell (mDC) and the plasmacytoid dendritic cell (pDC). While both types of dendritic cells are present in the human lung, their relative localization within the lung is poorly understood.[5] Upon encountering antigen in the airway, dendritic cells migrate to local lymph nodes where they present antigen to T lymphocytes. Both pDC and mDC levels increase in the airway (and coincidently decrease in the blood) after exposure to inhaled allergen.[76–78] Because dendritic cells lie close to the epithelial barrier, they receive numerous signals from epithelial cells, which can influence their effect on T cells. Thymic stromal lymphopoietin (TSLP), the canonical alarmin and target of the monoclonal antibody tezepelumab, is produced by epithelial cells. This product promotes dendritic cells to drive T_H2 differentiation and recruit T_H2 cells to the airway.[5] Other epithelial cell–derived factors, such as GM-CSF, TNF-α, CCL-20, IL-1β, and TNF-related apoptosis-inducing ligand (TRAIL), have similar T_H2-promoting effects.[5] pDCs represent the lung's primary source of IFN-α, a potent antiviral cytokine. These cells are recruited to the lung during viral infections.[79] As viral infections commonly precede asthma exacerbations and may predispose infants to develop asthma, this role of the pDC should be emphasized.[80] The importance of pDC to the development of asthma was illustrated by a recent study which showed that levels of pDC in childhood were inversely correlated with number and severity of viral respiratory infections, increased episodes of wheeze, and increased asthma diagnosis.[81] The function of mDC is not as well known in human asthma, but the role of both cell types in contributing to the development and propagation of the disease will continue to be an important area of asthma research.

Structural Cells of the Airway

Other cellular components of the asthmatic response to be considered include structural cells of the airway: smooth muscle and airway epithelial cells.

Airway Smooth Muscle

Given that bronchospasm and bronchial constriction are central components of asthma, it is intuitive that the cell type responsible for this component, the airway smooth muscle cell, would be a key factor in asthma pathogenesis and pathophysiology. While this cell's importance seems obvious, the details of how airway smooth muscle function differs in the asthmatic airway compared with the normal airway have been elusive. It has been well documented that the smooth muscle layer surrounding the airway is thicker in asthmatics compared to nonasthmatic controls, likely due to remodeling via both smooth muscle hypertrophy and hyperplasia.[82] Increased inflammatory and mast cells can be found within the smooth muscle bundles of asthmatic airways, an indication of the increased communication between these cells, the airway epithelium, and the smooth muscle in asthma.[19] Numerous cytokines, chemokines, and growth factors are involved in these interactions, including those produced by the airway smooth muscle cells and by other cell types with which the airway smooth muscle cell communicates. Airway smooth muscle cells are more prolific producers of these cytokines and proliferate more rapidly in asthma compared with normal smooth muscles.[83]

Early efforts to treat asthma focused on preventing or reversing contraction of bronchial smooth muscles. β-2 agonists, both short- and long-acting, have long been key components in

the treatment of asthma, by directly acting on airway smooth muscle to produce bronchodilation. More recently, attempts to alter function of airway smooth muscle with the use of bronchial thermoplasty have shown improvement in asthma control, further supporting the role that airway smooth muscle plays in asthma pathophysiology.[84,85]

Airway Epithelial Cells

The bronchial epithelium lining the airway is an area of intense research, and its importance, beyond being a simple anatomic barrier, is being increasingly recognized and appreciated. The airway epithelium has a vast surface area (100 m^2) that is in contact with some 10,000 L of inhaled air daily.[86] As the area of initial contact between the body and the external airborne environment, functions of the airway epithelium are a key determinant of the body's response to airborne substances.

The airway epithelium is composed of three major cell types: ciliated columnar epithelial cells, mucus-secreting goblet cells, and surfactant-secreting Clara cells.[86] Both overproduction of mucus by goblet cells and underproduction of important anti-inflammatory peptides by Clara cells have been noted in patients with asthma.[87,88] The tight junctions between epithelial cells have also been noted to be defective in patients with asthma, which decreases the ability of the airway epithelium to act as a protective barrier.[86] The airway epithelium in asthma is also less capable of defending itself against reactive oxygen species, a defect that leads to damage when the airway is inflamed.[89] Epithelial cells in asthma produce lower amounts of type I interferon in response to respiratory viruses, which can increase the risk and severity of respiratory infections and promote asthma exacerbations.[90] More recently, the importance of epithelial-derived alarmins, including IL-25 and -33, which promote both T1 and T2 inflammatory responses, has been demonstrated in asthma linking the airway epithelium with the inflammation evident in both T2-high and non-T2 inflammation.[91,92] This realization has led to the development of monoclonal antibodies directed against TSLP (tezepelumab) and IL-33 (itepekimab). In a genome-wide association study, Shrine et al. found an association between polymorphisms in MUC5AC and moderate to severe asthma raising the possibility that this gene contributes to the development of more severe asthma.[93]

MOLECULAR MEDIATORS IN ASTHMA

The aforementioned cells are able to initiate, perpetuate, coordinate, and regulate the inflammatory process with the synthesis and secretion of several different classes of molecular mediators. These mediators have a variety of functions, as discussed below.

Cytokines

Cytokines are small-molecular-weight glycosylated signaling molecules that are secreted by a number of different cell types with autocrine, paracrine, or endocrine directive activities.[94] The term *cytokine* includes many categories of molecular mediators including interleukins, interferons, and growth factors.[94] Cytokine secretion is usually a brief, self-limited event that requires preformed pools of intracellular cytokines and new mRNA and protein synthesis, which takes place over a matter of hours rather than seconds or minutes.[95] A variety of cytokines have been implicated in the regulation of airway inflammation and thus in the pathogenesis of asthma (Table 43-1).[96] The support for cytokine involvement in asthma was based on the detection of these mediators in the airways of patients with asthma, particularly in bronchoalveolar lavage fluid after allergen challenge and in situ hybridization of retrieved cells or biopsy materials.[97,98] In addition, effective treatment with monoclonal antibodies directed against pivotal T2 cytokines, that is, IL-5, IL-4/IL-13, have demonstrated clinical efficacy; these data indicate a likely role for these cytokines as risks for exacerbations, airflow obstruction, and symptoms (Table 43-2). The overall effect of the complex cytokine network in the airway depends on a number of factors, including the relative abundance of the cytokines, their ability to recruit and perpetuate the actions of inflammatory cells such as eosinophils and lymphocytes, and their ability to amplify or suppress inflammation by interacting with structural cells of the airway.

Chemokines

Chemokines are small-molecular-weight proteins, 8 to 12 kDa, that are classified into four categories based on the organization of specific cysteine residues in their protein sequence: XC, CC, CXC, and CX_3C.[99] The predominant function of chemokines is the recruitment or chemotaxis of inflammatory cells, and some chemokines have additional signaling functions.[99] There are corresponding families of chemokine receptors for each class of chemokine. Notably, there is considerable overlap and redundancy in the chemokines and their target receptors. Since the localization of inflammatory cells into the airway is dependent to a large extent on chemotaxis via chemokine signaling, chemokine receptors have become an attractive target for asthma therapy, but none has yet made it to the clinic. There are currently chemokine receptor inhibitors for CCR5 as well as others in development as potential therapy for asthma.[100,101]

IgE

The initial association of IgE with asthma was based on several epidemiologic studies that demonstrated increased levels of IgE in patients with asthma.[102–104] With the improved understanding of the role of mast cell mediators in the pathogenesis of asthma, the importance of IgE in triggering mast cell activation and airway inflammation was increasingly recognized. This led to the development of a humanized monoclonal antibody directed against IgE to treat patients with uncontrolled allergic asthma.[105] The antibody (omalizumab) was shown to be effective in the treatment of severe uncontrolled asthma, reducing exacerbations and allowing patients to reduce corticosteroid dosage.[106]

Leukotrienes

The leukotrienes (LT) are a family of lipid compounds generated by the metabolism of arachidonic acid via the lipoxygenase pathway (Fig. 43-5).[107] These compounds are typically not preformed and stored in cells for release upon activation; rather, they are rapidly synthesized following activation of the source cell. LTC_4, LTD_4, and LTE_4 are potent bronchoconstrictors that are produced by several cell types, including eosinophils and mast cells. In contrast, LTB_4 is a neutrophil attractant.[107] The leukotrienes are also able to increase mucus secretion in the airway and facilitate plasma leak and edema in the airway wall.[107,108] The leukotriene receptor antagonist montelukast is currently used in the treatment of asthma.[109] Although effective in some patients, the leukotriene modifiers are limited by their limited potency in some patients with asthma.[110]

Aspirin-exacerbated respiratory disease is associated with chronic rhinosinusitis and nasal polyps and underlying severe asthma. These patients are characterized by an underlying overproduction of cysteinyl leukotrienes, that is, urinary LTE_4, which is released in higher concentrations with nonsteroidal anti-inflammatory drugs (NSAIDs) that provoke a severe asthma attack.[111] In this syndrome, the mast cell is considered the primary source of cysteinyl leukotriene production.

Prostanoids

The prostanoids are a family of lipid compounds generated from the metabolism of arachidonic acid via the cyclooxygenase pathway

TABLE 43-1 Cytokines and Lipid Mediators in Asthma

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
Interleukins		
IL-1	DCs, monocytes, macrophages, mast cells, B and T cells, neutrophils, endothelial cells, airway epithelial cells	*Basophils:* Increased production of cytokines and histamine *DCs:* Increased cytokine production, upregulation of MHC and co-stimulatory molecules *Macrophages:* Increased cytokine production *Mast Cells:* Increased cytokine production, degranulation, and survival *Neutrophils:* Increased survival and release of proteases *B Cells:* Increased antibody production *T Cells:* Increased proliferation—especially for T_H2 and T_H17 cells
IL-2	$CD4^+$ T cells	*T Cells:* Increased survival and proliferation, increased T_H2 cytokine production
IL-3	T cells, mast cells	*Basophils:* Increased survival and release of IL-4, IL-6, and histamine *Eosinophils:* Increased degranulation *Mast Cells:* Increased survival and histamine release *Hematopoietic Stem Cells*: Increased production of mast cells, basophils, neutrophils, eosinophils, macrophages, erythrocytes, megakaryocytes, and dendritic cells
IL-4	T cells, mast cells, basophils, eosinophils	*Airway Smooth Muscle Cells:* Increased airway hyperresponsiveness *Basophils:* Increased recruitment *Eosinophils:* Increased recruitment *Goblet Cells*: Increased mucus production *Mast Cells:* Increased recruitment, upregulation of FCεRI *B Cells:* Increased class-switching to IgE, upregulation of FCεRII *T Cells:* Increased recruitment, increased T_H2 differentiation, increased production of T_H2 cytokines, decreased differentiation of T_H1 cells, decreased IFN-γ production by T_H1 cells
IL-5	T cells, mast cells	*Basophils:* Increased proliferation, maturation, and functional activation *Eosinophils:* Increased proliferation, chemoattraction, maturation, functional activation, and degranulation
IL-6	Macrophages, DCs, mast cells, neutrophils, B and T cells, endothelial cells, airway epithelial cells	*T Cells:* Increased production of T_H2 cytokines, decreased differentiation of T_H1 cells, decreased IFN-γ production by T_H1 cells, promotes differentiation of T_H17 cells, downregulation of T_{Reg} cells
IL-7	Bone marrow stromal cells	*Eosinophils:* Increased activation and survival *B Cells:* Increased proliferation and survival *T Cells:* Increased maturation and survival
IL-8	Airway epithelial cells, neutrophils, eosinophils, monocytes/macrophages	*Eosinophils:* Chemoattraction *Neutrophils:* Chemoattraction
IL-9	T cells	*Mast Cells:* Increased recruitment and maturation, increased expression of proteases, upregulation of FCεRI *T Cells:* Increased growth and proliferation
IL-10	Monocytes/macrophages, B cells, T cells (specifically T_{Reg} cells)	*DCs:* Inhibits expression of co-stimulatory molecules thus inhibiting T_H cell activation *Eosinophils:* Inhibits survival, recruitment, and maturation *Monocytes/Macrophages:* Downregulates MHC class II expression, downregulates inflammatory cytokine production *T Cells:* Downregulates IFN-γ and IL-2 production by T_H1 cells and IL-4 and IL-5 production by T_H2 cells
IL-11	Airway epithelial cells, eosinophils, airway smooth muscle cells	*Airway Epithelial Cells:* Regulates proliferation *Macrophages:* Inhibits production of TNF-α, IL-1, IL-12 *B Cells:* Increases immunoglobulin production *T Cells:* Inhibits production of TH1 cytokines, increases IL-4 and IL-10 production
IL-12	Dendritic cells, B cells, macrophages	*NK Cells:* Increased IFN-γ production *T Cells:* Increased IFN-γ production, increased TH1 differentiation, decreased T_H2 and T_H17 differentiation

(continued)

TABLE 43-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
IL-13	Mast cells, T cells	*Airway Epithelial Cells:* Increased permeability, increased mucus production, production of inducible nitric oxide synthase *Airway Smooth Muscle Cells:* Increased airway hyperreactivity *Eosinophils:* Promotes migration and survival *Macrophages*: Activation and enhanced MHC class II expression *B Cells:* Increased class switching to and production of IgE
IL-14	T cells	*B Cells:* Increased proliferation, suppression of Ig secretion
IL-15	Monocytes/macrophages, DCs	*DCs:* Increased activation and survival, increased production of IFN-γ *Mast Cells:* Increased survival *Monocytes/Macrophages:* Increased phagocytic activity, increased production of IL-8, IL-12, MCP-1 *Neutrophils:* Increased survival and phagocytic activity, increased IL-8 production *NK Cells:* Increased maturation and survival, increased production of IFN-γ, TNF-α, and GM-CSF *T Cells*: Increased proliferation of memory $CD8^+$ T cells, increased proliferation of T_H17 cells
IL-16	T cells, airway epithelial cells, DCs, eosinophils, mast cells	*DCs:* Increased chemoattraction *Eosinophils:* Increased chemoattraction *Monocytes/Macrophages:* Increased chemoattraction, upregulation of MHC class II expression *T Cells:* Increased migration, maturation, and proliferation
IL-17	T cells, NK cells	*Airway Epithelial Cells:* Increased production of IL-6, IL-8, G-CSF, PGE 2 *Eosinophils:* Increased chemoattraction *Neutrophils*: Increased production from stem cells, increased chemoattraction
IL-18	DCs, monocytes, macrophages, neutrophils, airway epithelial cells	*Basophils*: Increased production of cytokines and histamine *DCs:* Increased cytokine production, upregulation of MHC and co-stimulatory molecules *Macrophages*: Increased cytokine production *Mast Cells:* Increased cytokine production, degranulation, and survival *Neutrophils*: Increased survival and release of proteases *NK Cells:* Increased IFN-γ production *T Cells:* Promotes T_H1 differentiation
IL-19	Monocytes	*T Cells:* Increased production of T_H2 cytokines and downregulation of IFN-γ production
IL-20	Monocytes	Unclear
IL-21	T cells	*B Cells:* Increased proliferation of IgA, IgG, IgM producing plasma cells and decrease in IgE-producing plasma cells *T Cells:* Increased differentiation into T_H17 cells, upregulation of T_H1 cytokine production
IL-22	T cells, NK Cells	*Respiratory Epithelial Cells:* Increased production of antimicrobial peptides
IL-23	DCs	*Macrophages:* Increased TNF-α production *T Cells:* Increased IL-17 production, promotion of T_H17 differentiation
IL-24	Monocytes, T cells	Unclear
IL-25	Airway epithelial cells, eosinophils, mast cells	*T Cells:* Increased production of T_H2 cytokines
IL-26	Monocytes, T cells	Unclear
IL-27	Macrophages, DCs	*T Cells:* Increased differentiation into IL-10-producing T_{Reg} and T_H1 cells, decreased development of T_H2 and T_H17 cells
IL-28 (IFN-λ2, -λ3)	DCs	Inhibits viral replication *DCs:* Increase ability to stimulate production of T_{Reg} cells
IL-29 (IFN-λ1)	DCs	Inhibits viral replication *DCs:* Increase ability to stimulate production of T_{Reg} cells
IL-31	T cells	*Airway Epithelial Cells:* Attenuates proliferation of epithelial cells
IL-32	NK cells, airway epithelial cells, T cells	*Macrophages:* Upregulation of proinflammatory cytokines *Airway Epithelial Cells:* Decreased production of proangiogenic factors

TABLE 43-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
IL-33	Endothelial cells, airway epithelial cells, dying cells	*Basophils:* Increased production of cytokines and histamine *DCs:* Increased cytokine production, upregulation of MHC and co-stimulatory molecules *Eosinophils*: Increased proliferation, survival, and chemokine production *Macrophages*: Increased cytokine production *Mast Cells:* Increased cytokine production, degranulation, and survival *Neutrophils*: Increased survival and release of proteases *NK Cells:* Increased IFN-γ and T_H2 cytokines *T Cells:* Promotes T_H2 differentiation, enhances release of T_H2 cytokines
IL-35	T_{Reg} cells	*T Cells:* Decreased production of T_H2 cytokines, suppression of T cell proliferation
IL-36	Airway epithelial cells	*T Cells:* Increased T_H1 differentiation
IL-37	Hematopoietic cells	*Macrophages:* Decreased secretion of proinflammatory cytokines *Airway Epithelial Cells:* Decreased secretion of proinflammatory cytokines
Interferons		
IFN-α	Monocytes/macrophages	*Virus-Infected Cells:* Inhibition of viral replication
IFN-β	Monocytes/macrophages	*Virus-Infected Cells:* Inhibition of viral replication
IFN-γ	T cells, NK cells	*Macrophages:* Differentiation, activation, and expression of Fcγ receptor. Increased cytokine production *T Cells:* Increased differentiation to T_H1 cells, increased cytotoxicity of $CD8^+$ T cells
IFN-λ	See above	See above
Growth Factors		
bFGF	Endothelial cells	*Fibroblasts:* Proliferation and extracellular matrix formation
G-CSF	Monocytes, fibroblasts, airway epithelial cells	*Neutrophils:* Proliferation and differentiation
GM-CSF	T cells, airway epithelial cells, macrophages	*DCs:* Maturation *Eosinophils:* Increased survival, degranulation *Macrophages:* Differentiation, increased survival, increased cytokine production *Neutrophils:* Increased chemotaxis and survival
M-CSF	Fibroblasts, endothelial cells, macrophages, airway smooth muscle cells	*Hematopoietic Stem Cells:* Differentiation of monocytes
PDGF	Platelets, monocytes, macrophages	*Fibroblasts:* Proliferation and chemoattraction
SCF	Bone marrow stromal cells, fibroblasts	*Mast Cells:* Chemoattraction, induction of histamine release, differentiation, proliferation
TGF-β	Eosinophils, T cells, macrophages, airway epithelial cells, endothelial cells, airway smooth muscle cells	*Fibroblasts:* Chemoattraction and increased conversion to myofibroblasts, increased synthesis of collagen *Macrophages:* Chemoattraction *Neutrophils*: Chemoattraction *T Cells*: Increased differentiation of T_{Reg}, T_H9, and T_H17 cells, inhibition of T_H1 and T_H2 differentiation
VEGF	Macrophages, airway epithelial cells, T cells, eosinophils	*Airway Smooth Muscle Cells*: Hyperplasia and increased airway hyperresponsiveness *DCs*: Increased proliferation and activation *Endothelial Cells*: Increased angiogenesis and vascular permeability *Airway Epithelial Cells:* Increased proliferation, mucus production *Fibroblasts*: Promotion of subepithelial fibrosis
Other		
TNF-α	Monocytes/macrophages, DCs, mast cells, eosinophils, neutrophils, B and T cells, airway epithelial cells, airway smooth muscle cells, fibroblasts	*Airway Epithelial Cells:* Upregulation of adhesion molecules *Airway Smooth Muscle Cells*: Increased airway hyperresponsiveness *Endothelial cells:* Upregulation of adhesion molecules *Eosinophils*: Chemoattraction, increased activation *Fibroblasts:* Increased conversion to myofibroblasts *Macrophages:* Chemoattraction *Mast Cells:* Increased histamine release *Neutrophils:* Chemoattraction *T Cells:* Increased activation and cytokine release

(continued)

TABLE 43-1 Cytokines and Lipid Mediators in Asthma *(Continued)*

Cytokines		
Cytokine	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
Alarmins TSLP	Airway epithelial cells	*DCs:* Increased ability to attract T_H2 cells *Eosinophils:* Induced release of proinflammatory cytokines and chemokines *Mast Cells:* Increased production of T_H2 cytokines *T Cells:* Increased differentiation to T_H2 cells
Lipid Mediators		
Mediator	**Cell Sources**	**Proposed Cell Targets/Functions in Asthma**
Leukotrienes		
Dihydroxy Acid Leukotriene (LTB4)	DCs, monocytes/ macrophages, neutrophils	*B Lymphocytes:* Increased expression of CD23, CD54, and CD105 *DCs:* Recruitment, increased skewing of T_H0 cells to T_H1 type *Eosinophils*: Recruitment *Mast Cells:* Recruitment *Monocyte/Macrophages:* Increased production of IL-6, TNF-α, MCP-1 *Neutrophils:* Recruitment and activation *Airway Smooth Muscle Cells:* Increased proliferation *T Lymphocyte:* Recruitment
Cysteinyl Leukotrienes (LTC4, LTD4, LTE4)	DCs, eosinophils, mast cells, monocytes/macrophages	*Airway Smooth Muscle Cells:* Bronchoconstriction *DCs:* Increased migration to lymph nodes *Endothelial Cells:* Increased vascular permeability and upregulation of adhesion molecules *Eosinophils:* Recruitment *Goblet Cells:* Increased mucus production *Mast Cells:* Increased production of IL-5, IL-8, TNF-α, and MIP-1β *Monocytes/Macrophages:* Increased production of MCP-1, TNF-α, and MMP-9 *T Lymphocytes:* Increased T_H2 immune response
Prostanoids		
PGD2	Mast cells	*Airway Smooth Muscle Cells:* Bronchoconstriction *Eosinophils:* Recruitment, increased degranulation *Monocytes/Macrophages:* Increased cytokine production *Neutrophils:* Inhibition of activation *T Lymphocytes:* Recruitment, increased production of T_H2 cytokines, inhibition of IFN-γ production
PGE2	Airway smooth muscle cells, airway epithelial cells, endothelial cells, macrophages	*Airway Smooth Muscle Cells:* Inhibition of allergen-induced bronchoconstriction *Eosinophils:* Inhibits recruitment *Monocytes/Macrophages:* Decreased cytokine production, downregulation of MHC class II expression *T Cells:* Decreased proliferation, decreased T_H2 cytokine production
PGI2 (Prostacyclin)	Endothelial cells, mono-cytes/macrophages	*Endothelial Cells:* Vasodilatation *Eosinophils:* Inhibition of recruitment *T Cells:* Increased IL-10 production
Thromboxane A2	Platelets, endothelial cells, monocytes/macrophages	*Airway Smooth Muscle Cells:* Bronchoconstriction *Eosinophils:* Recruitment

TABLE 43-2 T2-Directed Anticytokines: Effects on Asthma Exacerbations, Lung Function, and Need for Oral Corticosteroids (OCS) in Patients with Severe Disease

Agent	↓ Exacerbations	↑ Lung Function	OCS ↓	Comment
Omalizumab (IgE)	25%	±	–	Only anti-IgE drug
Mepolizumab (IL-5)	50%	+	++	Indication for EGPA
Reslizumab (IL-5)	50%	++	–	Weight-based dose (IV)
Benralizumab (IL-5R)	50%	++	++	q 8 weeks causes ADCC
Dupilumab (IL-4/IL-13)	50%	++	++	FeNO response biomarker

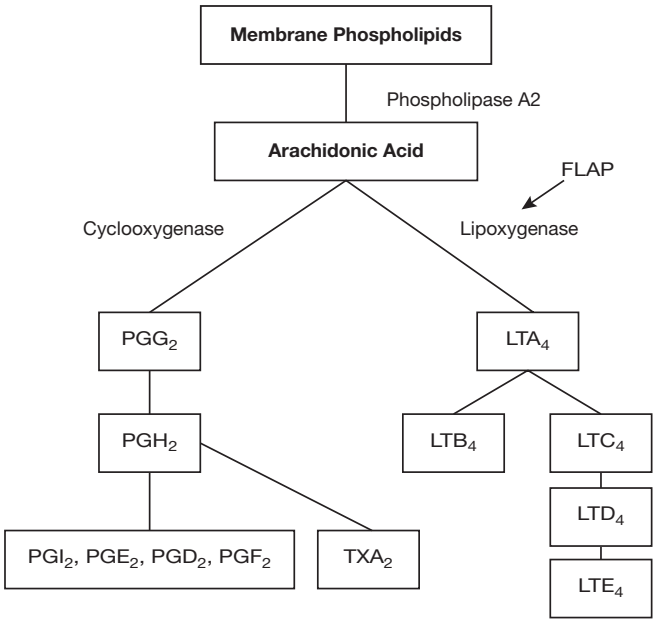


Figure 43-5 Formation of arachidonic acid metabolites. FLAP, 5-lipoxygenase activating protein; LT, leukotriene; PG, prostaglandin; TXA_2, thromboxane A2.

(Fig. 43-5).[112] Most of the prostanoids, that is, PGD_2, PGF_2, and TxA_2, are potent bronchoconstrictors and products of several cell types including eosinophils and mast cells.[112] In contrast, PGE_2 has bronchodilatory and anti-inflammatory activity.[113,114] The use of nonsteroidal anti-inflammatory medications to inhibit cyclooxygenase activity has not been shown to have an appreciable effect on airway inflammation to date. However, since PGD_2 is the predominant prostanoid involved in asthma,[115] specific PGD_2 receptor antagonists have been studied but failed to show exacerbation reduction in asthma.[116–119]

Nitric Oxide

The role of nitric oxide (NO) in the pathogenesis of asthma remains unclear. NO is continually synthesized at low levels in the airways of normal subjects. Sources of NO in the respiratory tract include airway epithelial cells (likely the primary source), smooth muscle cells, sensory nerves, endothelial cells, and macrophages.[120] At low levels, NO is a bronchodilator and vasodilator that antagonizes endothelin and has protective effects in the airway.[120] Higher levels of NO are found in asthma, secondary to increased inducible NO synthase (iNOS) expression that is induced by alarmins and cytokines such as TSLP and IL-13.[121] NO can react with superoxide anion in inflamed tissue to produce biologic oxidants that contribute to ongoing tissue damage and chronic asthmatic inflammation.[120] The production of NO is also thought to reflect the intensity or severity of airway inflammation. Thus, exhaled NO measurement has been utilized successfully as a tool to reflect the extent of airway inflammation as a measure of asthma control—in particular, the presence of eosinophils in the airway wall.[121]

Granule Proteins

Granulocytes, that is, mast cells, basophils, eosinophils, and neutrophils, all produce granular proteins that play significant roles in the pathogenesis of asthma.

Insights into the kinetics and importance of mast cell mediators were obtained from studies that measured BAL histamine and tryptase.[122] These studies demonstrated that mast cell activation is an early event: elevated BAL histamine and tryptase levels are seen 12 min after endobronchial antigen challenge. The levels of tryptase return to normal 48 h after antigen challenge while the levels of histamine remain elevated after 48 h. This suggests that other cell types that produce histamine (e.g., basophils) are recruited and activated to produce histamine at these later points or that mast cells generate and continue to release histamine over time following an initial activation.[122] Furthermore, BAL of allergic asthmatic subjects had only moderately elevated levels of tryptase at baseline but higher concentrations of tryptase following antigen challenge.[122]

Histamine is capable of inducing bronchoconstriction, increasing vascular permeability to cause edema, and increasing mucus secretion.[123] The role of tryptase is not well established, although there are data to suggest that it can activate inflammatory cells such as eosinophils, mast cells, and epithelial cells by cleaving a family of protease-activated receptors (PARs) on the cell surfaces.

The best known eosinophilic specific proteins include major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPX). MPB is the principal protein constituent of eosinophil granules. It is toxic to epithelial tissues, induces airway hyperresponsiveness, and causes histamine release from basophils.[124] ECP is more cytotoxic to the epithelium than MBP and damages target cells by membrane pore formation.[125] EDN, as the name implies, damages myelinated neurons.[126] EPX has different effector functions compared with neutrophil and monocyte myeloperoxidases (MPOs); it causes LTC_4 and LTD_4 degradation and causes histamine release from mast cells.[127] Data suggest that the presence of EPX in airways indicates eosinophil activation, and that EPX may be the dominant granule-associated protein associated with tissue inflammation.[128]

The primary granules of neutrophils contain MPO and lysozyme as well as hydrolases and proteinases, which are important to tissue penetration by neutrophils.[129] The primary neutrophilic granular proteins are myeloperoxidases, best known as autoantigens associated with p–antineutrophil cytoplasmic antibody (p-ANCA)-positive vasculitis such as eosinophilic granulomatosis polyangiitis (EGPA, formerly known as Churg-Strauss syndrome). The release of MPO and neutrophil elastase enhances host defense functions but also causes tissue damage to normal tissues, including airway epithelium.[129] Secondary granules contain lysozyme and collagenases, which can also potentially damage airway tissue and contribute to airway remodeling.[129] Neutrophil granule proteins are considered toxic to airway epithelium and tissue.

REMODELING IN ASTHMA

As occurs in most chronic inflammatory disorders in which there is a chronic cycle of "injury-repair," irreversible structural changes occur in the airway in asthma that are collectively called "airway remodeling." Airway remodeling involves epithelial changes, smooth muscle hypertrophy and hyperplasia, increased angiogenesis, increased fibroblast/myofibroblast activity, and increased subepithelial fibrosis that affect the structure and function of the large and small airways of the lung.[130] Prolonged infiltration of inflammatory cells and the cytokines, chemokines, and growth factors that they generate contributes to these structural changes and leads to irreversible obstructive physiology noted in many patients with asthma. Clinically, these are patients who have persistent obstructive physiology after maximal treatment with corticosteroids and bronchodilators. A therapeutic intervention that can improve lung function in these patients remains a significant unmet need in the field of asthma.

As mentioned previously, airway epithelium serves not only as an anatomic barrier, but also as a key player in asthma pathogenesis. Defects in airway epithelium are ubiquitous in human asthma. When injury occurs, the repair process has been likened to a chronic wound, which may not heal normally as a result of repetitive and

ongoing insults and may result in airway remodeling as discussed above.[131] As with other types of chronic wounds, epithelial cells attempt to heal by promoting the release of growth factors from the underlying mesenchyme. This, in turn, leads to increased extracellular matrix deposition, fibrosis, and hypertrophy and hyperplasia of airway smooth muscle cells.[132] This process has been likened to the function of the epithelial-mesangial trophic unit (EMTU), a key component of early lung morphogenesis that may become reactivated in chronic asthma.[132] The consequence of prolonged epithelial injury is a protracted release of proinflammatory alarmins, cytokines, and profibrogenic growth factors such as TGF-β. When this response is combined with the inflammatory milieu derived from immune cells recruited to the airway chronically, the result is chronic airflow obstruction that may not respond or only partially responds to pharmacologic treatment. It remains unclear if more precise treatment could reverse the chronic obstruction in these patients or if the airways are irreversibly remodeled.

PHENOTYPIC CLUSTERS IN ASTHMA

Several recent studies have begun to identify phenotypes, or subphenotypes, of asthma. These studies have confirmed that asthma is heterogenous disease and that there may be at least four different phenotypes of disease.[133,134] Specifically, studies by Haldar et al. in the United Kingdom used sputum eosinophilia, in addition to measurements of atopic status and symptoms, to identify phenotypes.[133] They identified multiple clusters of patients with concordant symptoms and inflammation but also patients who were highly symptomatic with very little eosinophilic inflammation and lacked evidence of atopic sensitization. Other subgroups fit a more "classic" pattern of asthma with evidence of eosinophilic involvement and atopic sensitization. Other clusters fell somewhere between the two. This study and others are probing the heterogeneity of the disease and discovering the reasons behind differences in disease course and response to conventional asthma therapy.[12,28]

CONCLUSION

Asthma is a complex inflammatory disease that is caused by the contributions of many different immune cells, structural cells, molecular mediators, and external factors to produce acute and chronic inflammation of the airway, airflow obstruction, and chronic symptoms. The study of these factors has led to a greater understanding and appreciation of the breadth of this disease, as well as its complexity and heterogeneity. It has also led to the realization that different phenotypes of asthma exist, and treatment of asthma based on a patient's predominant phenotype may soon be possible. Over the last decade, biologic therapeutics have been made to target specific inflammatory mediators in asthma. The fact that these treatments have not been universally successful speaks to the complexity of this disease and need for more discovery. As research delves further into the pathogenesis and pathophysiology of asthma, many more targets will emerge that reflect activation of pathways that will lead to novel therapies that will improve the lives of patients with asthma and our understanding of this chronic inflammatory airway disease.

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CHAPTER 44

The Epidemiology of Asthma

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INTRODUCTION

Asthma is an extremely common clinical syndrome and the most common chronic disease in children.[1] Asthma affects approximately 235 million people worldwide[2] and nearly 25 million Americans.[3] In the United States, asthma accounts for over 10 million medical visits yearly.[4] The estimated total annual cost of asthma care in the United States from 2008 to 2013 was more than 80 billion dollars.[5] These costs include $50.3 billion in medical expenses, $29 billion due to asthma-related mortality, and $3 billion due to missed work and school days.[5]

In 2018, 22% of those afflicted with asthma were children under the age of 18 years,[3] and most cases of asthma begin in preschool age.[6] This propensity to become clinically apparent early in life belies the fact that asthma originates in utero as an abnormality of fetal lung development. Asthma has important consequences in childhood and may have important consequences for adult obstructive lung disease. In addition to having clear genomic and prenatal developmental components, asthma risk and prognosis are influenced greatly by exposures including respiratory viruses, indoor allergens, maternal tobacco smoke, and other physical and social aspects of the environment. The paradox of this illness is that despite important strides in understanding etiologic environmental factors and mechanisms of airway inflammation characteristic of the syndrome, its prevalence and clinical burden remain unacceptably high. Although asthma morbidity and mortality rates have been steady for several years and have declined slightly recently,[7] the rates are dramatically higher than 30 years ago and continue to be significant, particularly for urban minority groups, low-income populations, and children.

The purpose of this chapter is to describe trends in asthma epidemiology and to examine potential reasons for these trends. We discuss the epidemiology of airway hyperresponsiveness, which is more prevalent than asthma, and review clinical heterogeneity in asthma and the concept of asthma endotypes. Environmental risk factors for asthma are discussed, with special attention to the emerging role of the human and environmental microbiomes. We conclude with a review of asthma natural history and the implications of the current trends, especially with regard to health disparities.

DEFINITION, PREVALENCE AND MORBIDITY OF ASTHMA

In 2007, the National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPPR3)[8] defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, including mast cells, eosinophils, neutrophils, T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing, wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is reversible either spontaneously or with treatment.

Because asthma is a clinical syndrome, there is no gold standard for its diagnosis. As such, physicians employ nonstandardized algorithms for making the diagnosis, such as a history of wheezing or a parental history of asthma in conjunction with evidence of obstruction on lung function testing and a favorable response to a bronchodilator to identify the asthmatic patient. Frequently, age, sex, and other patient characteristics such as smoking status or allergic sensitization may influence a physician's diagnosis.

In general, epidemiologic surveys have tended to rely on historic or questionnaire sources to identify patients with asthma. Asthma cases have been identified either by physicians or by surveys in which the definition of who is asthmatic has been left to the patients themselves, surrogates, or the report of the diagnosis having been made by the patient's physician. Clearly, each of these methods of identifying asthma patients has inherent weaknesses. One must, therefore, assume that some bias in the reporting of cases is present and that the biases in each method of gathering data are different.

Asthma Prevalence in the United States

The National Health Interview Survey (NHIS), a program of the Centers for Disease Control and Prevention (CDC), is an annual random population household interview survey that provides information on asthma prevalence in the United States. Its data demonstrate an almost doubling of asthma prevalence in the last two decades of the 20th century, from 3.2 per 100 population in 1981 to 5.5 per 100 in 1996.[9] In 1997 the NHIS questions and methodology were modified, limiting comparisons of prevalence before and after 1997. The most recent results from the CDC, which analyzed data from the NHIS through 2017, indicate a slower increase in asthma prevalence from 2001 through 2013, and a slight decrease since then from a maximum prevalence of 8.5% in 2011 to 7.9% in 2017[10] (Fig. 44-1). The prevalence in children under 18 years remains higher than in adults; in 2017, it was 8.4% in children compared with 7.7% in adults.[10]

Asthma prevalence trends over the lifespan differ between males and females. Males tend to have higher asthma prevalence during childhood, whereas sex ratios equalize in the pubertal years and females predominate throughout the rest of adult life. For example, in the United States, the prevalence for males under age 18 years in 2018 was 8.3% compared with 6.7% for females; however, in adults

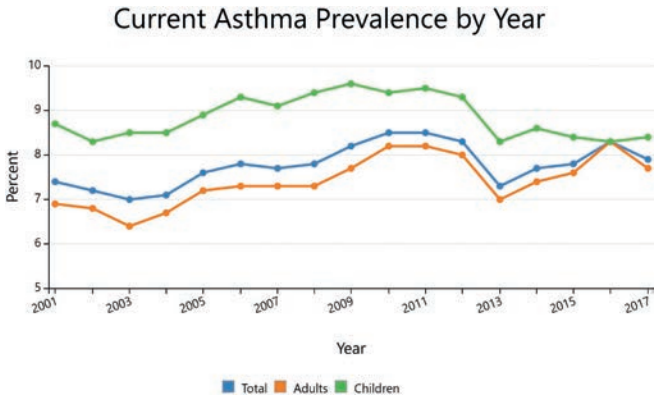

Figure 44-1 Current asthma prevalence figures from the National Health Interview Survey (NHIS), United States, by age group. *(Reproduced with permission from Centers for Disease Control and Prevention. Asthma Prevalence. www.cdc.gov/asthma/data-visualizations/prevalence.htm.)*

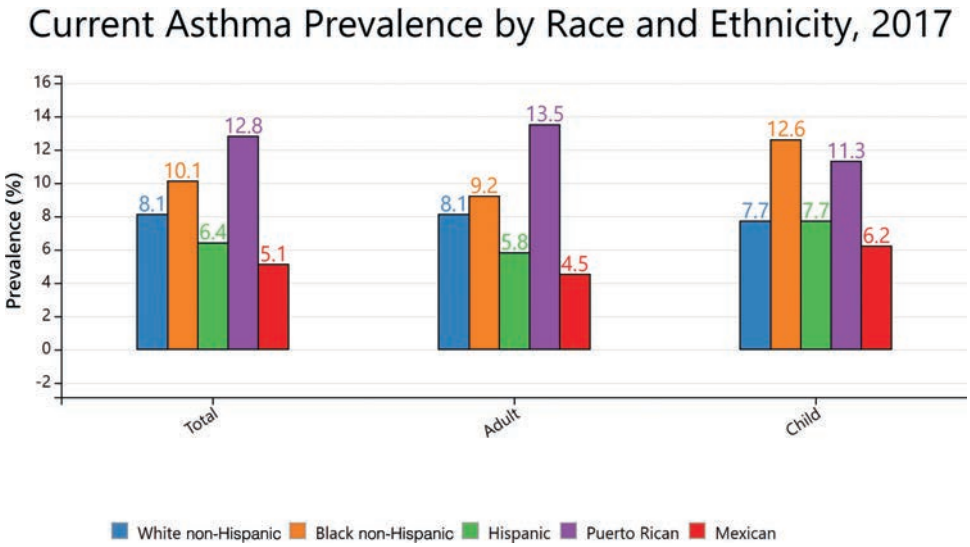

Figure 44-2 Current asthma prevalence figures from the National Health Interview Survey (NHIS), United States, by race and ethnicity and age group in 2017. *(Reproduced with permission from Centers for Disease Control and Prevention. Asthma Prevalence. www.cdc.gov/asthma/data-visualizations/prevalence.htm.)*

18 years and older, female prevalence (9.8%) is almost twice that for males (5.5%).[10] Thus, age and sex play important roles in modifying disease prevalence.

There is a striking difference in prevalence by racial/ethnic groups in the United States. The most recent data from 2016 to 2018 show that prevalence was 10.7% for black non-Hispanics, 6.5% for Hispanics, and 8.0% for white non-Hispanics.[3] It is noteworthy that the rate for Hispanics of Puerto Rican descent was very high at 14%.[3] In addition, there are marked differences in asthma prevalence by income group. Asthma prevalence was highest in 2018 among those below 100% of the poverty threshold (10.8%) and lowest among those in the highest income category, 450% of poverty threshold or higher (6.5%).[3] Figure 44-2 demonstrates these disparities using data from the United States in 2017.

Global Asthma Prevalence

Limited surveys have evaluated the global burden of asthma. The International Study of Asthma and Allergies in Children (ISAAC) used standardized surveys to determine asthma prevalence and severity in 6- to 7-year-old children in 61 countries and 13- to 14-year-old children in 97 countries between 2000 and 2003.[11] There was dramatic variation worldwide in prevalence of wheeze in the past 12 months. For example, current wheeze in 13- to 14-year-olds was reported in only 0.8% of respondents in Tibet but approximately one-third (32.6%) of respondents in Wellington, New Zealand.[11] There was a trend toward higher prevalence of current wheeze at higher-income study sites.[11] In contrast, among children with current wheeze, more severe symptoms were observed at lower-income study sites.[11]

The European Community Respiratory Health Survey (ECRHS) evaluated the prevalence, determinants, and management of asthma in 20- to 44-year-old adults from 48 centers, predominantly in Western Europe, with data reported through 1994.[12] Similar to the findings of ISAAC, ECRHS results showed marked differences in asthma prevalence between countries. Prevalence of wheeze ranged from a lower range of 4.1%–9.7% from centers in India, Algeria, and Italy to a higher range of 23.2%–32% from centers in Sweden, Denmark, Estonia, United States, United Kingdom, Australia, New Zealand, and Ireland.[12] The huge differences in asthma and wheeze prevalence between countries remains to be fully explained and likely reflects the large joint contributions of genetic and environmental factors on asthma risk.

Asthma Healthcare Utilization

The CDC in the United States collects information about physician office visits and emergency department visits from the National Center for Health Statistics and information about all-payer encounter-level hospital care data from the Healthcare Cost and Utilization Project. It also utilizes data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, which sample visits to office-based physicians, community health centers, and hospital emergency departments (EDs) and outpatient departments to evaluate medical service utilization.

Drawing from these sources, the rate of physician office visits for asthma declined among children under age 18 years from 2010 (776.8 per 10,000) to 2016 (332.9 per 10,000), while office visits for asthma remained stable among adults (372.0 per 10,000 in 2010 and 300.3 per 10,000 in 2016).[13] However, data from 2017 on ED visits and hospitalizations for asthma in the United States highlight that asthma still results in significant morbidity among the pediatric population and disproportionately affects this age group. Patients under age 18 years had more ED visits than adults: 85.3 per 10,000 compared with 38.3 per 10,000 population, and the rate was highest among those age 0 to 4 years: 139.6 per 10,000.[14] Similarly, children had more hospitalizations for asthma than adults (10.3 per 10,000 compared with 4.2 per 10,000), with the 0- to 4-year age group again having the highest asthma hospitalization rate at 17.2 per 10,000 population.[14]

The 2017 ED visit and hospitalization data for asthma in the United States also reveal staggering differences in healthcare utilization by race. There were 164.3 per 10,000 population ED visits and 13.1 per 10,000 hospitalizations for asthma among black individuals compared with 33.9 per 10,000 ED visits and 2.6 per 10,000 hospitalizations for asthma among white individuals.[14] These numbers indicate that ED visits and hospitalizations for asthma are five times more frequent in black individuals than white individuals in the United States.

Sex differences in asthma health care utilization are less striking. Males and females had similar rates of ED visits for asthma in 2017 (49.2 and 49.1 per 10,000, respectively), although hospital admissions for asthma were more frequent among females (6.5 per 10,000) than males (4.7 per 10,000).[14]

Trends in Asthma Mortality

Although asthma mortality rates are quite low, more than 3000 people die every year from asthma in the United States.[15] Recent data from 2001 to 2016 showed an encouraging decrease in the rate of death due to asthma from 15 per million to 10 per million.[15] The asthma death rate in 2016 was highest among adults age 65 years or older (29.2 per million); despite higher rates of pediatric ED visits and hospitalizations for asthma, individuals under age 18 years were nearly 5 times less likely than adults to die from asthma.[15]

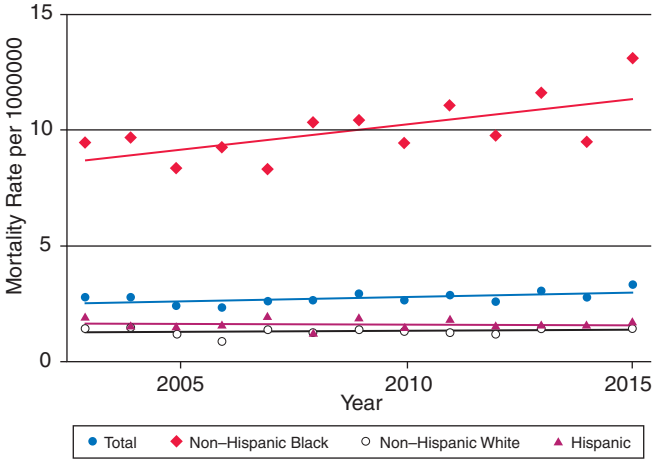

Figure 44-3 Pediatric asthma mortality rate in the United States by year among those age 3 to 19 years by race and ethnicity. *(Reproduced with permission from Arroyo A, Chee C, Camargo A, et al. Where do children die from asthma? National data from 2003–2015. J Allergy Clin Immunol Pract. 2017;6(3):1034–1036.)*

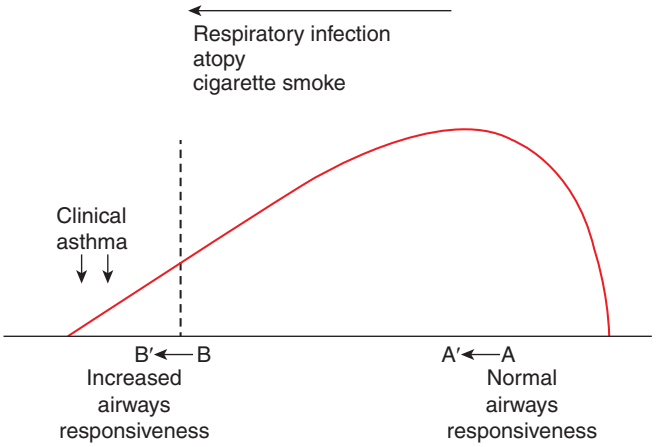

Figure 44-4 The effect of environmental exposures on the population distribution of airway responsiveness acting to move people in a more responsive direction. *(Reproduced with permission from Brown RW, Weiss ST. The influence of lower respiratory illness on childhood asthma: defining risk and susceptibility. Semin Respir Infect. 1991;6(4):225–234.)*

However, the downward trend in countrywide asthma mortality belies pockets of very high prevalence, morbidity, and mortality in certain populations. Between 2003 and 2015, there was actually an overall increase in deaths due to asthma among those under age 19 years, and non-Hispanic black children had an average annual mortality rate (10 deaths per million) 6 times higher than Hispanic children (1.62 deaths per million) and 7 times higher than non-Hispanic white children (1.33 deaths per million)[16] (Fig. 44-3). This disparity in asthma mortality between race groups in the United States has been observed since the 1980s.[17,18] While the absolute number of deaths due to asthma is very low, asthma mortality rates do represent a clear public health concern because almost all asthma deaths are preventable.

AIRWAY RESPONSIVENESS

Airway responsiveness is a defining characteristic of asthma and is both developmentally and environmentally determined. Airway responsiveness is measured by inhaling increasing doses of a bronchoconstrictor agonist, for example, methacholine or histamine, and repeatedly measuring lung function (usually FEV_1) after each dose. The dose of bronchoconstrictor that results in a 20% reduction in lung function from baseline is considered the provocative dose (or concentration), also called the PD or PD20. A low PD20 (usually less than 10 mg of methacholine) indicates significant airway responsiveness since the patient is responding to a low dose with at least a 20% drop in FEV_1.

Since flow in the airways is inversely proportional to the radius of the airway to the 4th power, small changes in airway size can have a big influence on PD20. An additional factor influencing the measurement is total lung size: the bigger the lung, the higher the PD20, and the less responsive the airway. These physiologic facts help explain some of the more relevant clinical correlates.

All individuals with active asthma have increased airway responsiveness, and it precedes and predicts asthma development,[19] but its presence in the general population exceeds the prevalence of asthma by about twofold.[20] This suggests that individuals genetically predisposed to develop increased airway responsiveness encounter relevant environmental stimuli such as viral illness, smoking, or occupational exposures and then increase their airway responsiveness and thus develop symptomatic asthma (Fig. 44-4).

Given the dependence on lung and airway size, airway responsiveness is highest at the extremes of age and in females at any given age.[21] It is known to be present at birth and correlates with gestational age, being greatest in preterm babies, which may explain why preterm birth is one of the strongest risk factors for childhood asthma.[22] In general, clinicians do not usually test for airway responsiveness in patients, preferring to infer the phenotype based on the presence of wheezing symptoms, and it is only in difficult cases where the diagnosis is in doubt that a test is required.

ASTHMA PHENOTYPES AND ENDOTYPES

Reversible airway hyperresponsiveness and inflammation are critical components of asthma pathogenesis. However, beyond these essential features, there is a wide range of clinical asthma phenotypes such that two individuals with asthma may dramatically differ in characteristics including age of asthma onset, disease severity, and comorbidities such as allergic sensitization and obesity. It is therefore now recognized that asthma is not a single disease.[23] Distinct clinical asthma phenotypes have been defined by applying analytic clustering techniques to data from large cohorts of subjects with asthma.[24–27] While methodologies and results have varied between studies, results largely converge around the existence of four phenotypes: early-onset mild allergic asthma, early-onset allergic moderate to severe remodeled asthma, late-onset nonallergic eosinophilic asthma, and late-onset noneosinophilic nonallergic asthma.[28]

While clinically intuitive, phenotypes do not map neatly onto specific disease mechanisms.[29] Just as distinct asthma phenotypes are now recognized, asthma *endotypes* have been proposed and are defined by divergent molecular and immunologic mechanisms.[30] The advent of the genomic era has enabled researchers to define asthma endotypes. The most widely recognized asthma endotyping concept categorizes individuals as having type 2 or non–type 2 asthma (Fig. 44-5). Approximately 50% of those with asthma fall into each of these categories.[31,32]

As has been recently reviewed,[22,33,34] type 2 inflammation involves activation of immune cells including T helper type 2 cells, type 2 innate lymphoid cells, eosinophils, and mast cells, as well as production of cytokines such as IL-4, IL-5, and IL-13 that together orchestrate allergic inflammation. Airway epithelial and stromal cells play a major role in the initiation of type 2 inflammation via production of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP). This type of immediate hypersensitivity immune reaction is not specific to asthma and can be seen in other allergic diseases such as eczema,

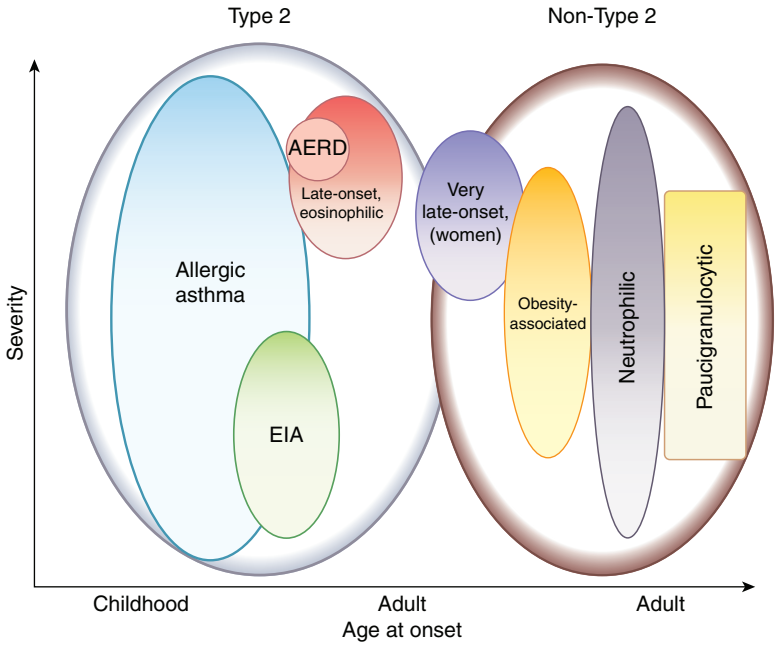

Figure 44-5 Theoretical grouping of asthma phenotypes based on the distinction between type 2 or non-type 2 asthma endotypes, age of onset and severity. Type 2 asthma consists of both early- and later-onset disease over a range of severities. Later-onset eosinophilic asthma and aspirin-exacerbated respiratory disease (AERD) are more likely to be severe, whereas exercise-induced asthma (EIA) is a milder form of type 2 asthma. Non-type 2 asthma includes very late-onset and obesity-associated asthma as well as neutrophilic asthma, and asthma in which affected individuals show little inflammation (paucigranulocytic). The intensity of the colors represents the range of severity, and the relative sizes of the subcircles suggest relative proportions of affected individuals. *(Reproduced with permission from Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18(5):716–725.)*

allergic rhinitis, and food allergy. Details on immune perturbations in asthma are provided elsewhere in this text (Chapter 43). Early-onset allergic asthma, eosinophilic asthma, and exercise-induced asthma all fall into the category of type 2 asthma, which is frequently accompanied by aeroallergen sensitization and may develop as sequelae of repeated viral infections in early life.

In contrast, non–type 2 asthma can be defined by the absence of type 2 inflammation.[35] Non–type 2 asthma encompasses heterogeneous mechanisms and may involve activation of cells such as T helper type 1 or 17 cells and neutrophils and production of cytokines such as IL-6, IL-8, IL-1β, and interferon-γ.[23,32] Neutrophilic asthma and paucigranulocytic asthma fall into the category of non–type 2 asthma, and those with non–type 2 asthma may have more severe disease.[23,35]

Obesity-related asthma also tends to fall in the category of non–type 2 asthma. This phenotype commonly begins in childhood and is associated with frequent asthma exacerbations.[36] A mechanical effect is postulated to be the result of decreased tidal volume and decreased functional residual capacity in obesity.[37] However, the critical links between obesity and asthma involve more than mechanical effects and may be related to shared genetic susceptibilities, events during fetal development, comorbidities such as gastroesophageal reflux disease, shared environmental exposures such as pollution, or common dietary and microbiome perturbations.[36,38] Immune effects may also contribute to obesity-related asthma; for example, proinflammatory cytokines can be induced or produced by adipocytes.[39] Clearly, much remains to be learned about the endotypes underlying obesity-related asthma.

Several biomarkers have been identified to differentiate asthma endotypes. Sputum cell counts are frequently used to ascertain the degree and type of asthmatic inflammation, with major categories including eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic.[40,41] Other biomarkers of type 2 asthma include peripheral eosinophilia, elevated total IgE, and presence of allergic sensitization.[33,34] Fractional excretion of nitric oxide (FeNO) is another relevant biomarker:[42] enzymatic production of nitric oxide in the lower airway is induced by type 2 inflammation,[43] and elevated FeNO is associated with eosinophilic inflammation[44] and asthma severity.[45,46] Although less available outside of research settings, evaluation of microRNA and gene expression has been performed for endotype discovery and led to recognition of bronchial periostin expression as a type 2 asthma biomarker.[47]

Like asthma phenotypes, the asthma endotype concept has limitations. A single person with asthma may exhibit multiple contributory molecular and immunologic mechanisms or may exhibit some but not all of the characteristics of a specific endotype. For example, many individuals with asthma exhibit eosinophilia but do not have comorbid allergic sensitization or disease.[28] Additionally, different studies have used different input data types and statistical methods to define endotypes. As a result, there is no consensus endotyping schema, endotype groups necessarily overlap, and individuals with asthma are frequently not easily categorized. It is highly likely that the use of multiomic data may lead to more robust endotyping in the not-too-distant future.

Nonetheless, the endotyping concept has been critical for the development of treatments that target specific disease mechanisms, as has been reviewed.[28,34] Endotype-tailored drugs currently available for moderate and/or severe type 2 asthma include the anti-IgE omalizumab for those with evidence of allergic sensitization; the anti–IL-5 agents mepolizumab, benralizumab, and reslizumab for those with an eosinophilic phenotype; and anti-IL4ra dupilumab for those with an eosinophilic phenotype or oral corticosteroid dependence. Non–type 2 asthma is associated with poor response to glucocorticoid treatment,[35] and fewer treatments have been identified as beneficial in non–type 2 asthma, although macrolide antibiotics may be effective.[48] This topic is discussed in detail in Chapter 45.

THE ROLE OF THE MICROBIOME

The microbiome refers to the collective genomic contents in a particular environment, while the microbiota refers to the specific organisms resident in that environment.[49] The human microbiota has the capacity to profoundly influence its biochemical environment, and it has several known essential functions including nutrient harvest, vitamin synthesis, and development and maintenance of immune function.[50–53] Germ-free mice have reduced T regulatory cells, elevated IgE, and increased susceptibility to anaphylaxis and allergic inflammation, indicating a key role of the microbiome in asthma and allergic pathophysiology.[54]

Findings from germ-free mice dovetail with the concept originally framed as the "hygiene hypothesis," which posited that

reduced microbial exposure is responsible for the increased prevalence of allergic disease observed in countries like the United States. This was first proposed via an observation in 1989 that larger household size is associated with reduced hay fever[55] and has evolved into a "microbiota hypothesis" whereby a variety of early-life risk factors impact microbiome composition and thereby increase risk of allergy and asthma. Since asthma has its beginnings in early life, investigation into factors that influence the composition of the early life microbiome is intensifying. Environmental and lifestyle factors that are known to affect the microbiome and that have been linked to reduced risk of asthma and allergies include breastfeeding, living on a farm, owning a dog during infancy, birth by vaginal delivery, daycare attendance, and absence of antibiotic treatment.[56,57] Thus, environmental exposures may act through changes in the composition of the microbiome to bring about disease. The concept of "dysbiotic drift," whereby modern environmental forces drive microbial dysbiosis in a way that disproportionately impacts socioeconomically disadvantaged populations, could be a unifying hypothesis on the origins of asthma and health disparities.[58,59]

There are four major mechanisms whereby microbes could impact disease risk. First, pathogenic microbes can directly cause or worsen disease; for example, upper respiratory viral illnesses are well-known causes of wheeze and asthma exacerbations.[60] A second mechanism, discussed further below, is microbial production of bioactive metabolites. A third mechanism is elaboration of pathogen-associated molecular patterns that can directly engage with host receptors such as Toll-like receptors. For example, the amount and strength of Toll-like receptor engagement by fecal microbial lipopolysaccharides are associated with asthma and autoimmune diseases.[61] Finally, specific microbes can contribute to colonization resistance, whereby pathogenic microbes have reduced ability to establish a niche; or groups of microbes with complementary functions could form communities and together impact disease risk.[62] The role of this last mechanism is less well-established in asthma.

Both microbes present in the human host and in the surrounding environment have been associated with development of asthma and with existing asthma. These findings are discussed in this section and depicted in Fig. 44-6.

The Airway Microbiome

Although fungi and archaea are likely to play a role in asthma development, viruses and bacteria have been studied more extensively. Viruses have a well-established role in asthma development, with respiratory syncytial virus (RSV) and rhinovirus in particular implicated as causes of early-life wheeze that predispose to subsequent asthma.[60,63] RSV is the major cause of bronchiolitis in children, and RSV infection is associated with IgE production, airway inflammation, and increased airway responsiveness. Human rhinoviruses, which are more common causes of upper and lower respiratory infections than RSV, also may cause bronchiolitis;[64] rhinoviruses, especially of the rhinovirus-C serotype, have been associated with asthma onset.[65] Respiratory tract infections by parainfluenza viruses, influenza virus, and human metapneumovirus during infancy are all also associated with childhood wheezing.[63]

It is hypothesized that susceptibility to asthma associated with viral infection in early life results from the interaction of developmental, genetic, and environmental factors. In particular, the progression from wheezing with viral illness to subsequent asthma has been linked to the atopic march, as children with pre-existing atopy are at highest risk of asthma after a rhinovirus wheezing illness, perhaps in part due to the inhibitory effects of Th2 inflammation on antiviral immune responses.[65] Jackson and colleagues[65] showed that while human rhinovirus was the dominant factor in developing asthma by the age of 6 years, the risk was highest when concomitant allergic sensitization was present. This concept is supported by evidence that treatment with the anti-IgE monoclonal antibody omalizumab increases IFN-α production in rhinovirus-treated peripheral blood mononuclear cells and, in children with asthma, resulted in reduced frequency and duration of rhinovirus infection and reduced frequency of asthma exacerbations.[67,68]

In addition to their role in asthma development, viral respiratory illnesses trigger asthma exacerbations and induce nonspecific increases in airway responsiveness and airway obstruction.[69,70] A number of studies have demonstrated a close temporal relationship at the individual and population levels between viral infections and asthma exacerbations, and they have demonstrated that those with asthma may have increased susceptibility to viral lower respiratory infections.[71,72]

In contrast to viral infections, bacterial infections are not associated with asthma exacerbations,[73] and the relative importance of the bacterial versus viral airway microbiome in asthma development has not yet been determined. The lower airway was previously thought to be sterile under normal conditions, but now it is known to be colonized, most likely with microbes that originate in the upper airway and oropharynx. Studying the airway microbiome is challenging for multiple reasons. For example, it is not clear which anatomic compartment along the airway is most relevant, contamination is more of a consideration when sampling low-biomass areas such as the lower respiratory tract, and treatments such as inhaled steroids can influence airway microbiome composition.[74]

Studies in children most often utilize upper airway samples such as nasal or oropharyngeal swabs to study the airway microbiome. Longitudinal cohort studies have found that colonization early in life with *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* is associated with subsequent recurrent wheeze.[75] These taxa and other bacterial microbiome perturbations have also been associated with RSV, rhinovirus, and lower airway symptoms during respiratory infections,[76–79] raising the question of whether these bacteria have causal importance or are simply associated with pathogenic viruses.

In addition to impacting asthma development early in life, airway microbiome perturbations have been observed in children and adults with existing asthma. In particular, Proteobacteria, including the genus *Haemophilus*, is enriched in the airways of subjects with asthma.[80–83] The impact of the microbiome on asthma phenotypes, endotypes, and responses to treatment is an area of active research. Several studies have demonstrated differences in the airway microbiome between asthmatic subjects with sputum eosinophilia and those with sputum neutrophilia, or in association with blood eosinophilia.[83–87] Airway microbiome composition has been associated with other disease-related features, including airway hyperresponsiveness, lung function, and Th17-related gene expression.[83,84,88,89] Microbiome alterations may also inform response to asthma pharmacologic treatments. Of particular interest, corticosteroid resistance has been associated with airway microbiome features including enrichment of *Haemophilus parainfluenzae*.[90,91]

The Environmental Microbiome

A landmark study of the impact of the environmental microbiome on asthma compared Amish farmers from Indiana and Hutterite farmers from South Dakota.[92] These populations are genetically similar, but Amish people live in closer proximity to animal dwellings including cow stables compared to Hutterites. Interestingly, Amish children have a fourfold lower prevalence of asthma compared with Hutterites. Dust collected from Amish homes had higher perennial allergen levels, higher endotoxin levels, and different bacterial compositions compared with dust from Hutterite homes. These differences in environmental microbial exposures could contribute to differences in asthma risk. In a mouse model of OVA-induced allergic asthma, intranasal treatment of mice with

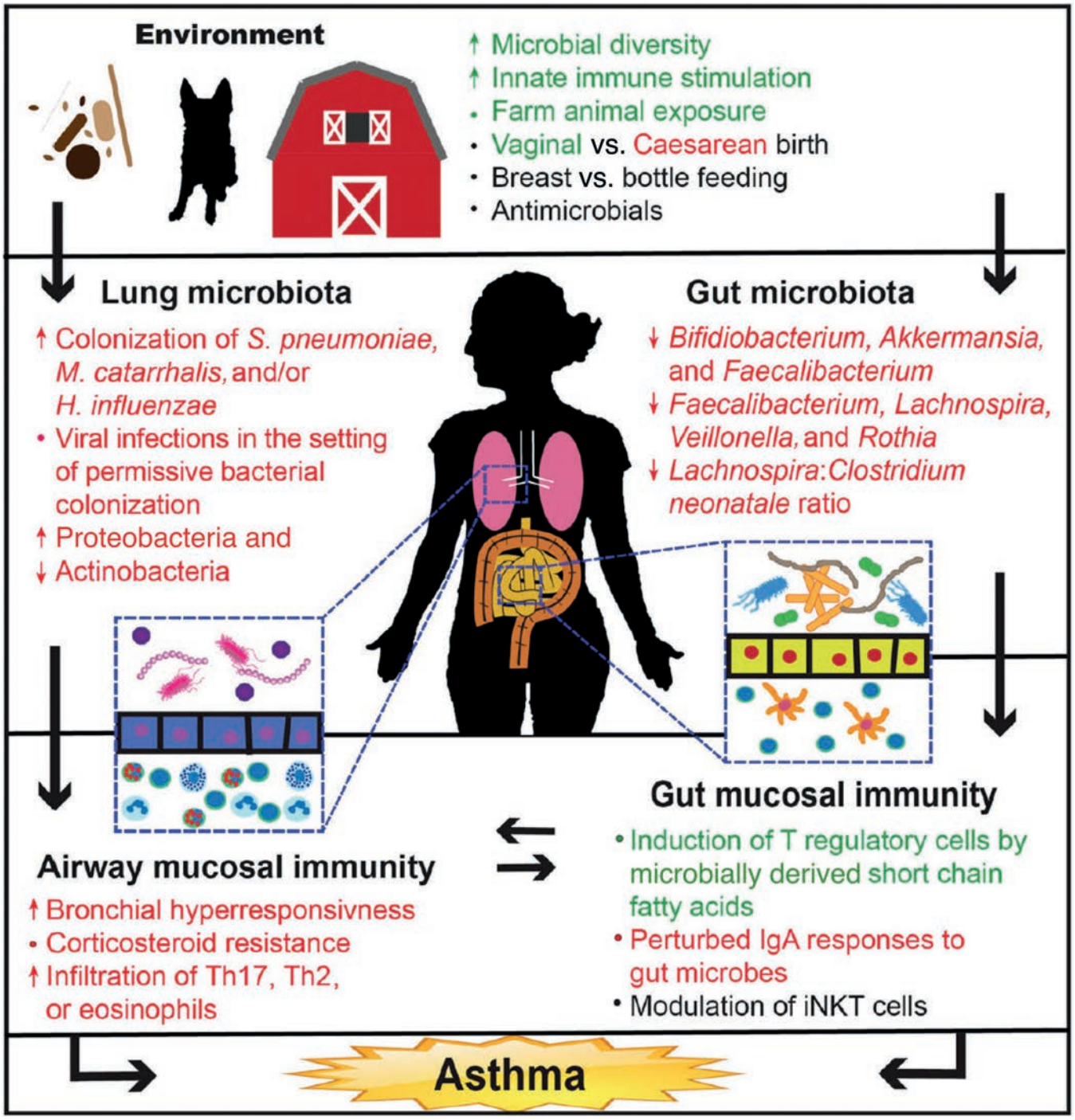

Figure 44-6 Overview of potential microbial influences on asthma. Green type denotes protective factors, and red type denotes risk factors for asthma development. *(Reproduced with permission from Ver Heul A, Planer J, Kau AL. The human microbiota and asthma. Clin Rev Allergy Immunol. 2019;57(3):350–363.)*

Amish house dust abrogated airway resistance. The protective effect of Amish house dust was reduced in MyD88 and MyD88-Trif knockout mice, demonstrating a dependence on innate immune pathways such as Toll-like receptor activation.[92] Based on this and other studies,[93,94] there is compelling evidence for a protective effect of farm environments with a key role for innate immune activation, although the specific microbes and mechanisms at play are not fully defined. Exposure to a wider array of microbial agents via farm animals and ingestion of raw, unpasteurized milk have been postulated to mediate the effects of early life exposure to farming environments,[92,95] and it may also affect the development of the child's intestinal microbiome.[96]

Other factors are likely to impact the environmental microbiome with relevance for asthma risk. For example, although existing asthma is associated with allergic sensitization to cats and dogs,[97] living with a dog during infancy has been associated with reduced risk of subsequent asthma or wheeze.[98,99] The connection between dog ownership and asthma may be mediated by changes to the household microbiome, as pets contribute significantly to household endotoxin levels.[100,101] While a pooled analysis of 11 European birth cohorts did not find any effect of pet ownership on asthma and allergic rhinitis in school-age children,[102] it is likely that there are subsets of children for which early exposure to dogs and other pets may be helpful.[103] The protective effect of early-life dog exposure is in contrast to the effects

of early exposure to other indoor allergens, such as dust mite, which is associated with increased risk of subsequent asthma as discussed in "Indoor and Outdoor Allergens," below.[104,105]

The Gut Microbiome

Although distant from the lung, the gut harbors the most numerous and diverse collection of microbes in the human body, and microbial activity in the gut can have effects in organs throughout the body.[106] Data from several birth cohort studies demonstrate that differences early in life in gut microbiome composition can be detected between children who subsequently develop asthma and those who do not.[107–110] These differences have been seen in the first months of life, but not later,[108,109] suggesting a transient "window of opportunity" for the microbiome to impact asthma risk. In contrast to the numerous published studies on the gut microbiome in early life and development of asthma, little is known about the gut microbiome in existing asthma. In one of the few studies on this topic, an increased abundance of histamine-secreting fecal microbes was found in adults with asthma compared to healthy controls.[111]

Gut microbial metabolites are felt to be major mediators of the link between gut bacterial composition and asthma risk. Short-chain fatty acids are a class of metabolites that include acetate and butyrate and have been well studied in the context of asthma. Short-chain fatty acids are derived from bacterial fermentation of dietary fiber and have several health effects including tolerogenic effects on multiple facets of immune function.[112] Both animal and human cohort studies have provided evidence of a protective effect of short-chain fatty acids on asthma development.[108,113–115]

12,13-diHOME, a metabolite of the omega-6 fatty acid linoleic acid, also plays a role in asthma development. 12,13-diHOME is enriched in stool samples from infants at risk of subsequent asthma and atopy.[109] In mouse models, peritoneal injection of 12,13-diHOME increases airway inflammation and IgE and reduces lung T regulatory cells.[116] A subset of gut microbes, but not human cells, express epoxide hydrolases that are required in the production of 12,13-diHOME; genes that encode these enzymes are present in higher abundances in stool samples from infants at risk of asthma and atopy.[116] Other classes of microbial-derived metabolites likely impact asthma risk or morbidity, including other polyunsaturated fatty acids, tryptophan metabolites, and bile acids.[117]

GENETIC SUSCEPTIBILITY AND GENE-ENVIRONMENT INTERACTIONS

Asthma is considered a complex disease that has both genetic and environmental determinants. Since the completion of the Human Genome Project in 2000, more than 100 genes have been directly linked to asthma through association studies. These studies look at single nucleotide polymorphisms (SNPs) across the genome and relate them to asthma occurrence using either a case-control or a family-based design. These genome wide association studies utilize the association of SNPs with each other, that is, their correlation, or linkage disequilibrium, to cover the whole genome by analyzing a subset of SNPs. While these studies have a variety of threats to their validity, through increasing sample size and replication, many genes for asthma have been identified.[118,119]

In 2007, in the second GWAS study ever performed, a locus on chromosome 17q21 was identified as being associated with asthma.[120] This was replicated in multiple other studies and seemed to be strongest for childhood asthma and asthma onset.[121] The locus is complex, as there are at least five genes—ORMDL3, GSDMB, GSDMA, ZPBP2, and IKZF3—that are tightly correlated with each other in the region.

Most of the initial functional work has focused on ORMDL3 and GSDMB. In 2009, a causal functional variant at this locus, rs12936231, was identified. This SNP is predicted to disrupt the binding of an insulator, CTCF, in ZPBP2 and is correlated with expression of both ORMDL3 and GSDMB.[122] In 2016, a second SNP, rs4065275, in the locus on the same haplotype was demonstrated to have a similar functional effect and was tied to IL-2 levels.[123]

Another important feature of the genetic epidemiology of the 17q21 locus is that a variety of environmental factors, including vitamin D, tobacco smoke, antibiotics, furry pets, inhaled corticosteroids, and viral respiratory illness, all interact with this locus, suggesting that it might be central to the origin of asthma.[121]

Much recent work has been done to determine the functional effect of the genes in the 17q21 locus on asthma and how they interact with the environment. Mice expressing the ORMDL3 transgene exhibited spontaneous increases in airway hyperresponsiveness, associated with airway wall remodeling and peribronchial fibrosis and airway smooth muscle hypertrophy without airway inflammation.[124] ORMDL3 is known to inhibit the enzyme serine palmitoyltransferase, the rate-limiting step in sphingolipid production.[125] In accordance with this, siRNA knockdown of ORMDL3 in human bronchial epithelial cells led to increased sphingolipid pathway metabolites,[124] and ORMDL3-overexpressing transgenic mice were found to have reduced levels of sphingolipids.[126]

Recently ORMDL3 genetics were combined with metabolomics to strengthen this association in human studies. Non-atopic childhood asthmatics were shown to have lower levels of circulating sphingolipid metabolites, and these lower levels were linked to SNPs (rs7216389 and rs8076131).[127] These SNPs are eQTLs (expression quantitative trait loci) that are correlated with ORMDL3 expression. Other recent work showed that the genetic locus was rich in vitamin D receptor binding sites and that vitamin D levels interacted with the causal rs12926321 SNP to determine childhood asthma susceptibility, that both mother and child genotypes at this locus were relevant to genetic risk, and that both vitamin D and the ORMDL3 SNP rs12926321 were linked to sphingolipid levels.[128] To summarize this portion of a complex and still developing story, higher ORMDL3 expression is associated with lower sphingolipid levels and increased airway hyperresponsiveness, and hence higher asthma risk. Vitamin D can downregulate ORMDL3 expression and also has a direct effect to increase sphingolipid levels and hence decrease asthma occurrence. This effect was observed in both white subjects and African-Americans.[128] Of note, African Americans have lower vitamin D levels than other Americans.[129]

Much work still needs to be done on this locus, including on GSDMB and how viral illness interacts with the locus to produce childhood asthma, as well as elucidating how the other approximately 100 known asthma loci contribute to disease development. However, the beginning outlines of how genes and environmental factors interact to cause asthma are now clear, and 17q21 is a central part of this story.

ENVIRONMENTAL RISK FACTORS

Below we present some of the most important environmental risk factors for the development or exacerbation of asthma not discussed earlier.

Perinatal Factors

Asthma originates in utero as an abnormality of fetal lung development. As such, several perinatal factors impact asthma risk. Prematurity is one important factor that carries an increased risk for the development of asthma. A meta-analysis showed that infants born at less than 37 weeks' gestation are at greater risk for developing asthma than term infants.[130] More recently, it was shown that the risk for asthma is likely mediated through the effects of prematurity on the development of obstructive lung function deficits.[131]

Prematurity is also associated with bronchopulmonary dysplasia,[132] a disease characterized by increased airway responsiveness and asthma symptoms. Some investigators have found that low birth weight independent of prematurity has been associated with asthma risk.[133,134] The strength of the association between prematurity and/or low birth weight on asthma or asthma symptoms appears be greatest in very young children, and the effects decrease over time.[135,136] Note that black individuals have higher rates of prematurity than white individuals; thus, prematurity may contribute to racial differences in asthma prevalence and morbidity. Despite much research, there is no conclusive evidence that breastfeeding influences atopic sensitization or the development of asthma.

Recent studies have focused on maternal diet during pregnancy and its effect on the development of asthma and allergies, with the hypothesis that nutritional deficiency or excess may lead to programming of the fetus for adult disease.[137] These studies have mostly used nutrient intake estimates derived from food frequency questionnaires that assess how often a particular standard serving of a food or drink is eaten. The responses to the questionnaire, in conjunction with a database of nutrient composition of foods, are then used to calculate the amount of a particular nutrient over a specified time period.[138] A few studies have measured the particular nutrient in either maternal or cord blood samples. A meta-analysis found that there was weak support for protective effects of higher maternal intakes of vitamin A, D, E, and zinc for the prevention of asthma in children.[139]

Vitamin D

In the strict sense of the word, vitamin D is not actually a vitamin, since humans are able to produce the compound in the skin on exposure to UVA rays from the sun. While the first report of an effect of vitamin D on asthma and allergies appeared in 1934,[140] research into the effects of vitamin D did not begin in earnest until the last decade. There are two opposing hypotheses regarding the role of vitamin D in asthma. Wjst and Dold suggested that fortification of food with vitamin D and the widespread use of multivitamins in childhood contributed to the rise in asthma and allergies.[141] On the other hand, given the documented decrease over time in the levels of the circulating form of vitamin D in population studies,[142] Litonjua and Weiss hypothesized that the increasing prevalence of vitamin D deficiency led to the increase in asthma prevalence worldwide.[143]

Many epidemiologic studies have investigated the role of vitamin D in the development and control of asthma. With regard to the development of asthma and allergies, most studies have investigated either estimated maternal intakes of vitamin D from foods and supplements or maternal levels of 25-hydroxyvitamin D (25OHD). Four observational cohort studies have reported beneficial effects of a higher maternal intake of vitamin D in pregnancy on outcomes in their children.[144–147] However, other studies have not replicated these findings.[148–151] Two clinical trials of vitamin D supplementation in pregnancy have been completed.[152,153] While neither study on its own showed a statistically significant effect, a combined analysis showed a significant protective effect of maternal vitamin D supplementation on early wheezing and asthma by age 3 years.[154] The protective effect, however, did not persist through age 6 years.[155] It is likely that there are subsets of early wheezing phenotypes that may respond to vitamin D supplementation in utero, and further studies will be needed to determine this. Additionally, both clinical trials performed vitamin D supplementation only in pregnancy. There may be additional effects of postnatal vitamin D supplementation for asthma and wheeze prevention.[156]

As for the role of vitamin D in asthma control and management, observational studies have shown that asthmatics with higher circulating vitamin D levels have greater lung function,[29,30] lower risks for exacerbations,[157,158] and generally less severe indices of disease.[159] An initial small trial of 48 children with newly diagnosed asthma showed that vitamin D supplementation led to a significant reduction in the number of exacerbations over a period of 6 months.[160] Subsequent larger studies in adults and children[161] with chronic asthma did not show an effect of vitamin D supplementation in the prevention of asthma exacerbations.

Omega-3 Fatty Acids

Omega-3 and omega-6 fatty acids are major forms of polyunsaturated fatty acids (PUFA). The essential fatty acids alpha-linolenic acid and linoleic acid are the simplest members of the omega-3 and omega-6 fatty acid families, respectively.[162] Dietary PUFAs are critical sources of bioactive metabolites and cell membrane phospholipid components: alpha-linolenic acid metabolites include eicosapentaenoic acid and docosahexaenoic acid, and linoleic acid metabolites include arachidonic acid. Diet is a major determinant of the proportions of omega-3 and omega-6 metabolites. Major food sources of omega-3 fatty acids include oily fish such as salmon, mackerel, and herring.

Omega-3 PUFAs are generally thought to be anti-inflammatory, while omega-6 PUFAs contribute to inflammation.[163] During the course of the 20th century, changes in the Western diet led to increases in consumption of omega-6 over omega-3 PUFAs, primarily due to increased consumption of linoleic acid–rich soybean oil.[164] This shift has been proposed as a potential cause of the increased occurrence of allergic disease over the past half century.[165]

With regard to asthma prevention, a trial of fish oil (omega-3 PUFAs) versus placebo (olive oil) was recently completed. The trial showed that supplementation of 2.4 g of omega-3 PUFAs beginning at 24 weeks of gestation decreased the risk for persistent wheeze or asthma at 3 years of age. This trial was notable for the high dose of PUFA used as the intervention. Prior prenatal omega-3 PUFAs supplementation trials using lower doses (400 mg[166] and 800 mg[167]) did not show an effect on childhood lung function or allergic outcomes, respectively. With regard to the role of omega-3 PUFAs in established asthma, a trial of fish oil supplementation (4 g/day) in obese asthmatics did not show any difference in asthma control when compared with placebo.[168]

■ Indoor and Outdoor Allergens

Indoor allergen sources include animals (cats, dogs, rodents); insects (mites, cockroaches); and fungi. For many decades, the prevailing hypothesis of early asthma development was that it was caused by exposure to allergens, particularly house dust mite allergens.[104,169] Allergens are well-known precipitants of asthma exacerbations and increased morbidity.[170,171] However, studies of trials of allergen reduction or avoidance have not produced definitive results. A Cochrane meta-analysis of 54 trials using varying methods of mite-allergen reduction (physical methods, chemical methods, and a combination) concluded that there was no clinical benefit of dust mite allergen reduction.[172] Factors that could explain these findings include that adherence to the demanding protocols for control of allergen exposure is difficult and may not always result in sufficient reduction in personal aeroallergen exposure, and that allergens are ubiquitous in other settings outside the home (e.g., schools and daycare[173]). Evidence that exposure to some sources of indoor allergens, such as dogs, in early life may actually be protective against asthma development is discussed in "Role of the Microbiome," above. It is likely that mechanisms are complex, and that exposure to a wide array of microbes related to dogs may override the effects of exposure to dog allergen.

Outdoor allergens include trees, grass, and weed pollen constituents. The evidence for outdoor allergen exposure relates to asthma

morbidity rather than asthma development. Susceptible individuals may have increased asthma symptoms at times of pollination.[174] Assessment of sensitization to indoor and outdoor allergens is part of the management of asthma, as is monitoring of levels of outdoor allergens.[175]

Smoking, Second-hand Tobacco Smoke Exposure, and E-cigarettes

Maternal cigarette smoking is a major risk factor for the development of asthma in the first year of life. Both a meta-analysis[176] and a pooled analysis[177] showed that the risk of developing asthma ranges from around 40% to 85% greater among children born to mothers who smoked during pregnancy versus children born to mothers who did not smoke. This effect appears to be strongest in children who developed asthma before 2 years of age.[176]

Second-hand smoke exposure exacerbates asthma in children of all ages.[178] Wilson and coworkers evaluated a cotinine-feedback behavioral intervention administered to caregivers that successfully reduced second-hand smoke exposure and health care utilization by children with asthma at 1 year follow-up.[179] However, in a follow-up study, the effect was seen only in the children at highest risk for exacerbation.[180] In adults, cigarette smoking is associated with the development of airway hyperreactivity.[181] Whether this hyperreactivity represents asthma or COPD can be difficult to determine. Cigarette smoking and asthma produce a synergistic and accelerated decline in lung function.[182,183] Additionally, the response to corticosteroid therapy used for asthma is reduced in active smokers.[182]

In recent years, the prevalence of electronic cigarette (e-cigarette) use has increased to epidemic proportions. E-cigarettes are electronic devices that heat a liquid and produce an aerosol or a mix of small particles in the air. They are known by many different names including "e-cigs," "vapes," "vape pens," and "electronic nicotine delivery systems (ENDS)." Epidemiologic studies have shown an increased risk for asthma among e-cigarette users.[184]

Other Pollutants

Outdoor pollutants implicated in the development or exacerbation of asthma include ozone, sulfur dioxide, particulate matter, and components of motor vehicle exhaust.[185,186] Measuring exposure to potential pollutants is difficult, and correlating exposure with symptoms and exacerbations of disease is very expensive. Most monitoring of pollutants is from fixed external stations. Sometimes proxy measures of pollutant exposure, such as traffic counts, are used. Although potentially more accurate, monitoring of personal exposures is particularly difficult and expensive.[187] Assessing which of the many possible simultaneous outdoor inhalants affects asthma morbidity is also a formidable task. Conclusions drawn from such data may be indirect. An example is the observation that asthma morbidity is highest among low-income individuals who tend to live in less desirable areas, which are frequently those with high traffic volumes and pollution.

There has been much interest in indoor environmental pollutants, such as nitrogen dioxide, sulfur dioxide, volatile organic compounds, and particulate matter, and their possible association with asthma, particularly in inner-city homes.[188,189] As with studies of outdoor pollution, difficulties in measurement over time, controlling for other exposures such as allergens, infectious agents, and social determinants of health, and linking exposures to symptoms and physical findings make research challenging.

Acetaminophen

It has been postulated that acetaminophen use may increase the risk of developing asthma or asthma morbidity due to its prooxidant effects (by depletion of the antioxidant glutathione in lung tissue).[190] Several studies have reported on the association of acetaminophen use, in pregnancy, in early life, and in adulthood, and the development of asthma.[191–195] However, the issue with studies that investigate over-the-counter medications such as acetaminophen is the possibility of confounding by indication, meaning that these individuals have comorbidities (e.g., respiratory infections) for which they may take the acetaminophen for its antipyretic or analgesic effects. A clinical trial in young children with mild persistent asthma did not show a difference in the incidence of asthma exacerbations or loss of asthma control between the as-needed acetaminophen arm versus the as-needed ibuprofen arm.[195] While this study suggests that acetaminophen intake does not affect asthma morbidity, it does not address the potential effect of acetaminophen on asthma development, and additional studies will need to be done.

NATURAL HISTORY

The natural history of asthma in early childhood can be gleaned from data from the Tucson Children's Respiratory Study.[196,197] By following a cohort of children through the first 6 years of life, study investigators characterized four groups of children: "persistent wheezers," who wheezed both before and after the age of 3 years; "transient early wheezers," who wheezed before the age of 3 years and then stopped; "transient late wheezers," who wheezed after age 3 years but not before; and "never wheezers." Fully 40% of all children wheezed in the first year of life.

Significant predictors of persistent wheezing, and hence children at greatest risk for developing chronic asthma, were young maternal age, IgE level at 9 months, parents with asthma, maternal cigarette smoke exposure in utero, abnormal lung function at birth, and male sex. It is likely that early-life wheezing is predominantly a mechanical factor and less due to severe and chronic airway inflammation. It also seems unlikely that allergen exposure predominates as a factor in early childhood.

The characteristics of older children who wheeze are atopy, female sex, and active and passive cigarette smoking. By preadolescence, atopy and environmental allergen exposure are important risk factors for wheezing in children.

In roughly half of all childhood asthmatics, symptoms decrease or disappear by late adolescence and early adulthood. Characteristics that suggest a good prognosis include male sex, precipitation of attacks by viral respiratory illness, and children with airway parenchymal dysanapsis (i.e., small airways relative to lung size). These children are predominantly male and, although often atopic, still are likely to outgrow their asthma.

In a longitudinal study of children from East Boston, initially 5 to 9 years of age followed over a 13-year period, the effect of asthma on lung growth was different for boys than girls.[198] Boys with asthma had larger growth in vital capacity than boys without asthma and tended to have mild disease. This was associated with fewer hospitalizations for asthma, despite somewhat greater prevalence than in girls. Asthmatic girls, however, had persistent reductions in FEV_1 and were more likely to be hospitalized for asthma, despite an initially reduced prevalence relative to the boys. These data are consistent with asthma being milder in boys in that boys are more likely to "outgrow" their asthma.

In contrast, the Childhood Asthma Management Program (CAMP) followed lung function of 1041 children (420 girls and 621 boys) with mild to moderate persistent asthma, who participated in a clinical trial of asthma treatment.[199] The authors used lung function data of 5415 nonasthmatic children from the Harvard Six Cities Study for comparison. In children of both sexes aged 6 to 18 years, the FEV_1/FVC ratio was significantly lower and FVC was significantly higher for asthmatic children, compared with nonasthmatic children. In contrast to the East Boston study, boys had lower FEV_1 between the ages of 10 and 18 years, whereas there were no

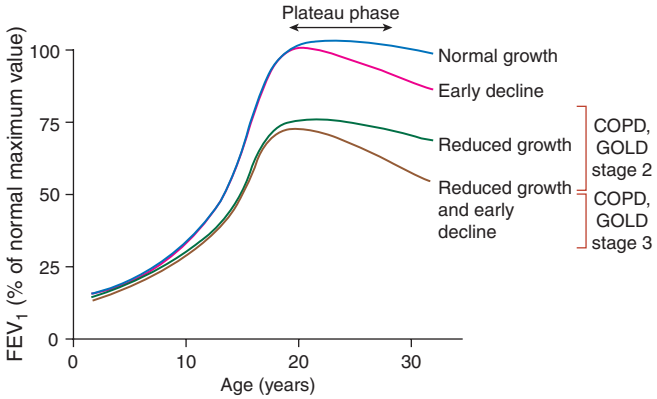

Figure 44-7 Patterns of longitudinal lung function trajectories. Normal lung growth continues after birth and reaches a peak in early adulthood. A plateau phase then ensues from the 20s to the mid-30s for most individuals. After that, gradual decline of lung function follows, mirroring physiologic aging. Perturbations of normal grown may occur, depending on environmental and other exposures over the life course of the individua. A pattern of normal growth and early decline may occur if the individual achieves normal peak lung function, but there is no plateau phase and more rapid decline starts soon after achieving peak lung function. Two other general patterns may also occur if peak lung function is not attained—that is, if reduced growth is observed. After reduced growth, a period of normal decline may ensue, or a period of early and rapid decline. These latter two patterns may increase the risk for the development of COPD later in life. *(Reproduced with permission from McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. N Engl J Med. 2016;374(19):1842–1852.)*

significant differences in girls. Taken together, these studies suggest that asthma that starts in early life (i.e., by age 6 years) leads to decrements in lung function that are persistent through adolescence. These patterns have been borne out in other longitudinal studies (reviewed in Grad and Morgan[200]).

In both adolescents and adults, airway responsiveness predicts the development of asthma[19,201–204] and antedates and predicts accelerated decline in lung function.[205,206] Both persistent symptoms[207] and active smoking[183] conferred more rapid rates of lung function decline in longitudinal studies. The severity of adult asthma is clearly predicted by the severity of childhood asthma, and the persistence of symptoms in childhood and early adulthood is associated with reduced lung function and more severe disease later in adult life.

The influence of childhood asthma on later adult disease continues to be elucidated by longitudinal studies. Normal patterns of lung function growth and decline have been established. In individuals with no lung disease, FEV_1 increases until early adulthood and remains stable for several years (the plateau phase). Lung function then gradually declines related to physiologic aging. Perturbations of this normal pattern give rise to increased risks for lung disease later in life (Fig. 44-7). The CAMP continuing study investigated longitudinal lung function (FEV_1) patterns among 684 children with persistent asthma.[208] About 25% of the children had a normal growth and decline pattern when compared with National Health and Nutrition Examination Survey participants who did not have asthma. The investigators categorized the rest of the children into different patterns of growth and decline: normal growth and early decline, reduced growth, and reduced growth and early decline. Each of the categories contained about 25% of the total number of children studied. At the end of the period of observation, when the mean age of participants was 26 years, 73 (11%) met spirometric criteria for chronic obstructive lung disease.

Findings from longitudinal lung function studies from CAMP and other cohorts have given rise to the idea that perturbations of lung function growth and decline can lead to increased risks for chronic obstructive pulmonary disease (COPD) or the recently recognized asthma-COPD overlap syndrome (ACO).[209] ACO is a condition that comprises clinical and biologic features of both asthma and COPD, and it applies to subgroups of patients with asthma and persistent airflow obstruction or COPD patients who have variable airflow obstruction and/or evidence of type 2 inflammation.[210,211] Because a consensus definition of ACO remains elusive, the epidemiology of ACO remains to be defined. Nevertheless, longitudinal studies of asthma in children and adults suggest that improved control might modify the risk for fixed obstructive disease later in life. For example, Sears and colleagues[212] showed that in a cohort of children followed from 9 to 26 years of age, those who had persistent wheezing consistently had lower lung function than those without persistent wheezing. Similarly, in a cohort of adult moderate to severe asthmatics with an initial mean age of 27 years and median follow-up of 11 years, participants with exacerbations had greater declines in FEV_1, such that one severe exacerbation per year was associated with a 30.2-mL greater decline per year.[213]

In summary, most asthma begins in childhood. Attention needs to be paid to the presence of risk factors that may lead to the development of asthma in childhood. Once asthma is established, it is imperative that efforts are focused on achieving good control of the disorder and preventing exacerbations, so as to limit the risk for developing more severe asthma, COPD, and ACO in adulthood.

HEALTH DISPARITIES IN ASTHMA

As discussed at the beginning of this chapter, asthma prevalence and especially morbidity and mortality are higher in some groups of individuals, notably including non-Hispanic black individuals, Hispanics of Puerto Rican descent, and those with lower household income. The extent to which these differences in asthma prevalence, hospitalization, and mortality are attributable to inadequate treatment and access to medical care remains unclear, but there is indisputable evidence of unequal treatment of minority and low-income groups by health professionals.[214]

Perceptions of a person's race influence social experiences, including those with the health system. In a study of women in the United States, black and Hispanic women were more likely to report a doctor's diagnosis of asthma, had higher total IgE levels, and were more likely to be sensitized to aeroallergens; however, they were less likely to report a diagnosis of hay fever or eczema.[215] These findings could represent underdiagnosis of hay fever and eczema by medical personnel, perhaps related to fewer referrals to an allergist or other specialist, or underreporting of symptoms by patients. Genetic differences alone are unlikely to explain differences in sensitization, which more likely relate to environmental exposures.

Socioeconomic factors tend to be inseparably linked to ethnicity and race for historic and political reasons. As a result, environmental factors that are the products of poverty, such as psychosocial stressors, poor dietary quality, and exposure to tobacco smoke or other pollutants or allergens, contribute to disparities in asthma prevalence and morbidity[216,217] (Fig. 44-8). A growing body of research on racial and socioeconomic disparities in asthma has focused on the effect of stress and violence in the pathogenesis of asthma and morbidity related to asthma.[218] Psychosocial stressors are associated not only with increased asthma occurrence, but also with reduced response to asthma medications such as inhaled beta-agonists.[219–221] Individuals in high-risk minority groups are frequently exposed to several asthma risk factors simultaneously, and this unequal exposure starts at conception and continues through childhood and into adulthood. For this reason, there is an

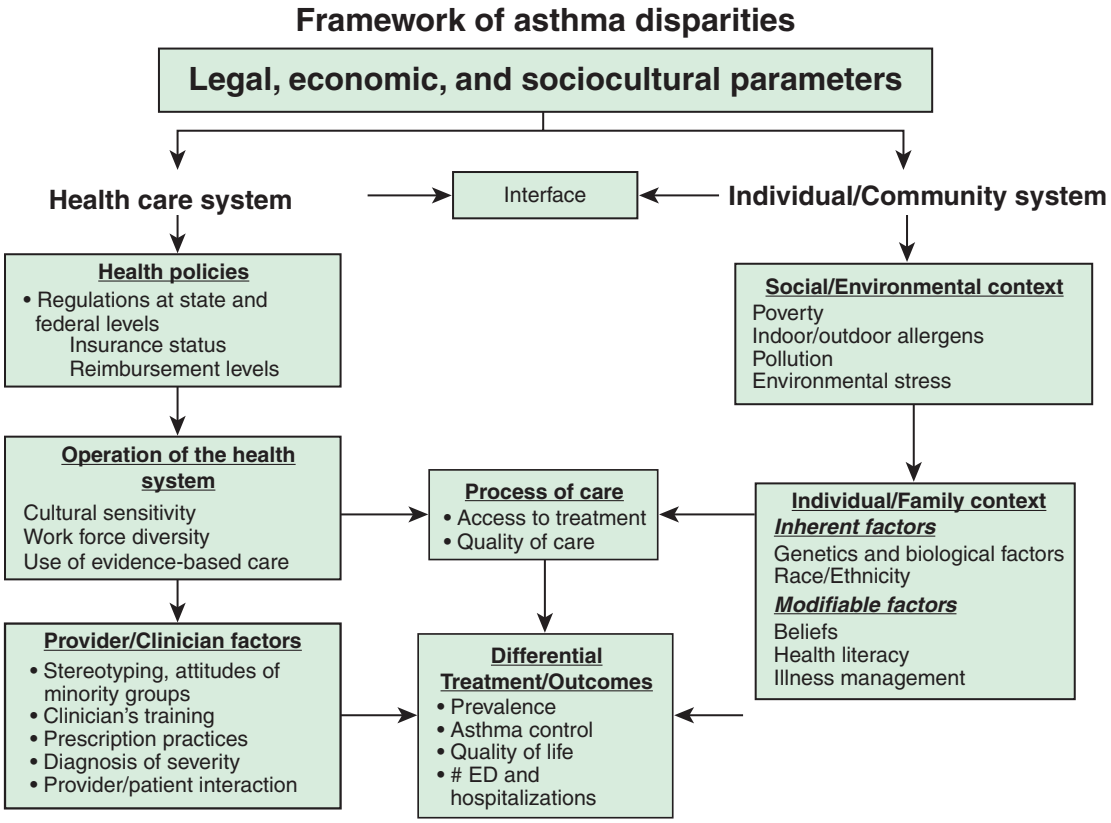

Figure 44-8 Multilevel model of asthma disparities. *(Reproduced with permission from Canino G, McQuaid EL, Rand CS. Addressing asthma health disparities: a multilevel challenge. J Allergy Clin Immunol. 2009;123(6):1209–1217.)*

imperative to tackle multiple environmental and social factors if the goal of reducing asthma disparities is to be achieved.

CONCLUSIONS

Although asthma prevalence, morbidity, and hospitalizations have remained stable recently, the absolute levels remain unacceptably high, particularly for certain minority groups and low-income populations. Risk factors such as obesity, prematurity, young maternal age, vitamin D deficiency, low intake of omega-3 fatty acids, and cigarette smoking are all associated with these same patient groups and speak to ongoing social and healthcare disparities. Differences in many relevant exposures are reflected by the environmental and host microbiomes, which may represent key links between exposures and asthma risk. This idea is encapsulated by the concept of "dysbiotic drift," whereby modern environmental forces drive microbial dysbiosis in a way that disproportionately impacts socioeconomically disadvantaged populations.[58] Certainly, genetic differences also exist from patient to patient. Understanding how genetic variants interact with one another and with environmental exposures to result in various asthma phenotypes will be critical to piecing together the mechanisms behind asthma prevalence and outcome disparities. With recent unprecedented computational and technologic advances in our ability to query the complex systems involved with asthma pathophysiology, we expect coming years to bring many new insights into factors that lead to distinct asthma endotypes and phenotypes and new strategies for tackling asthma disparities.

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CHAPTER 45

Asthma: Clinical Presentation and Management

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ASTHMA—A HETEROGENEOUS DISEASE

Asthma is a chronic inflammatory disorder of the airways characterized by marked temporal variability in airflow obstruction that is often reversible, either spontaneously or with treatment.[1] This inflammation presents clinically in susceptible patients with recurrent symptoms of wheezing, chest tightness, cough, and, occasionally, dyspnea and contributes to heightened airway hyperresponsiveness to specific and nonspecific stimuli—a pathognomonic feature of asthma. Increased airway hyperresponsiveness manifests in patients as intolerance to smoke, dust, air pollution, and strong odors, where exposure to such agents in healthy individuals does not induce such symptoms. Asthma is not a single disease entity with a unique pathogenesis, but rather recognized to be a clinical syndrome and heterogeneous disease;[2] that is, asthma comprises multiple endotypes that manifest common symptoms but have distinct and probably different pathophysiologic and etiologic mechanisms with an interplay between genetic and environmental factors. This phenotypic heterogeneity in the expression of asthma is multidimensional and includes variability in pathologic, clinical, and physiologic parameters among different patients.[3] Recent attention has directed focus on traits that are identifiable and treatable in patients with asthma, such as persistently elevated blood eosinophils, in order to achieve precision treatment with the hope of better patient outcomes.[4]

RISK FACTORS FOR ASTHMA

Several risk factors for asthma are considered below.

Atopy and Allergens

The most important factor predisposing to asthma is atopy (Table 45-1). Asthma has been classified as *atopic* (extrinsic) *or nonatopic* (intrinsic) depending on the suspected role of allergens as etiologic factors. Atopic asthma involves an exaggerated immune response characterized by immunoglobulin E (Ig-E) activation and mast cell degradation. Atopy can be clinically elicited with a positive skin prick test or specific antibodies to IgE in serum against common aeroallergens such as house dust mite, grass and tree pollens, *Aspergillus* mold, cat and dog fur, rodents (in laboratory workers), and cockroaches (in inner-city populations). House dust mite is recognized as a significant cause of asthma throughout the developed world, although the relative importance of different indoor allergens may vary among populations. Patients with atopic asthma commonly suffer from other atopic diseases, including allergic rhinitis that may be seasonal (hay fever), and may be found in over 80% of asthmatic patients; allergic conjunctivitis; and atopic dermatitis (eczema). Nonatopic asthmatic patients (approximately 10%) have a negative skin prick test, normal serum IgE concentrations, and usually show later onset of disease (adult-onset asthma). In this group, asthma is more severe and persistent, there is more sensitivity to aspirin, and commonly patients have concomitant nasal polyps. This classification, although appropriate from a pathologic perspective, does not readily help clinicians as it does not aid in establishing an etiologic diagnosis, nor does it help in defining treatment strategies.[5] There is a high prevalence of atopy among nonasthmatics and a large percentage of skin prick–sensitive persons report no allergic symptoms. About 50% of asthma can be attributed to atopy in the developed world, and the prevalence of atopy among asthmatics is determined mainly by the general prevalence of atopy in the population.[6,7] In addition, the immunopathology in bronchial biopsies and sputum in patients with nonatopic asthma appears to be identical to that found in atopic asthmatic patients. Therefore, the finding that an asthmatic is atopic does not imply that the disease is allergic in nature or that atopy is causing asthma. Moreover, respiratory tract viruses have emerged as the most frequent triggers for exacerbations in both children and adults and may play a more prominent role than allergens as triggers of acute exacerbations in most patients.[8] House dust mites are the most common indoor allergen, where particles excreted from the digestive tract contain the principal allergen *Dermatophagoides pteronyssinus*. Other main sources of inhaled indoor allergen are cat and dog fur and cockroaches (Table 45-1). Although asthmatic symptoms often improve when the allergen is removed, rigorous allergen avoidance has not shown any evidence for a reduced risk of developing asthma.

Although allergens are often triggers of acute exacerbations of asthma, allergens themselves may induce subclinical airway inflammation that may lead to enhanced airway responsiveness

TABLE 45-1 Risk Factors and Triggers Involved in Asthma

Endogenous Factors	Environmental Factors	Triggers
Atopy	Allergens—indoor	Allergens (especially house dust mite, animal dander, cockroach, indoor fungi, perennial allergens, and seasonal pollens)
Airway hyperresponsiveness	Allergens—outdoor (fungi, pollens)	Changes in the weather (cold air, thunderstorms)
Ethnicity	Obesity	Drugs (angiotensin-converting enzyme inhibitors, aspirin, β-blockers, NSAIDs)
Gender	Occupational sensitizers	Exercise and hyperventilation
Genetic predisposition	Parasitic infections	Extreme emotional expression (laughing, stress)
	Respiratory infections (early childhood, viral)	Irritants (household sprays, paint fumes)
	Socioeconomic status	Respiratory infections
	Tobacco smoking (active and passive)	Sulfur dioxide and pollutant gases
		Tobacco smoking

and greater susceptibility to the provocative effects of other triggers such as respiratory viral infections and exercise. In this regard, it is important to understand the distinction between triggers and etiologic risk factors. A trigger is any agent capable of inducing or exacerbating asthma, and whereas triggers may lead to symptoms, they do so only in susceptible persons who already possess the underlying asthmatic diathesis.

Viral Infections

Acute upper respiratory tract viral infections are the commonest triggers of exacerbations of asthma and most are due to rhinovirus infections. Viral infections not only give symptoms of the common cold and cause acute inflammatory rhinitis, but may also play a role in asthma development and, potentially, airway remodeling through increasing inflammation in the lower airways.[9] Asthma is recognized to be more common in children who have had croup or lower respiratory tract infections in early life, although viral infections in the absence of atopy do not appear to be risk factors for the development of asthma.[10] Other viruses commonly implicated in acute exacerbations of asthma are respiratory syncytial virus, influenza virus, and parainfluenza virus. Bacterial infection with species of *Mycoplasma* and *Chlamydia* are also associated with exacerbations of asthma, whereas other bacterial infections are not.

Occupational Exposure

Occupational asthma accounts for approximately 5% of all adult cases of asthma, and the disease can often be classified according to its etiology. In these circumstances, not only is the specific agent that triggers the symptoms known, but the same agent is usually the underlying cause of asthma.

Exercise-Induced Asthma

Many asthma patients have worsening of symptoms on or after physical exercise; another category of asthma is exercise-induced, where exercise per se is not the cause of asthma but rather one of many nonimmunologic triggers that produce symptoms in patients who already have the disease. In this condition, the trigger is thought to be the drying of the airway mucosa as a result of hyperventilation that leads to osmotically induced mast cell mediator release and bronchospasm.[11]

Obesity

Obesity is a major risk factor for asthma where abdominal obesity (waist circumference) and general obesity (BMI) both show a strong correlation with the risk of new-onset asthma.[12] Obese asthmatics often have excessive symptoms and are less responsive to corticosteroid therapy.[13]

Drugs

Drugs that may worsen asthma control include β-blockers, occasionally angiotensin-converting enzyme (ACE) inhibitors, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Small Airways Disease

Although not a risk factor in the true sense, it is increasingly being recognized that untreated small airways inflammation disease may predispose patients to worsening asthma, and studies show that the prevalence of small airways disease is approximately 50% in the asthmatic population.[14,15]

CLINICAL PRESENTATION AND DIAGNOSIS

Asthma is a clinical diagnosis made on the basis of a medical history of typical symptoms, with consideration to provocative factors, and supported with objective confirmation of variable airflow obstruction. As the disease is heterogeneous in its presentation and severity, the clinical features of asthma show great variability both between individual asthmatics, and also within the same patient over time. It is also important to recognize that asthma is often associated with different comorbidities, including allergic rhinitis, atopic dermatitis, rhinosinusitis, gastroesophageal reflux disease, diabetes, depression, and obesity, all of which may affect the clinical expression and severity of the disease.[16] The following clinical features and laboratory assessments are important in the consideration of the diagnosis of asthma.

Medical History

The typical symptoms of asthma are paroxysmal wheezing, cough, breathlessness, and chest tightness, which may temporally be related to exposure to triggers or exercise. Cough may be productive of clear or yellow/green discolored sputum, where the latter may be tenacious and difficult to expectorate and reflect the underlying airway inflammation rather than a respiratory infection. Indeed, cough may be present in isolation to other symptoms and as the sole manifestation of an episode of asthma.[17] Breathlessness may occur as a result of the dynamic lung hyperinflation that accompanies acute asthma episodes, and patients may report the sensation of difficulty in "getting air in" their lungs. Exertional symptoms may not be apparent if the patient's ability to exert themselves is limited by other health conditions such as rheumatologic or cardiac disease, and therefore asthma may be underdiagnosed in the elderly. No single symptom is specific or more significant for asthma, although wheezing is a useful sign, as nonasthmatics rarely report frequent wheezing. In younger patients, the symptom of chest tightness is helpful, since it occurs more often in association with asthma than with other pulmonary or cardiac disorders. The pattern of symptom occurrence, the precipitating or aggravating factors, and the profile of a typical exacerbation are important elements in the clinical evaluation.

In patients with poorly controlled asthma, symptoms may temporally evolve slowly over days or weeks, or present abruptly. The severity and frequency with which symptoms occur vary greatly within the asthmatic population. The recurrent paroxysmal nature of symptom presentation is characteristic of asthma, and symptoms improve, sometimes rather spontaneously, although usually with treatment. Nocturnal episodes are common in adult asthmatics, and typically patients awake in the early hours of the morning with symptoms. Distinguishing whether nocturnal symptoms are due to asthma, angina, or gastroesophageal reflux may be difficult, but early-morning asthma symptoms are usually relieved with administration of inhaled bronchodilators, in contrast to cardiovascular symptoms which occur at any time during the night, and gastroesophageal reflux which tends to cause symptoms soon after the patient reclines at night.

Chest symptoms that vary by season and are accompanied by symptoms of irritation of other mucus membranes, such as conjunctivitis and rhinitis, are typical of allergic asthma. Triggers such as indoor allergens (e.g., house dust mite, cockroach, animal dander proteins) are more likely to result in perennial symptoms, whereas pollens and some mold spores are likely to provoke seasonal symptoms. The presence of rhinosinusitis, nasal polyps, conjunctivitis, or eczema, coupled with a family history of asthma or atopy, may further support the diagnosis of asthma. Symptoms after heavy exertion, especially in the cold air, are highly suggestive of exercise-induced asthma, and patients typically experience symptoms at the end of exercise, rather than during its performance. Excessive coughing after exercise in the absence of wheeze may also be a sign of asthma. Premenopausal women with asthma may experience a deterioration of asthma control perimenstrually.[18] Indeed,

compared to men, women have a higher incidence of asthma and experience more symptoms with more recourse to rescue medication.[19] The medical history should elicit risk factors for asthma (Table 45-1), and special consideration should address symptoms induced by aspirin or those associated with the patient's occupation.

Asthma and Aspirin Sensitivity

The association of asthma and sensitivity to aspirin or other NSAIDs is well established.[20] Aspirin-sensitive asthma affects approximately 1% to 5% of all asthmatics, although it is more common in patients with severe asthma (~20%), in some ethnic groups (such as Eastern Europeans and Japanese), and in those frequently hospitalized for their asthma. This subtype of asthma is usually characterized by a tetrad of asthma, nasal polyps, chronic hypertrophic eosinophilic sinusitis, and aspirin intolerance.

Classically, perennial rhinitis is the first symptom in this syndrome, preceding the development of aspirin sensitivity, and then followed much later by nasal polyps that are usually bilateral and originate from the turbinates and the paranasal sinuses. Even in small doses, aspirin typically causes wheezing, facial flushing, rhinorrhea, and conjunctival irritation. Although aspirin-induced asthmatic episodes often resemble allergic reactions, there is no evidence that immunoglobulin (Ig)-E–related mechanisms are at work. Aspirin-induced asthma is due to blockade of cyclooxygenase 1 by nonsteroidal anti-inflammatory drugs and has been associated with enhanced leukotriene production and mast cell activation, but the cellular pathways responsible for these events remain unclear. The diagnosis of aspirin sensitivity is made on the basis of the clinical history and can be confirmed by a provocative aspirin challenge, although this test carries a potential health risk of anaphylaxis for the patient. Individuals with asthma, nasal inflammation, and recurring nasal polyps with sensitivity to aspirin have the condition known as "Samter's triad," characterized by dramatic worsening of respiratory symptoms as a reaction to taking aspirin or similar nonsteroidal anti-inflammatories.

Aspirin-sensitive asthma usually responds to standard therapy with inhaled corticosteroids (ICS), although the condition is associated with severe asthma, a condition comprising a group of patients often refractory to treatment with inhaled and oral CS. Hypothetically, antileukotriene therapy should be efficacious in these patients, but it has been found to be no more effective compared to their use in patients with allergic asthma. Aspirin desensitization may sometimes be needed and should only be performed in specialized centers. In all asthmatic patients with aspirin sensitivity, the nonselective cyclooxygenase (COX) inhibitors should be avoided, but when an anti-inflammatory analgesic is needed, the selective COX-2 inhibitors are usually safe to use.

Occupational Asthma

Occupational asthma is asthma arising de novo that is initiated as a consequence of exposure to a specific etiologic agent in patients without prior asthma. In contrast, work-exacerbated asthma is defined as the worsening of asthma, that is already pre-existing or concurrent, triggered by nonspecific irritants in the workplace.[21] Occupational asthma may be classified into: (1) that caused by a sensitizing agent in the workplace (sensitizer-induced asthma) where the specific sensitizing agent causes asthma through an identified underlying immunologic mechanism, and (2) asthma caused by exposure to irritant compounds (irritant-induced asthma) where the exposure agent is not considered to be sensitizing.[22] Table 45-2 highlights the causes of both sensitizer-induced occupational asthma and the common agents responsible for irritant-induced occupational asthma. The diagnosis of occupational asthma is based on a demonstrable link between asthma symptoms and workplace exposure, showing work-related variability in measurements of lung function made serially.[23] Classically, a typical history of asthma-like symptoms during the working week and improvement over the weekend or on vacation are elicited; symptoms may occur during exposure to the etiologic substance, or they may be delayed until the evening or night after the workday. Early detection and avoidance of occupational asthma is important because, if the patient is removed from exposure within the first 6 months of symptoms, there is usually complete recovery.

TABLE 45-2 Causes of Occupational Asthma

Sensitizing Agent-Induced Asthma	
Agent	**Workers at Risk**
Acrylate	Dental workers; adhesive handlers
Anhydrides	Workers using epoxy resin for plastics
Animal protein allergens	Veterinary workers; animal handlers
Cereals (grains)	Bakery workers; grain workers; farmers
Dyes	Textile workers
Enzymes	Pharmaceutical workers; bakery workers; laboratory workers
Formaldehyde, glutaraldehyde	Hospital and healthcare workers
Gums	Carpet makers
Isocyanates	Installers of insulation; manufacturers of plastics; rubbers and foam; spray painters
Latex	Healthcare workers; rubber workers
Persulfate	Hairdressers
Seafoods	Seafood handlers and processors
Wood dusts	Forestry workers; sawmill workers; carpenters

Common Agents Responsible for Irritant-Induced Asthma
Acids (acetic, hydrochloric, sulfuric)
Alkaline dust
Ammonia
Bleach
Chlorine
Cleaning agents
Diesel exhaust
Endotoxins
Formalin
Mustard
Oxide (calcium)
Paints (heated)

■ Physical Examination

The most typical physical finding in asthma is wheezing on auscultation, which is usually caused by turbulent airflow through narrowed airways. Wheezing may be heard throughout the chest and is classically polyphonic, and present to a greater extent during expiration, although it may also be heard during inspiration. The quality and character of wheezing is not specific to asthma or to the severity of the underlying disease. There may be no abnormal physical findings when asthma is under control—yet conversely, in cases of very severe airway obstruction, breath sounds and wheezing may be absent. Examination of the upper respiratory tract may reveal clinical signs of rhinitis, sinusitis, or nasal polyps.

During an acute exacerbation of disease, physical signs of increased ventilation may be observed with the use of accessory

muscles of respiration and chest signs of hyperinflation. A sign of severe airway obstruction is pulsus paradoxus, which is the exaggerated decrease in systolic blood pressure during inspiration by >10 mm Hg. As ventilatory effort can be diminished with respiratory muscle fatigue, pulsus paradoxus may be absent, but its absence does not preclude severe airway obstruction. Stridor is a high-pitched inspiratory sound and indicates airflow turbulence in the upper airways. In the acute setting, stridor should prompt a review of causes such as epiglottitis or foreign body. In chronic presentation, conditions such as upper airway tumors, tracheal–bronchial stenosis, vocal cord dysfunction/paralysis, and airway narrowing due to thyroid enlargement should be excluded.

Laboratory Investigation

The diagnosis of asthma is usually apparent from the medical history with symptoms of variable and intermittent airway obstruction, and objective measurements of lung function and spirometry support the diagnostic process. Similarly, the clinical history provides relevant information regarding the relationship between symptoms and allergen exposure, but skin prick testing and serology may be useful in identifying specific allergic triggers of asthma. Radiologic examination of the thorax, blood tests, and body plethysmography are not routinely indicated, unless there is some uncertainty in the diagnosis, where these tests may be used to exclude other conditions that may mimic asthma or complicate its clinical presentation.

Lung Function Tests

Peak flow meters are portable devices, readily available for patient use, that measure the peak expiratory flow (PEF). Serial readings of PEF that vary by more than 20% either spontaneously or in response to treatment are supportive of a diagnosis of asthma. Twice-daily PEF measurements, morning and evening, may also demonstrate diurnal variation, which is a typical feature of asthmatic patients.

Spirometry measures the expiratory volume and flow of air using forced maneuvers from full lung inflation, as a function of time. Simple spirometry is important for objectively demonstrating airflow obstruction, confirming the diagnosis of asthma, establishing the severity of the disease, and monitoring the response to therapy. Patients with asthma typically show a reduced forced expiratory flow in 1 second (FEV_1), reduced PEF, preserved forced vital capacity (FVC), and an FEV_1/FVC ratio of <0.7.[23] Home PEF monitoring may be of diagnostic use, confirming the diurnal variations in airflow obstruction, especially in patients who demonstrate normal spirometry during clinic visits. Spirometry also allows the assessment of the flow–volume loop, which shows a reduced maximum expiratory flow.

Bronchodilator reversibility is a measure of the magnitude of airway smooth muscle relaxation. A postbronchodilator increase in FEV_1 of >12% and 200 mL is often considered evidence of reversible airway obstruction, where measures are taken 15 min after an inhaled short-acting β_2-agonist (SABA). However, this level of increase is arbitrary and lacks sensitivity or specificity for detecting asthma. In addition, bronchodilator reversibility is diminished in well-controlled asthmatic patients, so it is not a good measure of asthma severity or response to therapy.

In some patients, bronchodilator reversibility may be demonstrated by a 2- to 4-week trial of oral corticosteroids (prednisone or prednisolone 30–40 mg daily). Bronchodilator reversibility may also occur in patients with chronic obstructive pulmonary disease (COPD).[24] Asthma and COPD are distinct diseases. Although an overlap "syndrome" of the two has been described, this term may be misleading due to the diversity of phenotypes arising from the variety of molecular, physiologic, and clinical features. Hence, the entity is better referred to as "asthma-COPD overlap" (ACO).[25–27] Asthmatic patients with features of COPD include smokers, patients with severe neutrophilic asthma, and chronic asthma with irreversible airway obstruction.

Body Plethysmography

Whole-body plethysmography is rarely required to establish a diagnosis of asthma in family practice, but it may help in patients where there is diagnostic uncertainty. In stable asthma, measurement of the lung volumes may reveal an increase in residual volume, which reflects airway closure at a lung volume that is higher than normal. Air trapping is typically seen in patients with severe asthma. Airway resistance is characteristically increased, and during acute episodes of disease exacerbation, functional residual capacity and total lung capacity also may be observed to be increased. Measurement of the diffusing capacity of the lung (D_{LCO}) may also differentiate patients with COPD from those with asthma. In stable asthma, D_{LCO} is usually normal, but there may be a small increase in some patients. In contrast, patients with COPD typically have a reduced D_{LCO}, which reflects alveolar septal destruction and loss of pulmonary capillary volume—characteristic features of emphysematous patients.

Bronchial Challenge Testing

Assessing bronchial hyperresponsiveness (BHR) is a sensitive tool that, although not routinely undertaken in clinical practice, may be helpful in diagnosing asthma, particularly when there is diagnostic uncertainty in the context of normal pulmonary function tests and unexplained chest symptoms (see Chapter 31).[28] Bronchial challenge tests assess the abnormally increased airway hyperresponsiveness observed in patients with asthma, by detecting the exaggerated response to inhaled bronchoprovocative agents. The provocation agents can be classified into two categories: direct and indirect. Direct stimuli such as histamine and methacholine, which are normally used in the clinic, act on airway smooth muscle receptors, whereas indirect stimuli act through intermediate pathways that include the release of mast cell mediators, and/or through local and central neurologic reflexes. Indirect stimuli include adenosine monophosphate (AMP), mannitol, exercise, hypertonic saline, and isocapnic hyperventilation.

Increased BHR is typically defined as the inhaled concentration of the bronchoprovocative agent that reduces FEV_1 by 20% (PC_{20}). This criterion for the test has maximal sensitivity but not maximal specificity and thus, when a diagnostic PC_{20} threshold of ≤8 mg/mL is used, pharmacologic challenges are sensitive tests with a high negative predictive value, that is, a PC_{20} >8 mg/mL excludes a diagnosis of asthma with a high degree of accuracy. Similarly, a positive result, although consistent with asthma, is not diagnostic. False-negative results can be obtained in patients who experience only intermittent symptoms and are tested when they are asymptomatic. The prevalence of abnormal responsiveness in nonatopic, nonasthmatic subjects who have no history of prior respiratory problems ranges between 5% and 10%. Knowledge of family history, personal atopy, and comorbidities clearly improves the prediction that abnormal airway responsiveness predisposes to the subsequent development of asthma.[29]

Technical factors related to the test procedure must be strictly controlled and follow standard operating procedures that include the aerosol generation, the method of inhalation (intermittent versus continuous), and the measurement and calculation of the response. Medications such as β_2-agonists, theophylline, long-acting muscarinic antagonists, and corticosteroids (CS) may influence the test and decrease airway responsiveness. Measuring BHR may have additional utility in the management of asthma. Patients whose disease is considered to be clinically controlled may still have BHR

and underlying airway inflammation. Studies have shown that using BHR to guide treatment with inhaled corticosteroids (ICS) leads to additional improvement in symptoms, lung function, and airway biopsy findings compared with conventional assessment.[30]

Exercise testing of patients using cycle, treadmill, or free running challenges is occasionally undertaken to show post-exercise bronchoconstriction if there is a suggestive history of exercise-induced asthma.[31] In professional athletes, asthma may be both under- or overdiagnosed, and objective confirmation by appropriate lung function testing with bronchodilator or exercise challenge is often needed.[32] Allergen challenge is rarely utilized in the routine management of patients with asthma and should only be undertaken by a specialized center if a specific causative or occupational agent is to be identified, such as aspirin.

Blood Tests

Blood tests are usually not helpful in establishing the diagnosis of asthma. The eosinophil count in the peripheral blood may be raised in atopic conditions, and eosinophilia may support a diagnosis of asthma; however, a normal level does not rule out atopy or exclude asthma. In patients receiving CS, eosinophilic counts may be normal or low. Because of their poor sensitivity and specificity, blood eosinophil counts are not recommended in the routine monitoring of asthma severity or as a barometer of airway inflammation. Markedly high levels may be present in disorders such as tropical parasitic eosinophilia, allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), and Loeffler's syndrome, as discussed elsewhere in this volume. In these hypereosinophilic conditions, clinical suspicion may warrant additional blood tests directed at ruling out vasculitis or ABPA, which are uncommon causes of asthma symptoms. Recently, blood eosinophil counts have been found to be useful in predicting which patients with severe asthma respond best to anti–IL-5 therapy.[33]

Total serum immunoglobulin E (IgE) may be measured in patients. Epidemiologic studies demonstrate an association between asthma and total serum IgE levels, standardized for sex and age. There is also a relationship between total serum IgE and asthma in patients with negative skin tests. Importantly, total IgE levels are used to calculate the dose of anti-IgE antibody therapy using anti-IgE monoclonal antibodies (e.g., omalizumab) in asthma treatment, as discussed below. Blood tests of specific IgE to inhaled allergens, radioallergosorbent testing (RAST), and ImmunoCAP may help identify or confirm allergy to specific allergens, such as house dust mite, cockroach, *Aspergillus* species, pollens, or animal dander.

In acute exacerbations of disease, arterial blood gases may reveal hypoxemia and the arterial Pa_{CO_2} may be reduced due to hyperventilation. With a severe exacerbation, the arterial Pa_{CO_2} may rise due to respiratory muscle fatigue and an inability to maintain the required alveolar ventilation.

Skin Tests

If the clinical history suggests specific aeroallergens are important triggers or when asthma symptoms in a patient are accompanied by other symptoms typical of allergic disease, such as conjunctivitis or rhinitis, skin prick tests may be helpful to determine whether the patient is allergic, and to investigate the role of specific allergens as a cause of asthma. Sensitivity to a particular allergen such as house dust mite, cockroach, *Aspergillus* species, or animal dander can be verified by skin tests or in vitro serum antibody studies (see above). Antihistamines and antidepressants should be avoided when undertaking testing, as these drugs can interfere with the response. Positive responses on skin prick testing may help encourage patients to undertake allergen avoidance measures or, in selected cases, may help develop immunotherapy regimens.

Chest Imaging

Chest radiography is usually unremarkable and normal in patients with mild to moderate asthma; however, in more severe disease, nonspecific findings such as hyperinflation, prominent hilar vessels, and bronchial wall thickening may be seen. In patients with an exacerbation of their symptoms, chest radiography may be useful to exclude a pneumothorax. Consolidation shadowing in the lung usually indicates pneumonia or eosinophilic infiltrates in patients with ABPA. High-resolution computed tomography (HRCT) of the chest may identify atelectasis, bronchial wall thickening, or areas of bronchiectasis in patients with severe asthma, but these changes are not diagnostic of asthma. Emphysema is absent. Multidetector computed tomography (MDCT) undertaken in inspiration and expiration provides additional information concerning the tracheobronchial tree during the entire respiratory cycle.

Exhaled Nitric Oxide

The measurement of fractional nitric oxide gas in the exhaled breath (FeNO) of patients is being utilized as a noninvasive test to assess intrapulmonary type 2 (T2) airway inflammation.[34] Portable, compact, handheld devices allow FeNO measurements to be undertaken at the bedside and in family practice.

Typically, asthmatic patients have elevated FeNO levels compared with healthy subjects; levels correlate with the number of eosinophils in sputum. ICS and oral leukotriene receptor antagonists have been shown to decrease FeNO levels. These observations suggest a possible role for FeNO as an index of asthma disease severity, as a test of treatment efficacy, and in the assessment of patient adherence with asthma therapy.

Measurements of FeNO have also been used successfully to titrate inhaled steroids without any loss of asthma control; thus, FeNO may be used as a tool in conjunction with other clinical measures to optimize asthma management as recommended by guidelines, that is, achieving disease control using the lowest doses of medications possible. Indeed, the combination of FeNO and blood eosinophil counts correlates with severe asthma exacerbations.[35]

In the research environment, FeNO can be partitioned into that arising from the central bronchial/conducting airways and that generated in peripheral alveolar regions, allowing an assessment of the site of intrapulmonary inflammation.[36,37] Patients with severe refractory asthma have shown greater alveolar NO concentrations compared to those with mild asthma. Increased FeNO may be a good predictor of which patients respond best to anti–IL-4/13 therapy, since IL-4Rα activation causes the release of NO from airway epithelial cells.[38]

Sputum Examination

The sputum differential count may be helpful. Induced sputum eosinophil counts have been used as an endpoint in clinical trials of therapeutic agents targeted at patients with eosinophilic lung diseases like asthma.[39] Research studies have shown that sputum eosinophilia predicts clinical outcomes, particularly asthma exacerbations, when CS are withdrawn. Induced sputum eosinophil counts have also been shown to guide anti-inflammatory treatment in patients with asthma in a management strategy that minimizes eosinophilic inflammation.[30] However, induced sputum remains a research tool, as it is a rather unpleasant procedure for the patient. Further studies are needed before measurement of sputum eosinophils can be widely used as a biomarker to monitor patients in clinical practice.

DIFFERENTIAL DIAGNOSIS

There are a number of conditions to consider in the differential diagnosis of asthma (Table 45-3). Usually, it is not difficult to

TABLE 45-3 Differential Diagnosis of Asthma

Upper Airway	Pulmonary	Cardiac	Other
Foreign body	Allergic bronchopulmonary aspergillosis (ABPA)	Angina	Anemia
Postnasal drip	Bronchiectasis	Left ventricular failure	Carcinoid
Upper airway obstruction	Eosinophilic granulomatosis with polyangiitis (EGPA)	Mitral valve disease	Functional
Vocal cord dysfunction	COPD		Gastroesophageal reflux
Tracheobronchomalacia	Cystic fibrosis Interstitial lung disease Lung cancer Pneumonia Pneumothorax Sarcoidosis		Hyperventilation Mastocytosis Obesity

differentiate asthma from other conditions causing wheeze and dyspnea. The degree of diagnostic accuracy is probably dependent on the age of the patient, where the diagnosis in young adults is usually not difficult since there are few other conditions that mimic asthma or confound its clinical presentation. With increasing age, cardiovascular disease and other forms of chronic lung disease are more common, and the differential diagnosis of episodic chest symptoms is broader.

Patients with upper airway obstruction can mimic severe asthma, and typically these patients present with localized wheeze and stridor of the large airways. Assessing the flow–volume loop in such patients will reveal a reduction in inspiratory flow as well as expiratory flow, and bronchoscopy can demonstrate the site of narrowing in the upper airways. Vocal cord dysfunction can be assessed using nasoendoscopy, which allows the observation of abnormalities in the movement of the vocal cords and is most helpful when adduction of the cords is detected in the presence of the patient's symptoms.[40] Persistent wheezing auscultated in a localized area of the chest wall may indicate endobronchial obstruction due to lung cancer or a foreign body. Eosinophilic pneumonias and systemic vasculitis, including EGPA and polyarteritis nodosa, may be associated with wheezing, and their systemic clinical manifestations may help in their identification.

COPD is usually easy to differentiate from asthma. The symptoms in patients with COPD are more persistent, show less variability, are progressive, and usually exhibit minimal reversibility to bronchodilator agents. As previously mentioned, the literature highlights an "overlap" in which patients with COPD have features of asthma with increased sputum eosinophils and a response to oral corticosteroids; these patients probably have both diseases concomitantly.[26] Important cardiologic causes to consider include left ventricular failure, where usually bibasilar lung crackles are present in contrast to the scattered polyphonic wheeze in asthma. Anemia should always be thought of as a cause of dyspnea, especially in elderly patients. The symptoms of gastroesophageal reflux disease (GERD) may be mistaken for those of asthma; however, it is important to recognize that GERD is common in patients with asthma and has been identified as a potential trigger for asthma symptoms.[41]

TABLE 45-4 Aims of Asthma Therapy

Control symptoms
Prevent (or minimize risk of) exacerbations
Eliminate emergency visits
Maintain lung function as close to as normal levels as possible
Decrease diurnal variation, especially nocturnal
Maintain normal levels of daily activities, including exercise
Eliminate or minimize adverse effects from medicine

TREATMENT OF ASTHMA

Treating asthmatic patients is generally straightforward; with effective and safe drugs, most asthmatics are now managed by family and primary care doctors. The successful management of asthma requires an appreciation of the heterogeneity of the disease with respect to etiology, clinical presentation, severity, natural history, and response to therapy. It is unlikely that a single management approach will work for all patients; hence, treatment should be tailored to the individual patient. It will also be recognized that symptom severity in patients varies over time with periods of remission that are interspersed with acute exacerbations; thus, the patient should be monitored regularly and treatment should be modified on an ongoing basis to meet the patient's current needs. There are several aims in the management of patients with asthma (Table 45-4), and although prominence has been placed on drug therapy, there are important patient-oriented approaches that focus on correct inhaler usage, emphasize self-management action plans, and address environmental control.

Inhaler Devices

Drug delivery to the lungs via the inhaled route remains the cornerstone of therapy for patients with asthma. Inhaled therapy targets drug directly to the lungs and allows a distinct therapeutic advantage over systemic therapy with the use of smaller drug doses, a more rapid onset of therapeutic action, and decreased adverse effects.[42]

There are several types of inhaler device and drug delivery systems used in clinical practice for the management of asthma; these include the pressurized metered-dose inhaler (pMDI), spacers, dry powder inhalers (DPIs), and nebulizers.[43] There are potentially more than 250 device drug combinations available, leading to confusion in prescribing among healthcare practitioners. Indeed, studies have shown that not just patients, but healthcare workers as well, are uncertain about the correct use of inhaler devices. Physicians' knowledge, in particular, remains poor and may be related to a lack of education and instruction about inhaler usage during their training.[44] It is confusing in the literature as there are 299 definitions of inhaler errors, but clearly it is recognized that a lack of knowledge and recognition with respect to the proper use and working of an inhaler might lead to worsening health outcomes for the patient.[45] It has been shown that training and counselling patients in their inhalation technique can increase their adherence to device usage, and patients may be assessed with respect to their suitability for a particular inhaler device by using portable handheld meters that assess inhalation flows.[46] Evidence-based guidelines from the American College of Chest Physicians[47] recommend the following points for consideration by healthcare practitioners when choosing an inhaler for their patient: (1) the clinical condition and disease severity; (2) availability of the inhaler device for the drug prescription; (3) the patient's ability to use the selected device correctly; (4) use of the same device type for all drugs; (5) the setting and convenience of outpatient and inpatient use; (6) the time required for drug

TABLE 45-5 Advantages and Disadvantages of Inhalation Devices

	Advantages	Disadvantages
Pressurized metered-dose inhaler (pMDI)	Compact and portable	High oropharyngeal deposition
	Multidose	Difficulty in hand–mouth coordination
	Quick treatment time	Propellants may cause "cold Freon" effect and affect climate change
	Drug in sealed canister	Difficult to assess empty canister
	Inexpensive	
Dry powder inhaler (DPI)	Compact and portable	Need adequate inhalation flow to disperse drug
	Quick treatment time	High oropharyngeal deposition
	Breath-actuated function removes need for coordination	Humidity can cause drug degradation
		Patients may be intolerant to additives, e.g., lactose
Nebulizers	Large doses of drug can be given	Bulky, cumbersome, and expensive
	Can be used with relaxed tidal breathing	Wasted drug in nebulizer reservoir
	Suitable for young, old, and acutely ill patients	Variation in aerosol output performance between models
	Many drug solutions can be aerosolized	Time consuming
		Need for power source
		Regular cleaning and maintenance

administration; (7) cost and reimbursement; and (8) the inhaler preference of the patient as well as the prescriber. The advantages and disadvantages of the common inhaler device types are shown in Table 45-5.

Pressurized Metered-Dose Inhalers

The pMDIs contain the drug as a liquid suspension or solution with propellant in a sealed canister, and other formulation ingredients may be present such as ethanol, chemical preservatives, flavoring agents, and surfactant. Most inhaler therapies are now free of chlorofluorocarbon (CFC) propellants, which have been replaced by non–ozone-depleting propellants such as hydrofluorocarbons (HFCs). Upon actuation of the pMDI canister, there is quick vaporization of the propellant that provides the force to aerosolize and propel the liquid drug out of the canister at high velocity. Vaporization of the propellant also causes cooling of the drug aerosol, which can sometimes give rise to the "cold Freon effect"—a sensation experienced by some patients of cold aerosol hitting the back of their oropharynx, which can stop them from inhaling the drug and sometimes causes paradoxical bronchospasm. Some of the formulation ingredients added to pMDIs described above have been shown to cause bronchospasm, wheezing, and cough in asthmatic patients. pMDIs are compact, portable, and inexpensive devices. Recent advances in the technologic design of pMDIs include the addition of a dose counter.

Optimal clinical efficacy with a pMDI is obtained when the device is actuated at the start of a deep, slow inhalation lasting for 5 s, followed at the end of inspiration by a breath-hold pause of at least 5 s. Patients should be instructed to inhale "slowly, gently, naturally, deeply, and comfortably" and actuate the device in the first second following inhalation. Failure to inhale slowly and deeply with pMDIs is a more common mistake than the actual patient discoordination between inhalation and actuation.[48] However, the latter problem is more pertinent in elderly patients, and add-on spacer attachments, device-holding adaptors, and breath-actuated pMDIs have been developed to overcome the problem. Breath-actuated metered-dose inhalers utilize the patient's inspiratory force to trigger and activate the inhaler device, although it has been shown breath-actuated pMDIs offer no advantage over good conventional pMDI inhaler technique.[49] In contrast, "breath-coordinated" devices are different from "breath-actuated" metered-dose inhalers in that they do not depend upon the patient's inspiratory flow for actuation and help patients achieve coordination with aerosol inhalation. Although the current HFA propellants in pMDIs have the potential to impact climate change, the advent of new inhaler propellants will allow the complete life-cycle carbon footprint impact of pMDIs to be equivalent to other inhaler devices used in clinical practice.[50]

Spacers

Spacer devices are used with pMDIs and are designed to assist in the delivery of inhaled drug to the lungs by promoting ease of pMDI use, and reduce oropharyngeal deposition by slowing the high velocity of the emitted aerosol cloud.[51] The plastic walls of the spacer trap the large drug particles and this decreases oropharyngeal impaction, which may lead to a decrease in local unwanted side effects, particularly with CS, and also a reduction in systemic adverse effects by minimizing the amount of drug absorbed via the gastrointestinal tract. In addition, increasing the distance the aerosolized drug travels (by using the spacer as an extension attachment to the pMDI device) slows the emitted aerosol cloud and allows more evaporation of the propellant, leading to relatively smaller drug particles that have a greater potential to deposit within the lungs. Spacers include valve-holding reservoir chambers with a one-way inhalation valve in the mouthpiece only allowing airflow through the chamber when the patient inhales; simple extension devices that are non-valved add-on products that require a reasonably good amount of coordination; and reverse-flow devices with which the aerosol spray is actuated away from the patient into a collapsible reservoir chamber or bag through which outside air is entrained to provide the airflow stream for inhalation.

Spacer devices each differ in their design characteristics and should be prescribed only with the pMDI they are compatible with, as each spacer–inhaler combination has distinct aerosol output characteristics.[52] To reduce the electrostatic charge in spacers, which can significantly contribute to decreased drug available to be delivered to the lungs, spacers should be primed with the pMDI prior to use, and one-dose actuation at a time from a pMDI into the spacer device should be employed, as opposed to simultaneous multiple-dose administrations. Spacers should be washed with ionic detergent and air dried. Antistatic spacer devices are available.

Dry Powder Inhalers

DPIs are propellant-free devices that contain finely milled, powdered drug particles bound into loose aggregates, or drug particles associated with larger carrier molecules, such as lactose. DPI devices are breath-actuated and critically rely on the patient's inspiratory effort to de-aggregate the drug from its carrier particle to achieve optimal delivery and deposition within the lungs. Studies have shown that DPIs are highly dependent on the patient's inspiratory flow for therapeutic success. In addition, reported observations are that patients with asthma and those with COPD use suboptimal inspiratory flows from DPIs, leading to low pulmonary deposition.[53] In a large database study, insufficient inspiratory effort from DPIs was the most common inhaler error in this device class and was associated with significant worsening of asthma and increased frequency of disease exacerbations.[54]

DPIs can be classified into single-dose and multiple-dosing delivery systems. Single-dose systems may require drug to be individually loaded into the inhaler prior to use, or may be devices from which individual doses are dispensed from punctured gelatin capsules. In contrast, multiple-dosing delivery DPIs avoid the inconvenience associated with repeated drug loading and can be divided into "multi-dose" or "multi–unit-dose" systems. Multi-dose systems deliver drug that is metered from a powder reservoir, whereas multiple–unit-dose devices contain either drug sealed in individual foil blisters or drug sealed in pockets on a moving strip. Deterioration of the drug may occur in damp and humid conditions; hence, all these devices should be stored in a dry environment. A newer generation of DPIs rely less on the patient's inspiratory effort, requiring either lower inhalation flows to aerosolize the drug or, in some circumstances, deliver the drug wholly independent of the patient's breathing maneuver.

Nebulizers

The main types of nebulizer commonly used in clinical practice can be divided into two categories: ultrasonic and jet nebulizers.[55] Ultrasonic nebulizers utilize the vibration from a piezoelectric crystal at a high frequency to produce aerosol clouds for inhalation from the liquid drug. Ultrasonic nebulizers are smaller and less noisy compared to jet nebulizers, but are usually less robust, more expensive, and not as effective in nebulizing liquid suspensions of drug. Jet nebulizers use either compressed gas or an electrical compressor to generate aerosolized particles. High-velocity air streams are generated and directed through a narrow Venturi opening, across the liquid drug solution/suspension, to produce aerosolized droplets within the nebulizing chamber.

Nebulizers require tidal breathing at rest for effective use and do not require much patient coordination. However, there is great variation in the aerosol output generated from each of the different nebulizer devices, and the inhalation maneuver will affect drug delivery to the lungs that can be greatly reduced with crying, as may occur with children, or when there are shallow and rapid inhalations.[56] Consideration should be given to the nebulizer–facemask combination, as incorrect mask insertion into the nebulizer may give rise to unwanted deposition of drug onto the face and eyes, particularly in children. Generally, nebulizer devices are large, lack portability, and have a longer treatment time than conventional inhalers.

There is now a newer generation of nebulizer devices that offer a marked improvement in the efficiency and precision of pulmonary drug delivery.[57] These devices are more costly than conventional nebulizers, but they may be cost-effective by decreasing drug loss from the nebulizer chamber, particularly during exhalation, and by delivering a reduced drug dose more effectively. Nebulizer systems have also been developed to control the patient's inhalation maneuver so as to minimize the variability in dose delivery that occurs during use. Finally, there are systems that provide feedback to the patient and allow an assessment of patient compliance.

THERAPEUTIC DRUGS

A wide variety of agents are used in the management of asthma. Additional discussion can be found in Chapter 145.

Bronchodilators

Bronchodilators reverse the bronchoconstriction of asthma, principally by acting to relax airway smooth muscle, and this results in the rapid relief of symptoms. Bronchodilators are not adequate to control asthma in patients with persistent symptoms, as they have little effect on the underlying airway inflammation. The classes of bronchodilators in current clinical use include β_2-adrenergic agonists, anticholinergics, and phosphodiesterase inhibitors, with β_2-agonists being the most efficacious.

β_2-Adrenergic Agonists

Inhaled β_2-adrenergic agonists are the drugs of choice for relief of respiratory symptoms due to acute airway obstruction.

Mode of Action β_2-Agonists activate β_2-adrenergic receptors resulting in an increase in intracellular cyclic AMP, which leads to relaxation of airway smooth muscle cells. β_2-Agonists act as functional antagonists; that is, they prevent and reverse the contraction of airway smooth muscle cells by bronchoconstrictors, and it is this action that mainly accounts for their efficacy as bronchodilators in asthma. These drugs also have nonbronchodilator effects, including the inhibition of mast cell mediator release, inhibition of sensory nerve activation, and reduction in plasma exudation—all of which may be clinically useful.[58]

Clinical Use SABAs, such as albuterol and terbutaline, have a rapid onset of action and a 3- to 6-h duration of activity. This pharmacodynamic characteristic of a rapid onset of bronchodilation allows these drugs to be used as quick-relief medications or "relievers" on an as-needed basis. As a matter of caution, increasing use of SABA indicates that asthma is not controlled and patients should be reviewed. Indeed, the overuse of SABA has been linked to high levels of mortality from asthma.[59]

At recommended doses, inhaled β-agonists have few adverse effects, although when used at higher doses by nebulizer, patients may experience short-lived side effects. Long-acting β_2-agonists (LABAs) include formoterol and salmeterol. Both drugs are given twice daily by the inhaled route and have a duration of action of more than 12 h. In particular, formoterol has an onset of action as rapid as albuterol and can be used as a "reliever" component in fixed-dose combinations of LABA with ICS medication.[60] LABAs should not be used as monotherapy for the control of asthma of any severity and should not be given in the absence of ICS therapy, as they do not control the underlying inflammation. However, fixed-dose combinations of LABAs with ICS are now increasingly used in the management of asthma and have proved to be highly effective in improving control, reducing disease exacerbations and allowing use of lower doses of ICS.[61] Studies have also shown the clinical benefits of LABA/ICS fixed combinations compared with the monocomponents administered using two separate inhalers. The combinations of formoterol and budesonide, and formoterol and beclomethasone dipropionate, have been demonstrated to be effective when used as both a controller and reliever agents (single maintenance and reliever therapy [SMART]), thus providing the advantage of a single device used for both purposes.[62] Recent approaches in the management of mild asthma suggest the use of ICS with formoterol in combination as rescue medication instead of SABA, although this is as yet unlicensed.[63,64]

Adverse Effects The most common adverse effects of β_2-agonists are palpitations and muscle tremors, which are unusual with drug administration using the inhaled route; these adverse effects are seen more commonly with high-dose nebulizer therapy and in elderly patients.

The safety of β_2-agonists has been an issue of concern. An association has been demonstrated between the amount of SABA used and asthma deaths, but thorough analyses demonstrate that the increased use of rescue SABA implies poor asthma control, which itself is a risk factor for asthma death. A slight increase in deaths from asthma has been observed with the use of LABA, but this is most likely related to the lack of use of parallel ICS, as the LABA therapy on its own fails to suppress the asthmatic airway inflammation, highlighting the need to always use ICS when LABAs are given. This can be achieved by using a combination ICS/LABA inhaler.[65] Patients should also be reminded to avoid β-adrenergic receptor–blocking drugs, including those contained in topical ophthalmic preparations, as they can precipitate severe and sometimes life-threatening asthmatic episodes. Accordingly, β-blockers are contraindicated during acute asthma exacerbations; the risk–benefit ratio should be considered before β-blockers are used in stable patients with asthma. Some patients experience deterioration in their asthma control following inhaled β-agonist treatment. Possible mechanisms and contributory factors include paradoxical bronchospasm, increased BHR, and tolerance to the drug. With prolonged exposure to a drug, downregulation of the β-receptor may occur, limiting therapeutic efficacy (i.e., tachyphylaxis). Indeed, β-receptor mutations and gene polymorphisms have been implicated in influencing the response to inhaled β-agonists.[66]

Anticholinergics

Anticholinergic agents are another class of drugs to be considered in asthma management.

Mode of Action Muscarinic receptor antagonists, such as ipratropium bromide, induce airway smooth-muscle relaxation by blocking muscarinic receptors on airway smooth muscle, inhibiting vagally mediated cholinergic tone and preventing mucus secretion.[58]

Clinical Use In general, the anticholinergic drugs are not as efficacious in the acute relief of symptoms compared to the β_2-agonists. Anticholinergics prevent the cholinergic reflex component of bronchoconstriction, whereas in contrast, β_2-agonists inhibit all bronchoconstrictor mechanisms. Hence, anticholinergics tend only to be used as add-on bronchodilator treatment in asthmatics who remain uncontrolled on other inhaled therapy. In the treatment of acute severe asthma, high doses of anticholinergic therapy may be given by nebulizer, but they should only be given following β_2-agonist treatment, as anticholinergics do not have a fast onset of bronchodilation. A combination preparation of albuterol and ipratropium bromide is available for nebulization therapy. Tiotropium is a muscarinic antagonist that has been used in the management of patients with COPD and is currently the only long-acting muscarinic antagonist monotherapy that has been licensed for use in asthmatic patients with poorly controlled asthma in steps 4–5 (see below). Tiotropium has a higher selectivity for antagonism of M_3 receptors and dissociates from receptors more slowly, collectively leading to prolonged smooth muscle relaxation and long-acting bronchodilation.[67] The combination of a LAMA with ICS and LABA in one single inhaler (fixed-dose triple inhaler) has recently been licensed for uncontrolled asthma; the LAMA in the preparation is glycopyrrolate.[68]

Adverse Effects Adverse effects are usually not a concern with anticholinergics, as there is minimal absorption into the systemic circulation. The most commonly experienced side effect is dry mouth; in elderly patients, glaucoma and urinary retention can occur.

Phosphodiesterase Inhibitors

Aminophylline and theophylline are oral phosphodiesterase (PDE) inhibitors primarily used as an adjunct bronchodilator treatment. However, due to their narrow therapeutic index and adverse effect profile, coupled with availability of safer and more effective alternatives, PDE inhibitors are now infrequently used in patients with asthma.[69]

Mode of Action Theophylline and aminophylline inhibit PDEs in airway smooth muscle cells (predominantly PDE3), which increases intracellular cyclic AMP, leading to a bronchodilator effect. However, the doses required for bronchodilator activity commonly cause adverse effects, which are mainly a consequence of direct PDE inhibition. Theophylline has been shown to exhibit anti-inflammatory effects, which are likely to arise through different molecular pathways; for example, theophylline has been shown to stimulate a key nuclear enzyme, histone deacetylase 2, which is an important intracellular mechanism for switching off inflammatory genes that have been activated.[69]

Clinical Use Theophylline is normally administered as an oral slow-release formulation, either once or twice a day, a regimen that results in more steady plasma concentrations compared with standard theophylline tablets. In severe asthmatic patients, theophylline may be used as an add-on bronchodilator treatment. Plasma concentrations of 10 to 20 mg/L are typically needed—levels usually associated with adverse effects. In contrast, the anti-inflammatory effects of theophylline seem to occur at plasma levels below the traditional therapeutic range of 10 to 20 mg/L; at low doses, the drug is better tolerated. Low-dose theophylline has additive effects to ICS and is particularly helpful in severe asthmatic patients, in whom withdrawal of theophylline may result in clear worsening of asthma control. Intravenous aminophylline is now seldom used for the treatment of asthmatic patients, and only very rarely in those with acute severe asthma exacerbations.

Adverse Effects The adverse effects of theophylline are directly related to drug levels in plasma and are infrequently observed at concentrations below 10 mg/L. Measurement of plasma theophylline may be useful in determining and guiding the correct clinical dose. Headaches, nausea, and vomiting are the most common adverse effects, which arise from the inhibition of PDE4. Palpitations and diuresis may be troublesome, and with higher plasma concentrations, epileptic seizures, cardiac arrhythmias, and death may occur due to adenosine A_1-receptor antagonism. Oral theophylline is well absorbed through the gastrointestinal route and is largely inactivated in the liver by the enzyme CYP450. Consequently, drugs that inhibit CYP450 activity, such as allopurinol and erythromycin, may increase plasma levels of theophylline causing a greater potential for adverse effects.

PDE4 inhibitors increase cyclic AMP in inflammatory cells and have anti-inflammatory effects. Although the PDE4 inhibitor roflumilast is approved as an additional therapy in severe COPD patients, there have been few studies in asthma. Its use is limited by frequent side effects (diarrhea, nausea, headaches) at therapeutic doses.

■ Corticosteroids

Corticosteroids (CS) are potent anti-inflammatory agents. When administered by the inhaled route, CS are the most effective therapy available for treating and controlling asthma and have greatly contributed to a reduction in asthma mortality in the Western world.[70]

Mode of Action

CS reduce the number of inflammatory cells, as well as their activation, in the airways. The reduction in eosinophils, activated T lymphocytes, and surface mast cells contributes to the decrease in airway hyperresponsiveness that is seen with CS therapy.

Several molecular mechanisms underlie the action of CS on airway inflammation. The main pathways center on the inhibition of transcription factors NF-κB and AP-1, which switch off

transcription of multiple activated genes encoding inflammatory proteins, such as cytokines, chemokines, inflammatory enzymes, and adhesion molecules.[71] Another key mechanism in the action of CS is the inhibition of the recruitment of histone deacetylase 2 to the inflammatory gene complex, which reverses the histone acetylation associated with increased gene transcription. CS increase the expression of β_2-receptors, which may contribute to the complementary clinical effects observed when CS are combined with LABA.[72] Transcriptional activation is responsible for most of the endocrine and metabolic adverse effects of CS.

Clinical Use—Inhaled Corticosteroids

CS are usually administered by the inhaled route for maintenance controller therapy in patients with asthma. ICS have been shown to prevent the symptoms of asthma, reduce severe exacerbations rates, improve lung function, and reduce airway hyperresponsiveness. Early and timely treatment with ICS appears to avert the irreversible changes in airway function that occur with chronic asthma. Patients with persistent asthma stabilized on ICS experience increased exacerbations when treatment is withdrawn, indicating that ICS suppress symptoms and inflammation but do not cure the underlying disease.

ICS are beneficial in treating asthmatic patients of any age and at any stage of disease severity. They are first-line therapy for patients with persistent asthma and are usually administered twice a day, although ICS may be effective given once a day in some patients with mild symptoms. The dose–response curve of ICS is relatively flat, meaning that higher doses are only incrementally better than low-to-medium doses. If low-to-medium doses of ICS do not control persistent asthma symptoms, it is usual practice now to add a LABA, preferably as a combination of the two drugs delivered from a single inhaler device.

Clinical Use—Systemic Corticosteroids

Oral CS are reserved to treat acute exacerbations of asthma. Typically prednisolone or prednisone, 30 to 45 mg, is given once daily for 5 to 10 days. Upon completion of the course of treatment, no tapering of the dose is required. A few asthmatic patients (approximately 1%) with severe disease may require maintenance treatment with oral CS; in these patients, it is important to determine the lowest dose necessary to maintain asthma control in light of the greater potential for adverse effects with higher doses. CS may also be administered intravenously (methylprednisolone or hydrocortisone) for the treatment of acute severe asthma, although studies have shown that oral CS are as equally efficacious and easier to take. The use of biologic therapies, such as anti-IgE and anti–IL-5, reduces the requirement for oral CS in selected patients with very severe asthma. All patients on maintenance oral CS should be considered for these therapies.

Adverse Effects

ICS may give rise to local oropharyngeal adverse effects, such as oral candidiasis, dysphonia, and hoarseness, but these may be lessened with the use of a spacer device. Concerns exist about the systemic adverse effects of ICS from swallowing of the oropharyngeal dose and lung absorption, but these effects depend upon the individual pharmacokinetic properties of the different CS. Overall, studies show that ICS have minimal systemic adverse effects.[73] At higher drug doses, ICS may suppress plasma and urinary cortisol levels, and in prepubertal children the initial decrease in attained height from use of ICS persists as a reduction in adult height; however, it is not progressive or cumulative and represents a loss in height of approximately 1 cm. Most importantly, ICS allow the effective control of asthma symptoms and disease, and maintenance therapy may decrease the need and number of prescribed courses of oral CS, thereby reducing the total systemic exposure to CS.

Oral CS give rise to greater systemic adverse effects than ICS, with a greater potential in those on chronic maintenance therapy. Adverse effects include bruising, diabetes, truncal obesity, osteoporosis, duodenal and gastric ulceration, hypertension, mood and behavioral changes, proximal myopathy, and cataracts. It is important to assess and monitor bone density if patients are administered chronic oral CS therapy so that preventive treatment for osteoporosis with bisphosphonates, or estrogen in postmenopausal women, may be initiated if levels of bone density are borderline or low. If CS adverse effects are a considerable problem, steroid-sparing agents may occasionally be considered.

■ Antileukotrienes

Leukotriene pathway inhibitors are a group of compounds that alter the pathophysiologic effects of leukotrienes derived from the 5-lipoxygenation of arachidonic acid. Two classes of agents are available: inhibitors of the 5-lipoxygenase enzyme (e.g., zileuton) and cysteinyl-leukotriene receptor type 1 antagonists (e.g., montelukast, zafirlukast, pranlukast).[74]

Mode of Action

Cysteinyl-leukotriene receptor type 1 antagonists inhibit the smooth muscle bronchoconstriction, microvascular leakage, and eosinophilic airway inflammation that occur through activation of $cysLT_1$ receptors. These agents act predominantly on the inflammatory mediators produced by mast cells in asthma and also, to a lesser extent, on mediators produced by eosinophils.

Clinical Use

Antileukotrienes have less effect on airway inflammation and provide modest clinical benefit compared to ICS. ICS are more effective anti-inflammatory agents and are clinically superior to antileukotrienes in controlling asthma. Antileukotriene treatments may be useful as add-on therapy in selected patients with mild asthma on low-dose ICS, although these agents are less efficacious than add-on therapy with LABA. Antileukotrienes may be helpful when CS use is poorly tolerated or not desired by the patient, or if there is concomitant rhinosinusitis. These drugs are usually given orally once or twice a day.

Adverse Effects

Antileukotrienes are usually well tolerated, but they can sometimes give rise to gastrointestinal upset, hepatotoxicity, and hypersensitivity reactions, including anaphylaxis and angioedema.

■ Cromones

Cromolyn sodium and nedocromil sodium are classified as asthma-controller drugs. Their main mechanisms of action seem to be to inhibit sensory nerve and mast cell activation; therefore, they are effective in blocking trigger-induced asthma, such as allergen- or exercise-induced symptoms. However, these drugs have a short duration of action, requiring inhalation up to four times a day, and consequently have relatively little benefit in the long-term control of asthma. They were popular in the treatment of children with asthma because they are remarkably safe, although they are inferior to ICS with respect to all relevant clinical outcomes and are no longer recommended in guidelines. Low-dose ICS are now favored in children, as they are more efficacious and have an established safety profile.

■ Corticosteroid-Sparing Treatments

Some patients experience serious adverse effects with CS therapy, especially oral CS therapy in those with severe asthma. In an attempt

to minimize CS exposure and reduce patient requirement, various immunomodulatory treatments have been tried. Steroid-sparing therapies include azathioprine, colchicine, cyclosporin A, gold, methotrexate, and intravenous gamma globulin; however, none of these treatments have shown long-term efficacy and, importantly, each has been associated with a high-risk adverse effect profile. They cannot be recommended in lieu of CS.

Anti-IgE Monoclonal Antibodies

Omalizumab is a monoclonal antibody to IgE that inhibits IgE-mediated reactions by neutralizing serum IgE without binding to cell-bound IgE. It is used as an adjunctive agent for atopic asthmatic patients who are dependent on CS therapy.[75] Studies in patients with moderate to severe CS-dependent asthma show an improvement in asthma control, a reduction in the number of disease exacerbations, and a significant steroid-sparing effect. However, anti-IgE treatment is very expensive. Its use is appropriate only for specific patients who have a high circulating IgE within a precise range and whose asthma is not controlled on maximal doses of inhaled or oral CS therapy. Omalizumab is usually given as a subcutaneous injection every 2 to 4 weeks. Although relatively safe with few significant adverse effects, anaphylaxis has occasionally been reported. As there are no good predictors of clinical response, a 3- to 4-month trial of therapy should be undertaken to ascertain any objective benefit with this treatment.

Anticytokine Therapy

Despite maximal inhaled therapy and maintenance courses of OCS treatment, a small proportion of patients with asthma are extremely difficult to control and may be candidates for biologic treatment of their disease. A number of immune system modulators have recently been licensed and approved for use in patients with severe asthma. Of these, the main biological therapies are inhibitors that target key cytokines involved in the chronic airways inflammation of asthma.[76]

Inflammation in patients with asthma is usually allergic, with activation of mast cells and of eosinophils mainly orchestrated by type 2 immunity, which involves T helper 2 (Th2) cells and type 2 innate lymphoid (ILC2) cells, IL-4, IL-5, and IL-13. These key cytokines have been targeted for therapeutic purposes.[76]

Anti–IL-5 Treatments

Currently, three anti–IL-5 treatments have been approved for use in selected patients with severe type 2 asthma: mepolizumab, reslizumab, and benralizumab.[77]

Mepolizumab is a blocking antibody to IL-5 administered by subcutaneous injection every 4 weeks. Initial studies in unselected patients and those with milder disease were unconvincing in demonstrating a benefit to patients. However, recent clinical trials in severe asthma patients using specific inclusion criteria, including ongoing respiratory symptoms, frequent disease exacerbations, and increased sputum eosinophils (>3%), showed a reduction in both disease exacerbations and the maintenance dose of OCS.[78] However, there was only little improvement in respiratory symptoms, pulmonary function, and quality of life; hence, ongoing inhaled maintenance therapy with ICS/LABA may still be needed.

Reslizumab is another blocking antibody to IL-5 administered intravenously every 4 weeks (a potential drawback compared to other treatments) that has shown similar benefit to mepolizumab. Once again, the clinical effectiveness is dependent on eosinophil counts (blood eosinophils ≥400/μL).[79] Higher doses of reslizumab than mepolizumab can be administered, so it may be considered in those patients who do not show a good response to mepolizumab.

Benralizumab is an antibody to IL-5 receptor α (IL-5Rα) administered subcutaneously every 4 to 8 weeks; it has been shown to benefit not only patients with severe asthma, but also those with milder disease.[80] In a study of patients presenting with an acute asthma attack, benralizumab administered as a single dose led to decreased disease exacerbations in the following 12 weeks post-exacerbation, particularly in those patients who were hospitalized because of their acute exacerbation.[81] Benralizumab induces death (apoptosis) of eosinophils, thereby rapidly clearing eosinophils in the airways. It may have a more rapid onset of action than antibodies targeting the cytokine. Increased blood eosinophil counts predict a better response; therefore, only patients with blood eosinophil counts greater than 300/μL should be considered for this therapy.

Anti–IL-4, Anti–IL-13 Treatments

IL-4 and IL-13 signal through a common receptor, IL-4Rα, and both cytokines promote eosinophilic airways inflammation. In adult patients with asthma, IL-4 expression is low, and poor outcomes in preliminary clinical studies directed attention to blocking IL-13 directly.[76] However, lebrikizumab, an antibody specifically blocking IL-13, showed marginal benefit in two recent clinical trials and has not been pursued for clinical approval.[82] Similarly, tralokinumab, also an IL-13 blocking antibody, performed poorly in recent clinical trials and was associated with minor changes in lung function, asthma control, and exacerbation outcome measures in patients with severe uncontrolled asthma.[83] In contrast, clinical trials with dupilumab, an antibody against IL-4Rα, have shown much better clinical benefit than those using IL-13 antibodies. Dupilumab, administered subcutaneously every 4 weeks, has been shown to improve symptoms and lung function and to markedly reduce asthma exacerbations in moderate to severe asthma poorly controlled on maximal inhalation treatments. Interestingly, in these patients FeNO was a good biomarker of response, but baseline blood eosinophil counts were not.[84] The drug is also licensed for use in patients with severe eczema and is effective in the treatment of rhinosinusitis and severe nasal polyposis.

Anti-TSLP Treatment

Blocking upstream cytokines, such as thymic stromal lymphopoietin (TSLP), that orchestrate type 2 inflammation may be more effective than targeting individual downstream cytokines. Tezepelumab, a blocking antibody to TSLP, has been shown to be effective in inhibiting responses to inhaled allergen (early and late) and in reducing blood and sputum eosinophils, FeNO, and IgE in patients with mild asthma.[85] In patients with severe asthma, clear reductions in acute disease exacerbations and decreases in FeNO and blood eosinophil counts have been observed.[86] Tezepelumab is also effective in patients with low or normal blood eosinophils, as it may also target T cells (Th1, Th17, ILC1, ILC3) that orchestrate neutrophilic inflammation.

Other Immunomodulating Treatments

Currently, many drugs are in development or in early human clinical trials in patients with subtypes of severe asthma that target various aspects of the inflammatory pathways, including those directed at cytokines (IL-25, Il-33, GM-CSF, IL-1, IL-6), transcription factors (GATA-3), neutrophils (TNF, IL-17), or chemokines (CCR3, CXCR).[76] Anti–TNF-α antibodies, although mechanistically promising, have not been shown to be effective in patients with severe asthma. New, broad-spectrum anti-inflammatory treatments include phosphodiesterase 4, NF-κB, and p38 MAP kinase inhibitors; these drugs act on signal transduction pathways that are common to many immune cells and present the risk of troublesome adverse effects, particularly when administered parenterally. Research is ongoing regarding potential delivery by the inhaled route.

Clear from clinical trials of biologics and the current interest in, and development of, drugs targeting the immune pathways

in asthma, is that appropriate patient selection, identification of responders, and development of biomarkers to monitor response are critical in order to guide clinicians when considering use of these very expensive treatments. The effectiveness of anti–IL-5 treatments is highly dependent on the baseline blood eosinophil count; greater clinical response is seen in patients with severe asthma with a blood eosinophil count ≥300/μL. In contrast, FeNO, rather than blood eosinophils, is a good predictor of response to anti–IL-4/13 treatments. For anti-TSLP treatment, effectiveness does not depend on raised blood eosinophil counts or FeNO.

It has also been recognized that existing specialist clinic resources must be directed at addressing nonadherence to inhaled therapy, as biologic interventions could end up becoming a very costly and expensive alternative to rectify nonadherence.[87] Most studies have been short-term (12 months). The long-term safety profile of these agents, particularly on the body's immune defense system against infections, is largely unknown. However, as licensed treatments are now being used, these data will be gathered during postmarketing surveillance.

Immunotherapy

Allergen-specific immunotherapy (ASIT) involves the repeated administration of allergen products to induce immunologic and clinical tolerance to the specific allergen. ASIT may be given subcutaneously.

Allergen immunotherapy is of benefit in highly selected patients with defined allergic triggers.[88] Asthmatic patients with a single specific allergic trigger and concomitant nasal symptoms derive the greatest benefit compared with patients with multiple allergic triggers. Allergen-specific studies have supported efficacy of this route of administration. There is a risk of adverse effects, including anaphylaxis. In contrast, sublingual ASIT has recently been shown to be an effective and safe alternative in patients with seasonal allergy. Clinical studies with house dust mite allergic asthma are underway.

NONPHARMACOLOGIC MANAGEMENT

Alternative therapies, which may be popular and more acceptable with some patients, include acupuncture, breathing control, chiropractic, homeopathy, hypnotherapy, and yoga. Placebo-controlled studies show these treatments lack efficacy; they should not be clinically recommended.[89] The concern with these therapies is that they may lead to discontinuation of effective drug therapy and destabilize asthma control. However, as these therapies are considered not to be harmful, patients may utilize them as an adjunct to their conventional pharmacotherapy.

Bronchial Thermoplasty

Bronchial thermoplasty (BT) is an endobronchial intervention for the treatment of adult patients with severe persistent asthma who remain uncontrolled with ICS and LABA. BT delivers controlled radiofrequency energy to heat the airway walls and reduces airway smooth muscle mass.

Three randomized controlled clinical trials of BT versus usual care or sham intervention in patients with severe asthma have supported its effectiveness and safety: the Asthma Intervention Research (AIR) trial[90] and the Research in Severe Asthma (RISA) trial,[91] both of which both compared BT to usual care, and the AIR2 trial,[92] which compared BT with sham intervention. The AIR2 trial observed a significant reduction in severe exacerbations of asthma, decreased emergency room visits, improved asthma quality of life questionnaire (AQLQ) scores, and fewer hospitalizations. These improvements persisted through 5 years of follow-up.[93]

Patients in the trials undergoing BT did report a transient increase in symptoms related to their asthma and, during the treatment phase, an increase in hospital admissions. An interim analysis of the 3-year follow-up results of BT in a postmarketing surveillance study mandated by the FDA (PAS2, Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma), confirmed findings observed from the AIR2 follow-up, with significant decreases in the percentage of patients with severe exacerbations (45%), emergency department visits (55%), and hospitalizations (40%).[94]

FUTURE TREATMENTS

Although current asthma therapy with CS and β_2-agonists is effective in controlling disease symptoms in the majority of patients, poorly controlled asthma still remains a problem in a considerable proportion of patients.[95] Poor adherence to prescribed controller therapy contributes to poor asthma control, and the use of combination LABA/ICS therapy delivered by a single inhaler device, or the use of combination LABA/ICS therapy as both a controller and reliever agent, may partly address this problem. LAMA have been used as add-on therapy in worsening asthma.[67] Recently, the combination of a LAMA (glycopyrronium) with ICS and LABA in one single inhaler (triple inhaler) has been licensed for uncontrolled asthma.[68]

In everyday practice, the vast majority of inhaler devices target treatment at the large airways. However, it is becoming increasingly recognized that it is important to target inhaled therapy to the peripheral lung regions in order to treat ongoing inflammation that may additionally be contributing to the patient's unstable clinical state.[96] Asthma continues to remain an unmet need, as the lifelong treatments currently used only address the clinical symptoms and have little effect on the underlying structural alterations associated with asthma. A pressing need exists for development of novel therapies for patients who have side effects from systemic CS.[97]

CS resistance is a particular problem in patients with severe asthma. Several molecular mechanisms have been elucidated that may lead to novel therapeutic approaches, including the reversal of this resistance by drugs such as theophylline and nortriptyline. Studies of the steroid-sparing effects of macrolide antibiotics in asthma management have yielded discordant results. Macrolides might benefit some patients with infection by atypical bacteria, but recent results are not encouraging; there may be an effect in patients with predominant neutrophilic asthma.

MANAGEMENT OF CHRONIC ASTHMA

Global directives in asthma now focus on the control of asthma symptoms using a stepwise approach to drug therapy.[1] There has been a shift away from treatment based on disease severity with the realization that asthma does not necessarily remain in the same clinical category indefinitely; it may change over months or years, and patients may move up or down in their asthma severity based on a variety of factors, such as the presence of allergens, correct or incorrect use of medications and treatments, and lack of adherence to the prescribed treatment regimen. If control at a particular step is not adequate, then treatment should be increased to the next level. Principles of therapy embody the fact that effective treatment should lead to better asthma control and allow the patient to move to a less severe category; therefore for ongoing management of asthma, classification by level of control may be more relevant and useful than disease severity. The aims of chronic therapy in asthma are highlighted in Table 45-4.

The Global Initiative for Asthma (GINA) stratifies patients into four categories of asthma control level: (1) controlled (therapy is maintained or stepped down), (2) partly controlled (consideration is given to stepping up therapy), (3) uncontrolled (treatment is stepped up until symptom control is achieved), and (4) exacerbation (patients are treated according to the exacerbation algorithms).[1]

Factors determining the level of control involve an assessment of the following: daytime symptoms experienced in the last week, limitations in activities of daily living, nocturnal symptoms or awakenings, need for rescue reliever medication during the week, lung function, and number of exacerbations (if any) in the last week and last year.

Stepwise Treatment

The stepwise approach to asthma management incorporates a description of the levels of treatment required to achieve good asthma control.[1] Some patients may experience acute worsening of asthma control, such as those with a concomitant upper respiratory tract infection, and may need to step up more than one step at a time.

Step 1

For all asthma patients, a SABA delivered by a metered-dose inhaler gives relief of acute symptoms. Updates to global strategy documents for the management of asthma and some national country guidelines now incorporate ICS treatment at step 1, recognizing the nature of asthma as chronic inflammatory disease and the need to control (and treat worsening) symptoms with ICS maintenance therapy.[98] The increasing use of a short-acting reliever medication more than three times a week, or triggering of symptoms from exercise, provide indications that controller therapy is needed. Recent studies in the management of mild asthma suggest the use of an ICS with formoterol in combination as a rescue medication, instead of a SABA; however, this approach is as yet unlicensed.[63,64]

An important, but often overlooked, part of asthma management relates to measures to control environmental triggers. Recognized triggers that worsen asthma control, such as aeroallergens or occupational agents, should be avoided, although this is not always possible. Patients with asthma may also have several triggers; therefore, the impact of avoiding a single trigger will vary considerably between patients. However, complete removal from exposure to house dust mite has been shown to reduce asthma severity and airway hyperresponsiveness.

Guidelines recommend that influenza vaccination should be administered in adult asthmatics. However, while studies suggest it is unlikely to induce asthma exacerbations, there is no conclusive evidence regarding the efficacy of vaccination on influenza-related asthma complications or on frequency of exacerbations. Asthmatic patients, especially the elderly or those with comorbid conditions that increase the risk of death from influenza infection, should receive inactivated influenza vaccine if there are no other contraindications. The CDC recommends a single dose of Pneumovax for adults from 19 to 64 who have chronic illnesses, including asthma.

Steps 2–3

When patient symptoms are no longer intermittent, addition of a daily long-term controller medication on a scheduled daily basis is recommended. The treatment of choice for all patients is an ICS to alleviate the underlying airway inflammation. It is usual to start with a low-to-intermediate dose of ICS twice daily (e.g., 200 μg beclomethasone dipropionate [BDP] or equivalent BID), and if symptoms are controlled after 3 months the dose should be stepped down. An alternative option is to prescribe as-needed low-dose ICS/formoterol. However, if symptoms persist and are not controlled, a LABA should be added as a fixed combination drug, with an ICS delivered from a single inhaler device, as studies show a clinical advantage compared with the monocomponents administered using two separate inhalers. Indeed, low-dose ICS in combination with LABA therapy shows complementary molecular action and has been shown to be as efficacious at high-dose ICS treatment.[99] The dose of the ICS should be adjusted up or down based on the need for rescue inhaler use and patient symptoms. Alternative add-on therapies to ICS that can be considered include an antileukotriene or low-dose ICS whenever a SABA is taken; however, these are less effective than the ICS/LABA combination.

Steps 4–5

In patients with worsening symptoms, addition of a long-acting muscarinic antagonist or a leukotriene antagonist to medium-dose LABA/ICS may be helpful. The addition of the inhaled long-acting anticholinergic tiotropium bromide to LABA/ICS treatment in patients with poorly controlled asthma significantly decreases asthma exacerbations and improves lung function.[100,101] For those whose disease remains uncontrolled, stepping up with high-dose ICS/LABA is a follow-on option.

In patients with severe asthma who fail to achieve symptom control, maintenance therapy with a systemic oral CS may be indicated; however, in view of the side-effect profile of oral CS, the clinician should always aim to titrate to the lowest possible daily (or every other day) dose that maintains asthma control.

Anti-IgE therapy with omalizumab may be tried in patients with severe allergic asthma, especially those who are CS-dependent and continue to remain uncontrolled. However, this treatment is only suitable for highly selected patients.

Anti-eosinophil biologic therapies may be considered for patients with uncontrolled severe asthma with increased blood eosinophils; benralizumab is given every 8 weeks, whereas mepolizumab and reslizumab are given by monthly injection. For asthmatics who have severe asthma with increased FeNO, dupilumab is preferred, especially in patients with concomitant nasal polyposis, rhinosinusitis, and atopic dermatitis. Allergen-specific immunotherapy may be considered in this group; however, the risk of severe events, including death, is highest in patients with severe asthma. Biologic therapy is also now indicated in a small proportion of patients.

Step-Down Treatment

Once symptoms of asthma are stable and the patient demonstrates stable peak flow readings, the clinician should slowly decrease therapy to find the optimal dose to control symptoms. Indeed, asthma severity may fluctuate and improve with time, owing to improved disease management, changes in environmental exposure, or the natural history of the disease. Most asthma guidelines recommend a step-down approach once patients are controlled.[1]

Overtreatment of patients, particularly with ICS, can cause significant morbidity and adverse effects, especially in moderate to severe asthmatics. Such treatment may also be unnecessarily costly. Unfortunately, in such patients there is a tendency to maintain a static treatment regimen, even after symptoms are controlled and clinical stability achieved. Studies have now supported the notion that stable asthmatic patients on high-dose ICS may be overtreated, and that reductions in the inhaled dose can be achieved without significant increases in asthma exacerbations, physician visits, or recourse to oral CS use.[102] Indeed, recent studies show that an efficient inhaler device may achieve a successful step-down without worsening symptoms, disease exacerbations, or hospitalizations.[103]

A gradual reduction in medications, starting with the treatment with the greatest toxicity, should be attempted once stability is achieved and sustained for several months. Symptoms should be monitored on a long-term basis using both objective lung function and subjective symptom measures. Most patients should be maintained on an ICS, and this treatment should not be stopped since it provides anti-inflammatory protection. For asthmatic patients who needed admission to hospital or ventilatory support, a longer period of stability on maintenance therapy may be justified before consideration of a step-down treatment approach.

MANAGEMENT OF REFRACTORY ASTHMA

Most asthmatic patients are controlled with appropriate stepwise therapy, but approximately 5% are difficult to control, do not remain symptom-free despite maximal inhaled therapy, and may require maintenance treatment with oral CS. In this group of patients, a thorough investigation of factors aggravating or contributing to poor asthma control should be undertaken. It is important to check adherence with medication and inhaler technique, particularly if the patient's disease is unstable, despite the maximal recommended dose of therapy. Nonadherence with medication remains an important factor for the poor control of asthma and may be particularly manifest with ICS, as patients may be concerned about adverse effects or describe lack of immediate clinical benefit from this treatment.[87]

Monitoring adherence to ICS therapy in the clinic is difficult, as there are no useful plasma measurements that can be made. However, in contrast, measurement of plasma cortisol suppression and absolute plasma drug concentrations may be useful in monitoring adherence to oral CS. Evidence suggests nonadherence may be more common in those with psychosocial problems or depression; these conditions should be actively sought and addressed during the clinical assessment.

A detailed review of factors, such as exposure to environmental allergens, unidentified occupational agents, or drugs that worsen asthma control, including aspirin or β-blockers, also should be undertaken.

Asthma may coexist with a number of disorders that can affect lung function, and the successful management of asthma often requires treatment of these associated conditions that are thought to aggravate asthmatic symptoms. Rhinosinusitis and gastroesophageal reflux disease are the most common of the disorders associated with poorly controlled asthma. The relationship between rhinosinusitis and asthma is well established as described in the "united airway disease hypothesis," according to which treating the inflammation of allergic rhinitis in the upper airways translates into improved asthma control.[104,105]

It has also been postulated that poor asthma control may arise as a result of the inability of current inhaler devices to target drug therapy to ongoing inflammation in peripheral lung regions. Conceivably, treatment of this lung compartment with targeted anti-inflammatory therapy may result in improved symptoms.[96] In spite of the lack of data from meta-analyses that fail to show a consistent effect of antireflux therapy on asthma symptoms and lung function, many clinicians assess and treat the possibility that gastroesophageal reflux disease may be aggravating asthma.[106]

As discussed earlier, patients with vocal cord dysfunction may present with wheeze and stridor and the need for an escalation in asthma therapy. Vocal cord dysfunction can be assessed using nasoendoscopy to observe abnormalities in the movement of the vocal cords; if the diagnosis is confirmed, patients should be weaned off CS. Speech therapy intervention may be helpful. Bronchoscopy or MDCT to exclude tracheobronchomalacia may be considered. A reconsideration of the potential differential diagnoses should be explored in the refractory asthmatic patient (Table 45-3).

Patients who require high doses of oral CS to maintain asthma control are referred to as "CS-dependent" asthmatics. In contrast, patients with complete "CS-resistant" asthma show a failure to respond to high-dose oral CS therapy. However, this is very uncommon, affecting less than 1 in 1000 patients. Several molecular mechanisms have been implicated in CS resistance and the impaired anti-inflammatory action, leading to the identification of new drug targets for future therapies.[107]

Evidence has shown that in asthmatic patients who smoke (approximately 20% of the population), smoking itself hinders the anti-inflammatory action of CS, leading to relative CS resistance and the need for higher drug doses to achieve asthma control. It is recognized that compared with nonsmoking asthmatics, smoking asthmatics have a faster decline in lung function, more severe asthma, more frequent hospital admissions, and a higher risk of death. Smoking cessation should be strongly pursued in this group, as this intervention has been shown to reduce CS resistance and improve lung function.

Some asthmatic patients have unstable disease, characterized by rapid variations in lung function that may lead to recurrent and severe attacks of asthma, despite appropriate treatment.[108] These patients may be divided into two categories: (1) type I brittle asthma, characterized by a sustained pattern of chaotic peak flow variability on a daily basis; and (2) type II brittle asthma, in which asthma symptoms and lung function are well controlled, but where abrupt and unpredictable falls in peak flow may be catastrophic and result in sudden death. These patients are difficult to treat, as they do not usually respond to maximal high-dose CS therapy and may rely on subcutaneous epinephrine injections. Assessment of treatment adherence and education on allergen avoidance are particularly important in these patients, who should wear an identification bracelet noting their condition. The importance of carrying a portable epinephrine autoinjector at all times and being taught to self-administer this treatment should be a central part of their management.

ASTHMA EDUCATION AND MONITORING

Asthma education and training are important, as patients need to understand the disease, its management, proper use of inhalers, adverse effects of treatment, and, importantly, timing of use of reliever and controller treatments. Education may improve adherence to treatment recommendations and engage the patient in self-management strategies, particularly in terms of symptom recognition, identification and avoidance of asthma triggers, objective measurement of deterioration in asthma control, and treatment of exacerbations of asthma in their earliest stages by stepping up therapy. Educating the patient in the self-administration of oral CS and access to healthcare advice are also important elements in a management program, which are designed to reduce emergency hospitalizations and patient morbidity.

Studies have shown that written personal patient action plans result in better asthma control, reduced emergency department visits and hospitalizations, and decreased morbidity, in both adults and children. Written plans are particularly useful and recommended in patients with unstable disease who have frequent exacerbations. The additional provision of a program of educational sessions (one-to-one or in small groups) with a knowledgeable healthcare professional has been shown to be more effective than provision of written materials alone. Like drug therapy, the educational program and the method and frequency of reinforcement should be tailored to the patient's individual needs. Patients should be reassured that with proper treatment, symptoms and occasional exacerbations can be minimized and, in most cases, a normal lifestyle and life expectancy can be anticipated.

Home monitoring of asthma symptoms and control is an important aspect of self-management programs. PEF measurements allow patients to be monitored on a long-term basis using simple, handheld, compact portable devices. Asthma treatment guidelines recommend patients use PEF measurements not only to monitor the course of the disease, but also to dictate self-administered treatment regimens.[1] Indeed, studies show improvements in measures of asthma control when peak flow measurements are used by patients (in relation to their personal best peak flow) to adjust medication usage.

However, despite the advantages of written plans, as discussed above, a study by the U.S. Centers for Disease Control and Prevention (CDC) analyzing data from adults and children between 2001 and 2009 in a national health interview survey showed that

only one-third of patients with asthma reported being given a written asthma action plan. Furthermore, just over two-thirds of patients had been taught the appropriate response to symptoms of an asthma attack.[109]

It should be recognized that not all patients are capable of comprehending and executing complicated treatment plans. In addition, peak flow–guided self-management may lead to overtreatment with medication and the potential for increased morbidity due to adverse effects. Similarly, patients with severe asthma for whom self-management plans are more readily recommended may tend to use more oral CS, even when it may be unclear whether increased use is appropriate or medically warranted (although the increase in medication may be initially viewed as a potential benefit of peak flow monitoring). Action plans should be written using clear, simple language and should be individualized based on patients' understanding of their asthma, its severity, and their demonstrated ability to comply with instructions. The use of digital technology to help monitor inhaler use, test lung physiology remotely, and link with home and work environmental data may help predict exacerbations and alert patients to worsening asthma control.[110,111] Preliminary studies show that digital systems improve asthma control and quality of life, including a reduction in severe disease exacerbations. However, longer-term studies are needed to show a health economic impact.[112]

MANAGEMENT OF ACUTE SEVERE ASTHMA

Asthma is characterized by exacerbations of disease, which can lead to substantial morbidity, occasional mortality, and considerable medical and economic costs. Patients with asthma fear disease exacerbations, as they can be life-threatening; exacerbation-prone patients seem to be at increased risk for attacks of near-fatal asthma. Analysis of asthma mortality data has showed that patients experience worsening symptoms and deterioration in asthma control over a period of several hours to several days before the event.[113] Indeed, life-threatening episodes may develop in any asthmatic patient, particularly those patients with severe and poorly controlled disease, who frequently access the emergency room, or who are hospitalized; all are recognized to be at high risk of life-threatening events. The importance of educating all patients with asthma should not be underestimated, and healthcare professionals should identify and closely monitor such at-risk patients.

Clinical Features

Patients with a moderate exacerbation of their disease notice a deterioration in their asthma control by an increase in daytime and nocturnal symptoms of cough, chest tightness, wheezing, and dyspnea; these symptoms do not respond to the patient's usual maintenance therapy and require more reliever drug. A history of prodromal symptoms may be elicited that precedes an asthma attack, such as itching under the chin, discomfort between the scapulae, or inexplicable fear (impending doom). A fall in home peak flow recordings also signifies a worsening of asthma. The GINA guidelines classify exacerbations based on the peak flow into mild (PEF >80% predicted), moderate (PEF between 60% and 80% predicted), and acute severe (PEF <60% predicted).[1]

Patients may become so breathless in acute severe exacerbations that they become exhausted, unable to talk freely in complete sentences, and show life-threatening features of confusion, agitation, and cyanosis. Clinical examination usually shows an increased respiratory rate, chest hyperinflation, and tachycardia. In acute severe asthma, pulsus paradoxus (accentuated decrease in systolic blood pressure of >10 mm Hg during inspiration), may be present. Life-threatening signs include a silent chest, bradycardia, and hypotension. Evaluation shows a marked fall in PEF and spirometric values; oxygen saturation on room air may be reduced, and arterial blood gases may reveal a low Pa_{O2}. Initially, Pa_{CO_2} is low due to hyperventilation. In life-threatening situations, PEF is <30% predicted; oxygen saturation (Sa_{O_2}) measured by pulse oximetry is <92%; and arterial blood gases on room air reveal a Pa_{O_2} <60 mm Hg (8 kPa). A rising Pa_{CO_2} indicates impending respiratory failure and requires immediate monitoring and therapy. A chest radiograph is not routinely recommended in the absence of a suspected pneumothorax, pulmonary consolidation, failure to respond to treatment satisfactorily, or a requirement for mechanical ventilation.

Pharmacologic Treatment

The cornerstone of therapy for worsening asthma control requires the escalation of both ICS and quick-relief inhaled β_2-agonists.[1] Exacerbations of asthma should never be treated by escalating bronchodilators alone. Asthma fatalities usually result when patients fail to promptly seek medical attention. Studies have shown patients dying from asthma commonly self-medicate with escalating doses of reliever bronchodilator medication in the days preceding an asthma attack. A short course of oral CS therapy for at least several days may be needed to control and prevent a mild to moderate exacerbation; tapering of the dose should be undertaken with close outpatient follow-up. Very mild or subacute exacerbations with mild persistent disease may be managed in some cases by escalating the dose of ICS in cases in which patients are taking low-dose CS. In less severe exacerbations, patients who promptly respond to treatment in the emergency department may be discharged, but close outpatient follow-up is essential.

In patients with an acute severe exacerbation presenting to the emergency department, oxygen at high concentrations and high flows should be given continuously by face mask to achieve oxygen saturations (Sp_{O_2}) between 94% and 98%. Hypoxemia is to be avoided at all costs, as patients die from hypoxemia in acute asthma. Oxygen therapy is critical to prevent death in severe acute asthma, so continuous monitoring of oxygen saturation is needed until there is a meaningful response to treatment.

High doses of inhaled SABA, given either by nebulizer (oxygen-driven) or via a pMDI with a spacer, should be the first-line agents in acute asthma and should be administered as early as possible. While generally well tolerated, nebulized bronchodilators occasionally cause arrhythmias; continuous electrocardiogram monitoring is required. In those patients in whom inhaled therapy cannot be used reliably, or in severely ill patients with impending respiratory failure, intravenous β_2-agonists may be given. In patients not responding to treatment, a nebulized anticholinergic (e.g., ipratropium bromide) may be added to provide additional bronchodilation. Systemic CS should be given in adequate doses in all cases of acute severe asthma for at least 5 days or until recovery; the CS should be tapered after this response over a 2-week period, particularly in cases of severe asthma exacerbations. In patients unable to take oral CS, intravenous therapy (e.g., hydrocortisone) should be administered in the emergency department.

A single dose of intravenous magnesium sulfate for patients has been shown to be effective when added to inhaled β_2-agonists. It is relatively well tolerated and can be considered in patients with acute severe asthma who have not had an initial good response to inhaled bronchodilator therapy or in those with life-threatening features.

Patients should be referred to the intensive care unit for intubation and mechanical ventilation if they have acute severe or life-threatening asthma that fails to respond to therapy, as indicated by a deteriorating PEF, worsening hypoxemia, a normal or rising Pa_{CO_2}, poor respiratory effort, or exhaustion or confusion. Intravenous aminophylline may be used, but the risks of toxicity are much greater than for inhaled β_2-adrenergic agonists. Sedatives should never be given, as they may depress ventilation. Antibiotics should not be routinely administered in the absence of clinical or radiologic signs of pneumonia.

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CHAPTER 46

Allergic Bronchopulmonary Aspergillosis (Mycosis) and Severe Asthma with Fungal Sensitivity

Geoffrey L. Chupp

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an idiopathic inflammatory disease of the lung, characterized by an allergic inflammatory response to colonization of the airways by *Aspergillus fumigatus* or other fungi. The entity was first described in 1952 by Hinson et al., and then again in 1967, when Scadding recognized an association between the disease and proximal bronchiectasis in areas previously affected by infiltrates (predominantly in the upper lobes).[1,2] The first adult case of ABPA was reported in the United States in 1968.[3] Although most cases entail hypersensitivity to *Aspergillus* spp. (i.e., *A. fumigatus* or *niger*), the finding of a virtually identical clinical syndrome associated with immune sensitivity to *Candida albicans* (most commonly), *Helminthosporium*, *Alternaria*, *Curvularia lunata*, *Drechslera hawaiiensis*, *Stemphylium languinosum*, *Saccharomyces cerevisiae*, or *Pseudallescheria boydii* has led some to use the term *allergic bronchopulmonary mycosis* to describe the syndrome.[4] However, since the predominant causative organism is *A. fumigatus* (and the commercially available laboratory testing is for this organism and *A. niger*), ABPA is primarily designated as the diagnosis. In addition, a recently recognized entity appears to be on the continuum between fungal allergy, at one end, and ABPA at the other: severe asthma with fungal sensitivity (SAFS).[5]

The precise prevalence of ABPA is unknown, in part due to variability in diagnostic criteria used in various studies, the lack of distinction between ABPA and mold-sensitive asthma, and delays in the diagnosis of patients with long-standing disease; however, it is clear that ABPA is a relatively common entity. Estimates are that true ABPA complicates approximately 7% to 14% of cases of chronic steroid-dependent asthma and approximately 7% to 15% of cases of cystic fibrosis (CF). Therefore, it is commonly encountered by pulmonologists and allergists.[6,7]

Most cases of ABPA are recognized in the third to fifth decade of life, but the disease can also present during childhood. In some patients, it is likely that ABPA starts early in life and continues, unrecognized, until adulthood. Interestingly, familial cases have been reported, suggesting that genetic factors may underlie the development of ABPA.[8,9] The spectrum of disease is broad, which can complicate the diagnosis and initiation of corticosteroid-sparing therapy. Patients may be asymptomatic, have mild to moderate asthma, or have severe and debilitating disease that leads to severe bronchiectasis, mucoid *Pseudomonas* colonization, and the need for lung transplantation. However, if recognized early and managed aggressively, ABPA is treatable, it may enter into remission, and progressive lung damage can be avoided.

For the purposes of this discussion, the focus will be on ABPA. However, clinicians should be cognizant that diagnostic testing for other fungi should be pursued when organisms other than *Aspergillus* spp. are suspected. In addition, in patients that don't quite meet criteria of ABPA, a diagnosis of SAFS should be considered as it will affect clinical management.

PATHOGENESIS

Although the pathogenesis of ABPA is poorly understood, it is believed to be the result of an exaggerated immunologic reaction to chronic airway colonization by *Aspergillus* (or other relevant fungal) species.[10] *Aspergillus* spp. are globally ubiquitous, thermotolerant fungi that reside in decaying organic matter and colonize most domestic environments, including carpets and air duct systems.

In humans, airborne *Aspergillus* spores or conidia that are inhaled are immunologically inert. In normal individuals they are cleared by innate immune system mechanisms that maintain airway homeostasis managed by neutrophils, macrophages, and dendritic cells. The result is immunologic tolerance to the presence of the spores. However, in susceptible individuals, conidia colonize airways and germinate into somatic hyphae, stimulating a chronic allergic inflammatory response that drives IgE production and eosinophilic inflammation. This results in tissue injury and the clinical features of ABPA.[7] In contrast to a true infection in which fungal hyphae invade the lung parenchyma, colonization of the airways with germinating fungal spores represents an abnormal state that remains within the airway and promotes an exaggerated Th2 inflammatory response. While details of the mechanisms that drive this process remain poorly understood, it appears that susceptibility to *Aspergillus* colonization and development of clinical disease depend on host factors that include genetic risk, T-cell responsiveness to *Aspergillus* antigens, the magnitude of tissue response to *Aspergillus*, and the level of environmental exposure to this ubiquitous fungus.

Investigations into the genetic risk factors that are associated with ABPA have identified several candidate genes. This suggests that the pathogenesis of ABPA is dependent on both host and environmental factors.[11] Best characterized is the association between gene mutations in the CF transmembrane conductance regulator (CFTR) and the pathogenesis of ABPA.[12,13] CFTR mutations are more common among patients with ABPA compared with the general population or with individuals with severe asthma without sensitivity to *A. fumigatus*. Another genetic link to ABPA is that Th2-type T-cell reactivity to selected *Aspergillus* antigens is determined by the presence of MHC class II DR2 or DR5 alleles, which may predispose patients to the disease, whereas the MHC DQ2 allele may be protective.[14,15] In addition, investigators have determined that there is an increased prevalence of polymorphisms in the promoter region of the pathogen-associated molecular pattern receptor Toll-like receptor 9 (TLR9) in individuals with ABPA compared with controls or patients with SAFS.[16] We recently determined that children with severe asthma and ABPA are more likely to carry the chitotriosidase 1 (CHIT1) exon 10 mutation.[17,18] Individuals with the exon 10 mutation have lower levels of, or lack, chitinase activity and are unable to degrade chitin, a structural polysaccharide in the cell wall of lower life forms such as *A. fumigatus*.[19–21]

At the microscopic level, ABPA is characterized by an intense eosinophilic and mononuclear cell inflammatory response, leading to areas of parenchymal scarring, airway remodeling, and bronchiectasis.[22,23] Immunologic studies demonstrate the presence of a type I hypersensitivity reaction, with elevated serum levels of total IgE and *A. fumigatus*–specific IgE in individuals with ABPA (Fig. 46-1). In addition, patients have evidence of an exaggerated type III hypersensitivity reaction, indicated by the presence of *A. fumigatus*–specific IgG antibodies (classically called "precipitins" or precipitating antibodies) and circulating immune complexes during

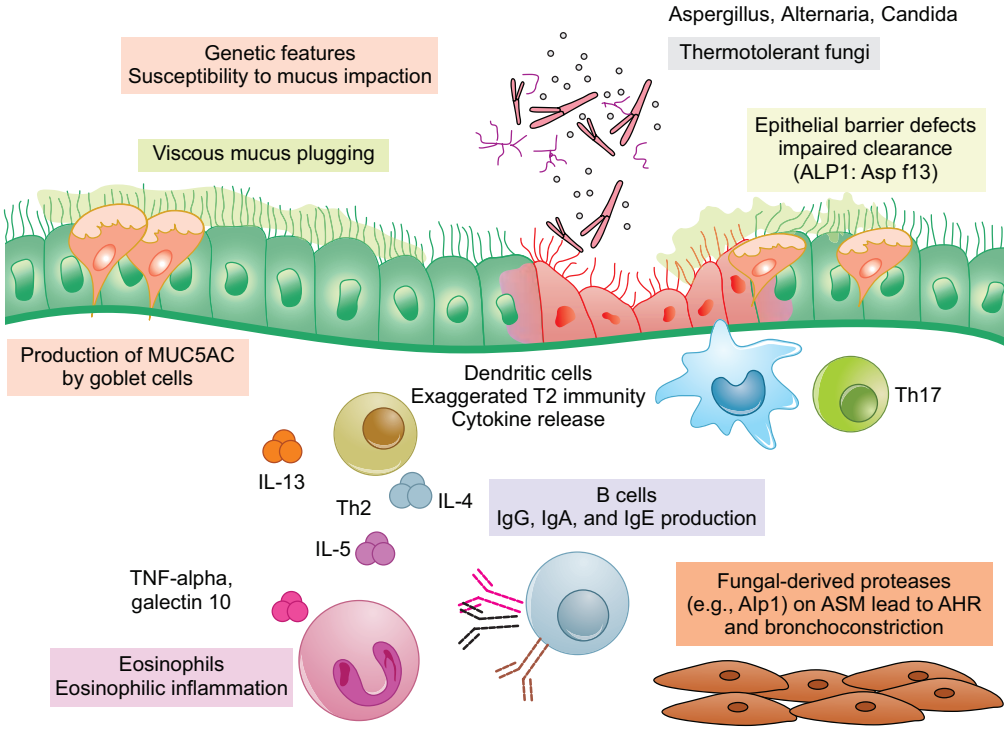


Figure 46-1 Inflammatory response ABPA. In susceptible individuals, conidia germinate into somatic hyphae. These hyphae then stimulate a chronic allergic inflammatory response that drives Th2 and Th17 with subsequent IgE production and neutrophilic and eosinophilic inflammation. This sequence of events eventually leads to tissue injury and bronchiectasis. *(Reproduced with permission from Wardlaw AJ, Rick EM, Pur Ozyigit L, et al. New Perspectives in the Diagnosis and Management of Allergic Fungal Airway Disease. J Asthma Allergy. 2021;14:557–573.)*

disease exacerbations. A type IV cell-mediated immune reaction also may be at work, based on the finding of dual (immediate and delayed) cutaneous reactions and in vitro lymphocyte transformation to *A. fumigatus* antigen stimulation in some patients.[24,25]

A substantial amount of research has been done on the immune response in ABPA, demonstrating that several cell types and pathways are involved in the pathogenesis of this destructive variant of asthma.[19,20] A pathogenetic role for helper T lymphocytes is suggested by a number of findings, including the presence of increased numbers of airway Th2 cells and elevated levels of soluble interleukin 2 (Il-2) receptors (suggesting T-cell activation) in the circulation of persons with active ABPA;[26] the derivation of *A. fumigatus*–specific T-cell clones with T helper 2 (Th2) patterns of cytokine production from the blood of patients with ABPA;[27,28] positive correlations between activated T-cell number, levels of the T cell–derived cytokines IL-4 and IL-5, and the elevated numbers of airway eosinophils in the disease; the critical role IL-5 plays in murine models of ABPA;[29–36] and increased reactivity of Th2 cells to *A. fumigatus* antigens among patients with ABPA as compared with patients with asthma and skin reactivity to *Aspergillus*.

In addition to lymphocytes, eosinophils and basophils may contribute to local airway injury; neutrophils also likely play a role in airway inflammation and tissue damage in ABPA. This is evidenced by the fact that sputum IL-8 levels correlate with sputum neutrophilia, matrix metalloproteinase levels, and FEV_1 among patients with ABPA.[37,38]

It is also clear that the fungus itself contributes substantially to the pathogenesis of disease. *A. fumigatus*–derived proteases contribute to epithelial cell injury and protective barrier disruption, triggering inflammation by allowing increased penetration of fungal antigens into the airway wall, which leads to immune hypersensitivity.[39] *Aspergillus*-derived proteases may also stimulate proinflammatory cytokines, such as IL-8, and release of growth factors; proteases also cause tissue damage that leads to bronchiectasis.[38]

A variety of other *Aspergillus*-derived antigens, including cytotoxins and heat shock proteins (demonstrated by their ability to bind IgE and IgG derived from the blood of patients with ABPA), also have been shown to drive both the IgE (hypersensitivity) and IgG immune responses. *A. fumigatus*–derived proteases with antibody-binding capacity also may amplify the inflammatory response. Other *A. fumigatus* antigens, such as Aspf1 (a cytotoxic protein), Aspf2 (a fibrinogen–binding protein), Aspf5 (a metalloprotease), Aspf6 (manganese superoxide dismutase), Aspf8 (a ribosomal protein), Aspf13 and Aspf18 (serine proteases), and Aspf3 and Aspf4, also have been implicated in the pathobiology of ABPA. Finally, host response to *Aspergillus fumigatus* antigens includes surfactant proteins (SP) A and D, which may play a protective role against ABPA by interfering with binding between *A. fumigatus* antigens and IgE. Notably, however, SPD levels do not correlate with acute exacerbations of ABPA in humans.[40–42]

CLINICAL FEATURES

Although ABPA typically presents in patients with a history of difficult-to-control asthma, the spectrum of presentation is highly variable and should be considered in any patient with difficult-to-control asthma and hypersensitivity to *A. fumigatus*.[42] Typical presenting complaints are often nonspecific and include dyspnea, wheezing, poor asthma control, cough (sometimes productive of thick, brown mucus plugs), malaise, low-grade fever, and occasionally, hemoptysis. There may be an antecedent history of recurrent asthma exacerbations in conjunction with pneumonias without a culture-identified bacterial source. In addition, atopy with rhinitis, drug allergy, and/or allergic conjunctivitis are common. It is often not until a patient has been repeatedly ill over weeks to months and unresponsive to standard treatments that the diagnosis is considered.[43] As patients with SAFS have the same clinical presentation, differentiation from ABPA is based on interpretation of laboratory testing and radiographic studies.[42]

TABLE 46-1 Criteria for the Diagnosis of ABPA

Seropositive ABPA (ABPA-S)
History of asthma (usually difficult to control)
Elevated total serum IgE (usually >1000 IU/mL)
Immediate skin test reactivity to *Aspergillus fumigatus or* elevated specific serum IgE to *A. fumigatus*
Presence of serum precipitins (by gel diffusion) or elevated specific serum IgG to *A. fumigatus*
ABPA central bronchiectasis (ABPA-CB)
Above criteria are positive
Central bronchiectasis by high-resolution CT scan or chest radiograph
Other supportive clinical findings
Peripheral blood eosinophilia (may be absent if patient is on oral or inhaled corticosteroids)
Patchy, fleeting infiltrates (may be absent if patient is on oral corticosteroids)
Expectoration of mucus plugs or bronchial casts
Mucoid-impacted bronchi evident on radiographic studies
Sputum culture positive for *A. fumigatus*

Diagnostic Guidelines

In general, the diagnosis of ABPA is based on appropriate clinical features in combination with supporting radiologic and serologic findings. While there are no specific diagnostic criteria, similar guidelines have been proposed by multiple expert panels to aid clinicians in the diagnosis of ABPA (Table 46-1).[22,44] These guidelines have evolved over time and have been updated by several societies. There is no agreement on clinical criteria that should trigger screening for ABPA, but in most asthma centers, all asthmatics with difficult-to-control asthma are screened by checking for an elevated eosinophil count, total IgE, and specific IgE *A. fumigatus*, *A. Niger*, and *Alternaria* spp.

Using the Patterson criteria, ABPA is classified into two different subtypes: ABPA-seropositive (S) and ABPA-central bronchiectasis (CB). Patients with ABPA-S usually display all of the following diagnostic criteria proposed by Greenberger and Patterson: (1) history of asthma; (2) total IgE >1000 IU/mL; (3) elevated serum anti-*AF* IgE and IgG (twofold higher than *A. fumigatus* allergic asthma controls); (4) positive immediate hypersensitivity skin test to *A. fumigatus*; and/or (5) serum IgG precipitating antibodies against *A. fumigatus*. The last criterion is considered positive when the double gel diffusion, the enzyme-linked immunoassay (ELISA), or the fluorescent enzyme immunoassay (FEIA) is positive for anti-*AF* IgG antibodies.[45] Patients with ABPA-S have normal chest radiographic studies, with no evidence of bronchiectasis. Patients with ABPA-S tend to have fewer symptoms, lower IgE levels, less severe airflow obstruction, and fewer exacerbations than patients with ABPA-CB.[46] In contrast, patients with ABPA-CB are positive for all of the criteria of ABPA-S and have features of advanced disease including bronchiectasis on high-resolution CT scanning or chest x-ray.[47,48] These patients may also expectorate mucus plugs or bronchial casts and are sputum culture positive for *A. fumigatus*. Although IgE levels fluctuate with disease activity, a normal IgE level in a symptomatic, untreated patient with asthma virtually excludes the diagnosis.[49] It remains unclear whether ABPA-S is a milder form of the disease (e.g., representing a different host response) or an earlier stage of illness. Identification of *Aspergillus* (or other relevant fungus) in the sputum and dual (immediate and delayed) cutaneous reactions to challenge with *Aspergillus* (by prick test or intradermal) also are common clinical features of ABPA. Rare cases lacking a history of asthma, but meeting the other major diagnostic criteria, have been reported.[43]

Severe Asthma with Fungal Sensitivity

The broad spectrum of clinical, laboratory, and radiographic abnormalities evident in patients with asthma and fungal allergy has led to the description of additional diagnostic categories of allergic fungal disease. The most clinically relevant of these diagnoses is based on studies that demonstrate that antifungal therapies are effective in patients with poorly controlled asthma who have some of the criteria for ABPA-S but do not reach the threshold for diagnosis. These patients have been designated as having SAFS. Whether SAFS is a unique disease or is on the continuum from asthma to ABPA is not known. However, the primary distinction between SAFS and ABPA is that patients with SAFS have a milder allergic reaction and lack the exaggerated IgG response that is typical of patients with ABPA. Patients with SAFS can be difficult to distinguish from patients with ABPA-S, as their clinical features are identical and both lack radiographic evidence of bronchiectasis.

The diagnosis of SAFS is based on the interpretation of *Aspergillus*-specific immunologic studies. The diagnostic criteria for SAFS (Table 46-2) overlap substantially with ABPA-S and include: (1) severe uncontrolled asthma (treatment requirement of >500 μg/d of fluticasone or the equivalent, need for near continuous oral corticosteroids for 6 months or ≥2 oral steroid tapers per year); (2) positive skin prick test or RAST for *A. fumigatus* or other fungi; (3) elevated total serum IgE, but <417 IU/mL or <1000 ng/mL; and (4) absence of IgG against *A. fumigatus* (by ELISA, gel diffusion, or FEIA).

Typically, patients with SAFS have normal radiographic studies and a milder immunologic response similar to patients with milder asthma. Although it remains unclear whether these patients are on the continuum from asthma to ABPA or are at risk of progressing to ABPA, the clinical importance of identifying patients with SAFS is based on several studies showing that antifungal therapies can improve asthma control and reduce oral corticosteroid exposure.[50–52]

The differential diagnosis of ABPA is broad and includes corticosteroid-dependent asthma without ABPA, SAFS, chronic obstructive pulmonary disease (COPD), chronic necrotizing aspergillosis, tuberculosis, parasitic infections, hypersensitivity pneumonitis, Churg–Strauss syndrome, acute eosinophilic pneumonia (including drug-induced pneumonitis), chronic eosinophilic pneumonia, lymphoma, idiopathic hypereosinophilic syndrome, autoimmune disease, crack cocaine use, CF, and other causes of bronchiectasis. The diagnosis of ABPA in patients with mold-sensitive asthma and

TABLE 46-2 Criteria for the Diagnosis of Severe Asthma with Fungal Sensitivity (SAFS)

1. History of poorly controlled asthma despite >500 μg/d of fluticasone or the equivalent, near continuous oral corticosteroids (>50% of the time), or ≥2 oral steroid tapers per year
2. Total serum IgE <1000 IU/mL
3. Positive immediate skin test reactivity to *Aspergillus fumigatus or* elevated specific serum IgE to *A. fumigatus*
4. Absence of serum precipitins (by gel diffusion) and elevated specific serum IgG to *A. fumigatus*
5. No radiographic evidence of bronchiectasis or infiltrates

CF poses a particular diagnostic challenge. In asthmatics, by definition, bronchiectasis is absent and serum precipitating antibodies to *Aspergillus* spp. may be present in up to 25% of patients, making the distinction from ABPA-S difficult.

Persons with mold-sensitive asthma or ABPA may have peripheral blood eosinophilia and/or elevated serum total IgE levels. However, most persons with ABPA have 2- to 20-fold higher serum levels of *Aspergillus*-specific IgE and total IgE than do mold-sensitive asthmatics without ABPA.

A diagnostic conundrum occurs when considering the diagnosis of ABPA in patients with CF, because patients with CF alone may manifest chronic airflow obstruction, recurrent exacerbations with infections and/or bronchoconstriction, underlying bronchiectasis, pulmonary infiltrates, chronic sputum production, *Aspergillus* colonization of the airways, and positive serum precipitins. Distinguishing ABPA in patients with CF is critical because infectious CF exacerbations and ABPA require different treatments. The steroid treatment required for ABPA may be detrimental in the setting of infection, yet antibiotics alone given for infection may be inadequate to control the inflammation associated with ABPA. Among patients with CF, factors associated with the risk of ABPA include adolescent age, atopy, severe lung disease, and colonization with *Pseudomonas aeruginosa*. ABPA should be suspected in patients with CF who develop clinical deterioration, exhibit a greater than fourfold increase in total serum IgE (especially >1000 IU/mL), have immediate cutaneous reactivity to *Aspergillus* or increased *Aspergillus*-specific IgE or IgG, and show a change in baseline chest radiograph. Annual screening of total serum IgE is recommended; if the level rises >500 IU/mL, immediate cutaneous hypersensitivity testing for reactivity to *A. fumigatus* or testing for serum anti–*A. fumigatus* IgE is recommended.[13,53] The titer of IgE reactive against the purified *Aspergillus* allergens Aspf3 and Aspf4 may be useful in distinguishing patients with ABPA and CF or *Aspergillus*-sensitive asthma from patients without ABPA, with rising or high titers being more indicative of ABPA than a bacterial-driven flare of CF.[12]

Clinical Staging of ABPA

Five clinical stages of ABPA have been recognized based on clinical, serologic, and radiographic characteristics (Table 46-3). A modified version proposed by the International Society for Human and Animal Mycology (ISHAM) has been developed but has not been widely adopted.[22,54]

Using the classic staging system, stage I, the *acute* stage, is characterized by symptoms of moderate to severe asthma, elevated total IgE (typically >1000 IU/mL), elevated anti–*A. fumigatus* IgE or hypersensitivity skin test to *A. fumigatus*, infiltrates on chest radiograph (with or without proximal bronchiectasis), peripheral blood eosinophilia (frequently >2000/mm^3), and positive precipitating or anti-IgG antibodies to *A. fumigatus* (up to fivefold concentration of serum may be required for detection of the precipitating antibodies).

Patients with stage II ABPA have disease that is in *remission*. This stage is characterized by the resolution of symptoms, radiographic clearing, and decreased of total IgE levels. Remissions are of varying length, may last several months to years, or may be permanent, allowing corticosteroid treatment to be tapered or discontinued.

Patients with stage III ABPA have *recurrent* disease or disease *exacerbations*. This stage of ABPA is common and is characterized by development of new pulmonary infiltrates and, usually, a substantial increase in total IgE. Elevation of IgE may precede clinical or radiologic worsening during this stage; an isolated increase in the severity of bronchospasm does not constitute an exacerbation in the absence of a change in biomarkers. Although a majority of disease exacerbations are associated with a concomitant increase in symptoms, exacerbations may occur in the absence of any increase in symptoms. Indeed, since up to one-third of patients with radiographic infiltrates may be asymptomatic, evolving progressive lung damage may remain unrecognized. Total serum IgE levels, pulmonary function testing, and chest imaging should be monitored intermittently. *Aspergillus*-specific IgA levels may also be elevated in an exacerbation of ABPA. Exacerbations are more likely to occur seasonally or in environments where mold counts are high.

Stage IV ABPA is defined as *steroid-dependent asthma*. In stage IV disease, total IgE, *Aspergillus* precipitins, and *Aspergillus*-specific IgE and IgG typically remain elevated, despite chronic steroid therapy. During this phase, the frequency of exacerbations may increase, become chronic, and be difficult to control.

Stage V is defined as *pulmonary fibrosis*. Stage V patients have chronic symptoms consistent with bronchiectasis that include cough and dyspnea. These patients are often steroid dependent because of persistent bronchospasm and have chronic sputum production, recurrent respiratory infections, and irreversible pulmonary function abnormalities (obstruction, restriction, and/or gas exchange abnormalities), and may have cyanosis or clubbing. The serologic profile of patients with stage IV disease is also evident in stage V. Stage V disease is generally thought to be the consequence of longstanding, often unrecognized disease, but it may occur occasionally among patients with little prior clinical evidence to suggest the diagnosis.

TABLE 46-3 Clinical Stages of ABPA

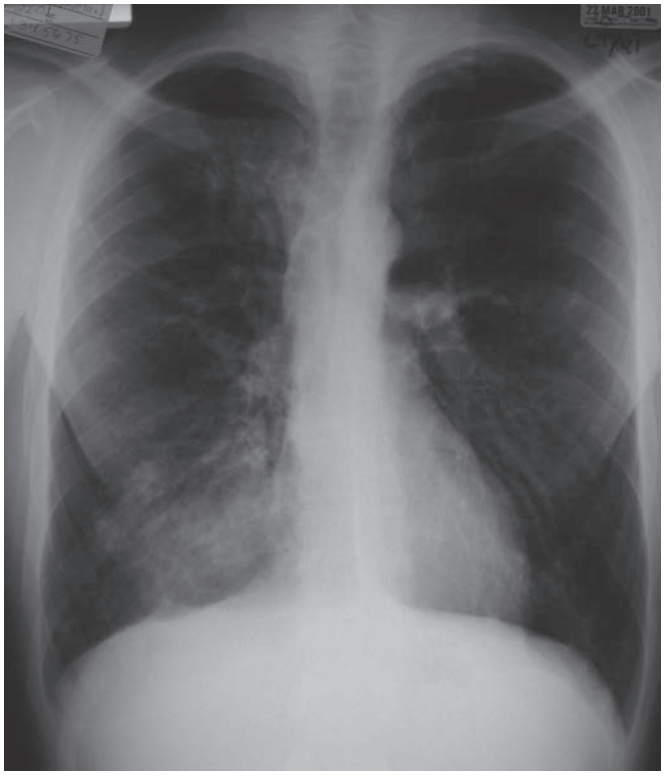
Stage I: Acute
Acute asthma symptoms
Elevated serum IgE (>1000 IU/mL)
Peripheral blood eosinophilia (may be absent in patients treated with oral corticosteroids)
Fleeting infiltrates on chest radiograph (may be absent in patients treated with oral corticosteroids)
Positive specific IgE, IgG, skin test reactivity, or precipitins to *Aspergillus fumigatus*
Responds to steroids/antifungal therapy
Stage II: Remission
Resolution of symptoms
Resolution of pulmonary infiltrates
Improvement in eosinophilia and *A. fumigatus* specific blood abnormalities
Stage III: Exacerbation/Recurrence
Recurrence/worsening of clinical symptoms
Recurrent pulmonary infiltrates
Rising IgE levels
Stage IV: Steroid-Dependent Asthma
Refractory steroid-dependent asthma
Persistently elevated serum IgE levels
Persistently elevated *A. fumigatus*–specific blood abnormalities
Stage V: Fibrotic Lung Disease
Refractory, steroid-dependent asthma
Fibrotic lung disease (irreversible obstructive and restrictive defects with impaired diffusing capacity)
Chronic bronchiectasis symptoms (sputum production, frequent infections)

DIAGNOSTIC STUDIES

In addition to the blood abnormalities described earlier in this chapter, analysis of BAL fluid from patients with ABPA often reveals

moderate eosinophilia (especially in steroid-naive patients) and increased levels of *Aspergillus*-specific IgE and IgA, but not IgG.[55] On bronchoscopy, mucoid impaction may be evident, and bronchial brushings may reveal mucus that contains aggregates of eosinophils, fungal hyphae, and eosinophil-derived Charcot–Leyden crystals. The finding of hyphae-filled mucus plugs is considered pathognomonic for ABPA. Pulmonary function tests typically reveal an obstructive ventilatory defect (due to bronchospasm or mucus impaction of the bronchi) during stages I, III, IV, and often V, and may not correlate with the duration of ABPA or asthma. Patients with stage V disease typically also have a restrictive ventilatory defect and a reduced DL_{CO}.

The typical radiographic manifestations of ABPA include parenchymal infiltrates and bronchiectasis (Figs. 46-2C and 46-3). The infiltrates are often irregular and transient (1–6 weeks) and have a predilection for the upper lobes, although all lobes may be affected. The bronchiectasis is classically cylindric and proximal (central), occurring within the proximal two-thirds of the lung (Fig. 46-2B). Mucoid impaction in dilated bronchi leads to a characteristic (but nonspecific) radiographic appearance of ABPA termed the "finger in glove" opacity on chest radiograph. "Tramline shadows" (parallel linear shadows extending from the hilum in bronchial distribution and reflecting longitudinal views of inflamed, edematous bronchi), "toothpaste shadows" (representing mucoid impaction of the bronchi), "ring shadows" (dilated bronchi with inflamed bronchial walls seen on end), local consolidation, or lobar collapse also are common features. Involvement of the small airways may lead to centrilobular nodules and branching tree-in-bud opacities (Fig. 46-2C). Less



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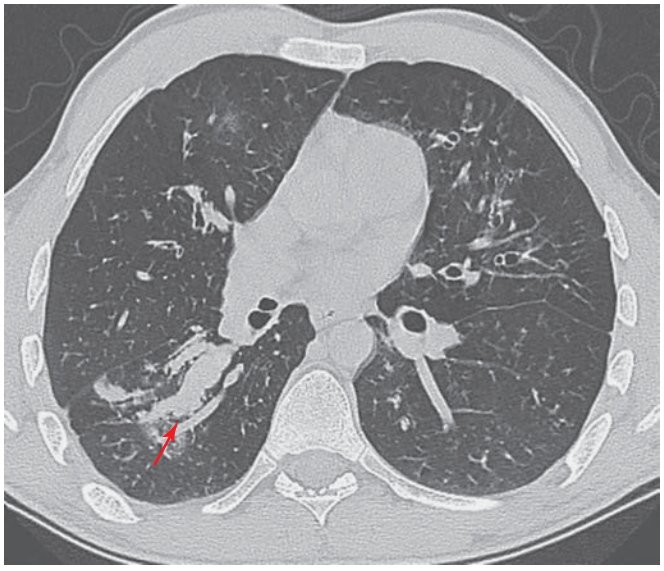

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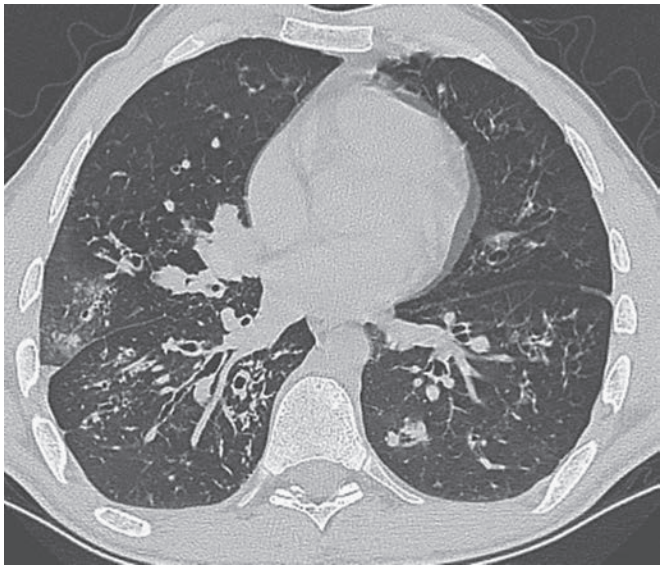

C

Figure 46-2 A 27-year-old man with a history of moderate asthma, recurrent bronchitis, and mild hemoptysis. Serologic studies were consistent with ABPA (IgE, 9490 IU/mL) and radiographic studies were consistent with bronchiectasis. **A.** PA chest x-ray shows hyperinflated lungs, bronchial dilatation, and right lower lobe opacity consistent with mucoid impaction. **B.** High-resolution CT scan image of impacted bronchus *(arrow)* and chronic inflammatory changes. **C.** Dilated central bronchus consistent with cylindrical/central bronchiectasis.

Figure 46-3 Representative CT image of the lungs of a 41-year-old woman who presented with stage V ABPA after a long history of mild asthma (IgE, 1500 IU/mL). Pulmonary function studies demonstrated severe combined obstructive and restrictive defects. CT shows bilateral upper lobe scarring and emphysematous changes.

common radiographic findings include bullous changes, pneumothorax, pleural effusion, cavitating nodular lesions, aspergilloma (Fig. 46-4), and migratory parenchymal opacities, with a ground-glass appearance. High-resolution CT scanning is the most reliable noninvasive means of detecting proximal bronchiectasis. It has largely supplanted chest radiographs to monitor ABPA patients over time and generally correlates with IgE and eosinophil levels.[56]

Surgical lung biopsy is usually not required to establish the diagnosis of ABPA and may not show specific findings, so it is generally not recommended. Histopathologic findings include intense bronchocentric inflammation with prominent eosinophilia, as well as lymphocytes, plasma cells, and monocytes. Bronchi may be filled and/or impacted with copious mucus plugs containing fibrin, Charcot–Leyden crystals, Curschmann spirals, and fungal hyphae. Bronchiectasis of segmental and subsegmental bronchi may be evident. Regions of bronchocentric granulomatosis, eosinophilic pneumonia, eosinophilic microabscesses, lymphocytic or desquamative interstitial pneumonitis, proliferative or obliterative bronchiolitis, lipoid pneumonia, or interstitial fibrosis also may be seen.

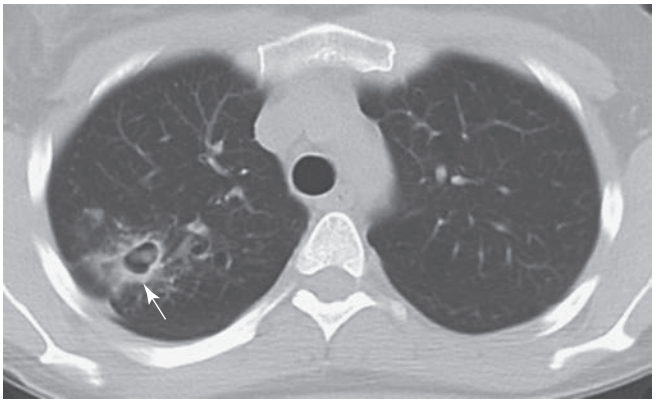

Figure 46-4 A 21-year-old woman with ABPA, who responded to treatment with oral corticosteroids and chronic antifungal therapy and then developed an aspergilloma *(arrow)* and hemoptysis. Amphotericin paste injection failed, and the patient ultimately underwent a right upper lobe lobectomy for chronic hemoptysis.

TREATMENT

The goals of treatment for individuals with ABPA consist of controlling symptoms, preventing exacerbations, and preserving normal lung function.

Systemic corticosteroids are the mainstay of therapy for ABPA. Without treatment, ABPA may cause significant irreversible lung damage due to bronchiectasis and pulmonary fibrosis. Therefore, initiation of appropriate treatment early in the course of disease is essential. Although most data are derived from small uncontrolled trials and definitive proof that corticosteroid therapy prevents the development of central bronchiectasis is lacking, retrospective studies suggest that early therapeutic intervention using corticosteroids reduces progression or irreversible lung damage.

Therapy for stage I or III disease (acute presentation and exacerbations of disease) should include prednisone, 0.5 to 1 mg/kg a day for 2 weeks, followed by 0.5 mg/kg every other day for 6 to 8 weeks with a taper (by 5–10 mg every 2 weeks) over weeks to months. The duration of treatment and pace of taper must be guided by activity and severity of disease with an aim of minimizing cumulative exposure to systemic corticosteroids. A low maintenance dose (e.g., 5.0–7.5 mg/d) may be required to control the disease and prevent recurrence in some patients.

Corticosteroid therapy leads to relief of symptoms, decreases in airflow obstruction, greater than 35% reduction in serum IgE, reductions in peripheral blood eosinophils, and resolution of pulmonary infiltrates. IgE levels should be monitored within a few months of an acute episode or exacerbation and should be followed periodically thereafter since levels may rise, reflecting increasing disease activity prior to an exacerbation in the absence of clinical symptoms. Escalation of steroid therapy should be considered if IgE levels rise more than 100%. Pulmonary function testing should be followed closely as well and imaging should be conducted intermittently if the disease is quiescent.

Although treatment of acute exacerbations is believed to be helpful in preventing fibrotic complications of ABPA, it is not known if early detection and treatment of disease flares has any effect on disease progression. Therefore, high-dose systemic corticosteroid treatment of asymptomatic individuals is not recommended. Patients with CF and ABPA flares may derive symptomatic or functional improvement from steroid treatment. However, patients with CF who are on steroids should be followed closely for the development of invasive or semi-invasive aspergillosis. It is unclear whether development of ABPA alters the course of CF disease progression.

Although not advocated as primary treatment, inhaled corticosteroids are useful for control of bronchospasm and may help minimize the dose of systemic steroid necessary to control symptoms. They can spare the need for systemic steroids during the treatment of ABPA exacerbations and the chronic management of symptoms. Adjuvant treatment with bronchodilators and antibiotics also helps control bronchospasm and secondary respiratory infections.

The development of oral antifungal agents has brought new hope to patients with ABPA.[57,58] Even though the current concept of ABPA is not that of a classic "infection," evidence is mounting to support use of the antifungal agent, itraconazole, in patients with ABPA. The presumed mechanism of action is that these agents minimize the degree of fungal colonization.

In one randomized controlled study, itraconazole (200 mg twice daily for 16 weeks) led to significant reductions in corticosteroid dose, decreased IgE levels, greater resolution of pulmonary infiltrates, and gains in exercise tolerance or pulmonary function.[59] Several clinical studies have demonstrated that treatment with itraconazole also reduces *Aspergillus* antibody titers and eosinophilia compared with placebo.[57]

Itraconazole treatment (200 mg/d or every other day) is generally recommended for patients with ABPA who are steroid dependent,

who have frequent relapses, and in whom the cost and risks are thought not to outweigh the potential benefits. Itraconazole has also demonstrated utility in ABPA associated with CF. If itraconazole is used, steady-state blood levels can be checked after 1 to 2 weeks, 4 h after the dose is given, to assess drug absorption.[60]

Since itraconazole interferes with the hepatic metabolism of several medications, including cyclosporine, oral hypoglycemics, tacrolimus, terfenadine, cisapride, and midazolam, particular caution should be exercised with its use among patients taking any of these medications. Physicians must also be mindful of adrenal insufficiency associated with itraconazole treatment among patients with ABPA using inhaled corticosteroids, as itraconazole may cause reduced steroid clearance and/or possible direct suppression of adrenal steroid production. Interval screening for adrenal insufficiency should be considered among such persons. In contrast, the efficacy of itraconazole in ABPA may be less among persons taking agents that raise gastric pH, as this can reduce drug absorption.

Other antifungal agents, including nystatin, amphotericin B, miconazole, clotrimazole, and natamycin, are generally ineffective in controlling ABPA. Ketoconazole may be effective, but its utility is limited by hepatotoxicity. Efficacy of voriconazole has not yet been studied in ABPA, but anecdotal reports from our center and others suggest similar results to itraconazole.[61–64]

More recently, the new biologically engineered antibodies against T2 inflammatory mediators may help to control symptoms and reduce the need for systemic corticosteroids in patients with difficult-to-control ABPA. The first of these biologics directed against IgE, omalizumab, has been used successfully in ABPA but has not been studied in large randomized trials. Given that the recommended dosing of this biologic is based on patient weight and serum IgE level, many patients with ABPA are outside of the dosing range used in asthma. However, multiple case reports and small series indicate that at conventional doses (up to 375 mg subcutaneously every 2 weeks), administration may improve disease activity and spare oral corticosteroid dosing.[65–74] In addition, the biologics developed more recently against IL-4/13 (dupilumab), IL-5 (mepolizumab and reslizumab), and IL-5R (benralizumab) are being used with some anecdotal success in ABPA.[75,76]

In addition to medical therapy, all patients with ABPA-related bronchiectasis should be prescribed standard airway clearance treatments, including hypertonic saline and mucus clearance device (positive expiratory pressure device) and/or percussion vest, depending on the severity of disease. In addition, patients with ABPA should avoid areas and environmental conditions associated with high mold counts, such as decomposing organic materials and moldy indoor environments. HEPA filters may be useful if such exposures are unavoidable, but data are limited.

PROGNOSIS

With appropriate treatment, long-term control of ABPA is feasible, and durable remissions are common. Treatment of stage I disease using corticosteroids typically results in decreased sputum production, improved control of bronchospasm, >35% reduction in total IgE within 8 weeks, clearing of precipitating antibodies, and resolution of radiographic infiltrates. IgE levels typically do not completely normalize, but they generally decrease by approximately one-half of peak levels seen in the acute stage. Progression of stage IV disease to pulmonary fibrosis may be prevented if patients are maintained on low-dose steroids; most patients with stage V disease have a stable course over several years. Persons with an FEV_1 persistently <0.8 L have a worse prognosis.

In addition to severe airflow obstruction and pulmonary fibrosis, long-term complications of ABPA occasionally include the development of aspergilloma (Fig. 46-4), chronic or recurrent lobar atelectasis, allergic *Aspergillus* sinusitis, or *Aspergillus* tissue invasion and semi-invasive *Aspergillosis*. Transplantation has been undertaken successfully among patients with ABPA but should not be considered a cure, as post-transplant recurrence of ABPA has been reported.

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