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review and meta-analysis to help differentiate asthma/chronic obstruc tive pulmonary disease overlap syndrome, and has been shown in some studies to correlate with the presence of eosinophils in the sputum and blood and with response to inhaled corticosteroids, although data are conflicting. For example, in a systematic review and meta-analysis, FeNO elevation increased the odds of having asthma in both children above the age of 5 years and adults. In another systematic review of FeNO utilization in the management of adults with asthma, the assess ment was helpful in the management of severe exacerbations but had no significant impact on overall exacerbations or inhaled corticoste roid use. Moreover, evidence suggests that tailoring of asthma therapy based on sputum eosinophil levels was effective in decreasing asthma exacerbations, but tailoring of therapy based on FeNO was not benefi cial in improving outcomes, and insufficient evidence was observed to advocate the use of either sputum analysis or FeNO in clinical practice. FeNO has also been shown to be influenced by ethnicity, and appropri ate reference standards for different ethnic groups have yet to be estab lished. While FeNO has been proposed as a potential clinical guide to management, its use has not been incorporated into all guideline rec ommendations, and it has not been formally approved for clinical use. ■ ■SWEAT TESTING Assessment of chloride concentration in sweat using pilocarpine ion tophoresis, or sweat testing, remains a key element in the diagnostic framework of cystic fibrosis (CF). This method utilizes pilocarpine to stimulate sweat production. As patients with CF suffer from alterations to the sodium chloride ion channel, measurement of electrolytes in their secretions such as sweat reveals elevated chloride concentrations, among other abnormalities. This testing has been considered the gold standard in the diagnosis of CF due to its functional nature, its relative noninvasiveness, the establishment of validated standards for its per formance, and its ability to discriminate between healthy individuals and those with CF at a chloride concentration of ≥60 mmol/L. The likelihood of a diagnosis of CF at a concentration of <40 mmol/L has been observed to be low, and an indeterminate range was defined as 40–59 mmol/L, which could be consistent with the disease if genetic and clinical manifestations were supportive. While functional testing such as sweat chloride testing remains an essential component of diagnostic algorithms in CF, the evolution of genetic analysis has led to identification of an extensive array of genetic mutations associated with varied phenotypic impacts in this disease. In this context, the indeterminate range of chloride concentrations of 40–59 mmol/L on sweat test analysis was found to inadequately identify milder or more heterogenous forms of the disease associated with newly identified genetic mutations. As a result, the Cystic Fibrosis Foundation provided updated guidance for the interpretation of sweat test results, with a decreased lower threshold to define an intermedi ate range of chloride concentration (changed from 40–50 mmol/L to 30–59 mmol/L), which could be consistent with the diagnosis of CF in the appropriate genetic and clinical context. In a subsequent analysis, utilization of the new guidance was found to enhance the probability of identifying patients with CF without

increasing the false-positive diagnosis rate in the population. Sweat testing is a critical component of the CF diagnostic algorithm but should be interpreted in the context of clinical manifestations of disease and correlated with genetic testing in those suspected of the diagnosis. ■ ■ALLERGY TESTING Allergy testing is often considered in the assessment of environmental exposures, including seasonal allergens, food allergens, and drug aller gens. In the case of drug allergens in particular, drug reactions are often reported based on remote history and are often unconfirmed. The hesi tancy to re-expose patients with an unconfirmed drug allergy can lead to limited options for treatment, to delay in treatment, and to utilization of treatments with more extended spectrum, potentially influencing the resistance patterns of these agents. Drug reactions can be medi ated by IgE (immediate-type reactions, type I), IgG or IgM (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions mediated by cellular immune mechanisms (type IV).

Skin testing, including patch testing and/or delayed intrader mal testing, is available to test exposure to particular allergens and determine reactivity. These tests have been shown to aid in clinical phenotyping of type I reactions and potentially in type IV reactions, though their role in type IV assessment remains more controversial. In the context of suspected type I reactions, patch testing is more cost effective and may be as effective as intradermal testing in identifying potential causative agents. The negative predictive value of intrader mal skin testing in assessing for IgE-mediated drug allergies is high; however, the high sensitivity of this testing limits its specificity, and results must be interpreted in the context of the pretest probability and the clinical experience of the patient. Skin tests have also been demonstrated to assist in identifying the causative agent in type IV reactions and to assess cross-reactivity between structurally related drugs. Intradermal testing may be more sensitive than patch testing to assess for type IV drug reactions. Though some debate continues regarding a mandatory role for skin testing in the assessment of potential drug allergies, drug provocation testing or rechallenge is generally regarded as safe in low-risk individuals with history of urti caria or immediate rash, whereas skin testing has been proposed as a preliminary assessment in higher-risk individuals with a history of two or more reactions, angioedema, or anaphylaxis, prior to consid eration of drug provocation testing.

Asthma CHAPTER 298 ■ ■FURTHER READING Callister ME et al: British Thoracic Society guidelines for the inves tigation and management of pulmonary nodules. Thorax 70:ii1, 2015. Deng CJ et al: Clinical updates of approaches for biopsy of pulmonary lesions based on systematic review. BMC Pulm Med 18:146, 2018. Dragonieri S: Methodological aspects of induced sputum. Adv Resp Med 5:397, 2023. Shepherd W: Image-guided bronchoscopy for biopsy of periph eral pulmonary lesions. In: UpToDate. Post TW (ed). UpToDate, Waltham, MA, 2023. Silvestri G et al: Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence based clinical practice guidelines. Chest 143:e211s, 2013. Thunnissen FBJM: Sputum examination for early detection of lung cancer. J Clin Pathol 56:805, 2003. Webb WR: Thin-section CT of the secondary pulmonary lobule: Anatomy and the image. The 2004 Fleischner Lecture. Radiology 239:322, 2006. Section 2 Diseases of the Respiratory System Elliot Israel

Asthma Asthma is a disease characterized by episodic airway obstruction and airway hyperresponsiveness usually accompanied by airway inflam mation. In most cases, the airway obstruction is reversible, but in a subset of asthmatics, a component of the obstruction may become irreversible. In a large proportion of patients, the airway inflammation is eosinophilic, but some patients may present with differing types of airway inflammation, and in some cases, there is

no obvious evidence of airway inflammation.

Genetic susceptibility Risk genes and atopy Symptomatic or asymptomatic asthma

• AHR

+/−

• Inflammation

• Structural changes Exposures and risk factors (See Table 298-1)

• Prenatal

• Childhood

• Adult Increased symptoms or exacerbations

+/−

• Increased AHR

• Increased inflammation

• Structural changes PART 7 Disorders of the Respiratory System FIGURE 298-1 Asthma development pathway. Illustration of how genetic susceptibility and development and exposure during the life span interact to produce a disease that can vary in intensity and chronicity. Disease expression is characterized by airway hyperresponsiveness with varying degrees of airway inflammation and airway structural changes accompanied by varying degrees of symptoms that can be influenced by exposure to triggers that can cause acute deterioration as well as chronic symptoms. AHR, airway hyperresponsiveness. MANIFESTATIONS Asthma most frequently presents as episodic shortness of breath, wheezing, and cough, which can occur in relation to triggers but may also occur spontaneously. These symptoms can occur in combination or separately. Other symptoms can include chest tightness and/or mucus production. These symptoms can resolve spontaneously or with therapy. In some patients, wheezing and/or dyspnea can be persistent. Episodes of acute bronchospasm, known as exacerbations, may be severe enough to require emergency medical care or hospitalization and may result in death. EPIDEMIOLOGY Asthma is the most common chronic disease associated with sig nificant morbidity and mortality, with ~262 million people affected globally. Cross-sectional studies suggest that 7.9% of the population in the United States is asthmatic as compared to ~4.3% prevalence world wide. Prevalence continues to increase (starting at 7.3% in 2001 in the United States) and is associated with transition from rural to urban living. Asthma is more prevalent among children (8.4%) than adults (7.7%). In children, the prevalence is greatest among boys (2:1 maleto-female ratio), with a trend toward greater prevalence in women in adulthood. In some patients, asthma resolves as they enter adulthood only to “recur” later in life. In the United States in 2016, prior to the effects of the COVID-19 pandemic, 1.8 million people visited an emergency department for asthma, and 189,000 were hospitalized.

The total economic cost in the United States in 2013 was estimated at $82 billion. In the United States, asthma is more prevalent in blacks than Caucasians, and black race is associated with greater case morbidity. The ethnicity with the greatest prevalence in the United States is the Puerto Rican population. Asthma mortality increased worldwide in the 1960s, apparently related to overuse of inhaled β2-agonists. Reduction in mortality since then has been attributed to increased use of inhaled corticosteroids. Asthma mortality declined globally from 0.44 per 100,000 people in 1993 to 0.19 in 2006, but further reduction in mortality has not occurred since that time. THE PATHWAY TO THE DEVELOPMENT

OF ASTHMA The pathway to development of asthma can be varied. As illustrated in Fig. 298-1, there is an interplay between genetic susceptibility (see below) and environmental exposure and endogenous developmental factors (e.g., aging and menopause [see “Etiologic Mechanisms, Risk

Triggers (See Table 298-2) Unknown factors Recurrent exacerbations Factors, Triggers, and Complicating Comorbidities” and Table 298-1]) that can lead to the development of asthma. Continued or additional exposures and triggers (Table 298-2) can affect the progression of disease and the degree of impairment. PATHOPHYSIOLOGY ■ ■MECHANISMS LEADING TO ACUTE

AND CHRONIC AIRWAY OBSTRUCTION The pathobiologic processes in the airways that lead to episodic and chronic airway obstruction of asthma are discussed below. Their patho logic correlates are highlighted in Fig. 298-2, illustrating the pathologic changes that can occur in asthmatic airways. These processes can occur individually or simultaneously. There can be temporal variation of these processes in an individual based on exogenous factors, discussed later in this chapter, as well as the aging process itself. These processes can involve the entire airway (but not the parenchyma), but there can be significant spatial heterogeneity, as has now been demonstrated using hyperpolarized gas ventilation studies and high-resolution com puted tomography (CT) of the thorax. Airway Hyperresponsiveness Airway hyperresponsiveness is a hallmark of asthma. It is defined as an acute narrowing response of the airways in reaction to agents that do not elicit airway responses in nonaffected individuals or an excess narrowing response to inhaled agents as compared to that which would occur in nonaffected individu als. A component of the hyperresponsiveness occurs at the level of the airway smooth muscle itself as demonstrated by hyperresponsiveness to direct smooth-muscle–acting agents such as histamine or metha choline. In many patients, the apparent hyperresponsiveness is due TABLE 298-1 Exposures and Risk Factors Related to the Development of Asthma

1. Allergen exposure in those with a predisposition to atopy
2. Occupational exposure
3. Air pollution
4. Infections (viral and Mycoplasma)
5. Tobacco
6. Obesity
7. Diet
8. Fungi in allergic airway mycoses
9. Acute irritants and reactive airway dysfunction syndrome (RADS)
10. High-intensity exercise in elite athletes

TABLE 298-2 Triggers of Airway Narrowing

1. Allergens
2. Irritants
3. Viral infections
4. Exercise and cold, dry air
5. Air pollution
6. Drugs
7. Occupational exposures
8. Hormonal changes
9. Pregnancy to indirect activation of airway narrowing mechanisms as a result of stimulation of inflammatory cells (which release direct bronchocon strictors and mediators that cause airway edema and/or mucus secre tion) and/or stimulation of sensory nerves that can act on the smooth Normal Airway Cross-section Asthmatic Airway Cross-section Submucosa Epithelium Smooth muscle Thin mucus layer Adventitia FIGURE 298-2 Pathologic changes that can be seen in asthmatic airways. Illustrated is a cross-sectional lumen of a bronchus. The left-hand side represents the normal airway, and the right represents an asthmatic airway highlighting the pathologic changes that can be seen in asthma. The asthmatic airway lumen is reduced by smoothmuscle contraction and hypertrophy, mucus in the airway lumen, and thickening of the submucosa due to edema and cellular infiltration. In addition, the ability of the lumen to increase in size with smooth-muscle relaxation may be impaired by deposition of collagen. The epithelium is disrupted, and there is evidence of vascular and neuronal proliferation. All these changes may not be present in one individual, and certain patients may have normal-appearing airways.

muscle or inflammatory cells. Agents and physical stimuli that elicit such responses are discussed later.

The apparent increased responsiveness of the airways in asthma may also have a structural etiology. In asthma, airway wall thickness is associated with disease severity and duration. This thickening, which may result from a combination of smooth-muscle hypertrophy and hyperplasia, subepithelial collagen deposition, airway edema, and mucosal inflammation, can result in a tendency for the airway to narrow disproportionately in response to stimuli that elicit increased airway muscle tension. A major therapeutic objective in asthma is to decrease the degree of airway hyperresponsiveness. Asthma CHAPTER 298 Inflammatory Cells While airway inflammation can be precipi tated by acute exposure to inhalants, most asthmatics have evidence of chronic inflammation in the airways. Most commonly, this inflamma tion is eosinophilic in nature. In some patients, neutrophilic inflam mation may be predominant, especially in those with more severe Invagination of airway mucosa due to smoothmuscle constriction Smooth muscle hypertrophy and proliferation Airway edema Mucus production Cellular infiltration Lumen Collagen deposition and thickening of the basement membrane Epithelial denudation and shedding Neuronal proliferation Vascular proliferation

asthma. Patients with both eosinophilic and neutrophilic inflammation may present with the most severe phenotype. Mast cells are also more frequent. Many inflammatory cells are present in an

activated state, as will be discussed in the section on inflammation. Airway Smooth Muscle Airway smooth muscle can contribute to asthma in three ways. First, it can be hyperresponsive to stimuli, as noted above. Second, hypertrophy and hyperplasia can lead to airway wall thickening with consequences for hyperresponsiveness, as noted above. Lastly, airway smooth-muscle cells can produce chemokines and cytokines that promote airway inflammation and promote the survival of inflammatory cells, particularly mast cells. Subepithelial Collagen Deposition and Matrix Deposition

Thickening of the subepithelial basement membrane occurs as a result of deposition of repair-type collagens and tenascin, periostin, fibronec tin, and osteopontin primarily from myofibroblasts under the epithe lium. The deposition of collagen and matrix stiffens the airway and can result in exaggerated responses to increased circumferential tension exerted by the smooth muscle. Such deposition can also narrow the airway lumen and decrease its ability to relax and thus can contribute to chronic airway obstruction. Airway Epithelium Airway epithelium disruption takes the form of separation of columnar cells from the basal cells. The damaged epithelium is hypothesized to form a trophic unit with the underlying mesenchyme. This unit elaborates multiple growth factors thought to contribute to airway remodeling. The airway epithelium is also a source of multiple cytokines, such as alarmins, and mediators that have been shown to promote a cascade of airway inflammation. Vascular Proliferation In a subset of asthmatics, there is a sig nificant degree of angiogenesis thought to be secondary to elaboration of angiogenic factors in the context of airway inflammation. Vascular leakage from postcapillary venules in response to inflammatory media tors can also contribute to the acute and chronic edema of the airways. Airway Edema Submucosal edema can be present as an acute response in asthma and as a chronic contributor to airway wall thickening.

PART 7 Disorders of the Respiratory System Epithelial Goblet Cell Metaplasia and Mucus Hypersecretion

Chronic inflammation can result in the proliferation of mucus cells. Increased mucus production can reduce the effective airway luminal area. Mucus plugs can obstruct medium-size airways and can extend into the small airways. These mucus plugs can result in persistent air way obstruction. Neuronal Proliferation Neurotrophins, which can lead to neuro nal proliferation, are elaborated by smooth-muscle cells, epithelial cells, and inflammatory cells. Neuronal inputs can regulate smooth-muscle tone and mucus production, which may mediate acute bronchospasm and potentially chronically increased airway tone. ■ ■AIRWAY INFLAMMATION (TYPE 2 AND

NON–TYPE 2 INFLAMMATION) Most asthma is accompanied by airway inflammation. In the past, asthma had been divided into atopic and nonatopic (or intrinsic) asthma. The former was identified as relating to allergen sensitivity and exposure, with production of IgE, and occurring more commonly in children. The latter was identified as occurring in individuals with later onset asthma, with or without allergies, but frequently with eosin ophilia. This paradigm is being superseded by a nosology that favors consideration of whether asthma is associated with type 2 or non–type 2 inflammation. This approach to immunologic classification is driven by a developing understanding of the underlying immune processes and by the development of therapeutic approaches that target type 2 inflammation (see later sections on asthma therapy). Type 2 Inflammation Type 2 inflammation is an immune response involving the innate and adaptive arms of the immune sys tem to promote barrier immunity on mucosal surfaces. It is called type 2 because it is associated

with the type 2 subset of CD4+ T-helper cells, which produce the cytokines interleukin (IL) 4, IL-5, and IL-13. As

shown in Fig. 298-3, these cytokines can have pleiotropic effects. IL-4 induces B-cell isotype switching to production of IgE. IgE, through its binding to basophils and mast cells, results in environmental sensitivity to allergens as a result of cross-linking of IgE on the surface of these mast cells and basophils. The products released from these cells include type 2 cytokines as well as direct activators of smooth-muscle constric tion and edema. IL-5 has a critical role in regulating eosinophils. It con trols formation, recruitment, and survival of these cells. IL-13 induces airway hyperresponsiveness, mucus hypersecretion, and goblet cell metaplasia. While allergen exposure in allergic individuals can elicit a cascade of activation of type 2 inflammation, it is now understood (see Fig. 298-3) that nonallergic stimuli can elicit production of type 2 cytokines, particularly due to stimulation of type 2 innate lymphoid cells (ILC2). These cells can produce IL-5 and IL-13. ILC2s can be acti vated by epithelial cytokines known as alarmins, which are produced in response to “nonallergic” epithelial exposures such as irritants, pol lutants, oxidative agents, fungi, or viruses. Thus, these “nonallergic” stimuli can be associated with eosinophilia. The development of anti–IL-5 drugs that dramatically reduce eosinophils has allowed us to determine that, in many asthmatics, eosinophils play a major role in asthma pathobiology. They may induce hyperresponsiveness through release of oxidative radicals and major basic protein, which can disrupt the epithelium. They produce cysteinyl-leukotrienes that directly stimulate smooth muscle contrac tion and resulting in airway constriction. In addition, recent CT imag ing has suggested that mucus plugs, which may contain significant amounts of eosinophil aggregates, may accumulate in the airways and contribute to asthma severity. Non–Type 2 Processes As shown in Fig. 298-2, multiple processes can contribute to airway narrowing and apparent airway hyperrespon siveness. While type 2 inflammatory processes are most common, non–type 2 processes can exist either in combination with type 2 inflammation or without type 2 inflammation. Neutrophilic inflamma tion, as shown in Fig. 298-3, can also occur. This type of inflammation is more commonly seen in severe asthma that has not responded to the common anti-inflammatory therapies, such as corticosteroids, that usually suppress type 2 inflammation. In some cases, it may also be associated with chronic infection, occasionally with atypical pathogens such as Mycoplasma, perhaps accounting for the response of some of these patients to macrolide antibiotics. It is also commonly seen in reactive airway dysfunction syndrome (see “Etiologic Mechanisms, Risk Factors, Triggers, and Complicating Comorbidities”). In a small subset of asthmatics, the pathologic changes seen in Fig. 298-2 may occur without any evidence of tissue infiltration by inflammatory cells. The etiology of such pauci-granulocytic asthma is unclear. ■ ■MEDIATORS Many chemical substances or signaling factors can contribute to the pathobiologic picture of asthma. Some of them have been successfully targeted in developing asthma therapies. Cytokines As illustrated in Fig. 298-3, and as discussed above, IL-4, IL-5, and IL-13 are the major cytokines associated with type 2 inflam mation. They have all been targeted successfully in asthma therapies. Thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 also play a role in the signaling cascade and are being actively studied as targets for treatment of asthma. IL-9 has been implicated as well. IL-6, IL-17, tumor necrosis factor α (TNF-α), IL-1β, and IL-8 have been implicated in non–type 2 inflammation. Fatty Acid Mediators Proinflammatory mediators derived from arachidonic acid include leukotrienes and prostaglandins. The cys teinyl leukotrienes (leukotrienes C4, D4, and E4) are produced by eosinophils and mast cells. They are potent smooth-muscle constrictors. They also stimulate mucus secretion, recruit allergic inflammatory cells, cause microvascular leakage,

modulate cytokine production, and influence neural transmission. Cysteinyl leukotriene

FIGURE 298-3 Inflammatory cells and mediators involved in type 2 and non–type 2 inflammation. Allergens and nonallergic stimuli can trigger activation of multiple inflammatory cells and release of mediators that are responsible for recruiting and activating these cells. The mediators can affect airway smooth-muscle proliferation and hyperresponsiveness and fibroblast proliferation and matrix deposition. BLT2, leukotriene B4 receptor 2; CRTH2, chemoattractant receptor-homologous molecule (PGD2 receptor); CXCL8, CXC motif chemokine ligand 8; CXCR2, CXC chemokine receptor 2; GATA3, GATA binding protein 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL, interleukin; ILC2, innate lymphoid type 2 cells; c-Kit, mast/stem cell growth factor receptor; LTB4, leukotriene B4; MPO, myeloperoxidase; NO, nitric oxide; OX40L/OX40R, OX40 ligand/OX40 receptor; PGD2, prostaglandin D2; ROS, reactive oxygen species; SCF, stem cell factor; TGF-β, transforming growth factor β; Th, T helper; TNF-α, tumor necrosis factor α; TSLP, thymic stromal lymphopoietin. modifiers have shown clinical benefit in asthma. The non-cysteinyl leukotriene, LTB4, is produced primarily from neutrophils but can also be synthesized by macrophages and epithelial cells. It is a potent neutrophil chemoattractant. Prostaglandins are for the most part proinflammatory. Prostaglandin D2 (PGD2) is produced by mast cells. Receptors for PGD2 (CRTH2 receptors) are present on TH2 cells, ILC2 cells, mast cells, eosinophils, macrophages, and epithelial cells, and the activation of these receptors upregulates type 2 inflammation. However, studies with drugs blocking CRTH2 have been relatively disappointing thus far. There are several classes of fatty acid–derived mediators that are responsible for the resolution of inflammation. These include the resolvins and lipoxins. Several studies suggest that deficiencies in these moieties may be responsible for the ongoing inflammation in asthma, especially in severe asthma. Nitric Oxide Nitric oxide is a potent vasodilator, and in vitro stud ies suggest that it can increase mucus production and smooth-muscle proliferation. It is produced by epithelial cells, especially in response to IL-13, and by stimulated inflammatory cells including eosinophils, mast cells, and neutrophils. Its precise role in the asthmatic diathesis is unclear. However, its production is increased in the airways in the presence of IL-13-induced inflammation, and it can be detected in exhaled breath and is reduced by interventions that interfere with IL-13 production or activity.

Asthma CHAPTER 298 Reactive Oxygen Species When allergens, pollutants, bacteria, and viruses activate inflammatory cells in the airway, they induce respi ratory bursts that release reactive oxygen species that result in oxidative stress in the surrounding tissue. Increases in oxidative stress have been shown to affect smooth-muscle contraction, increase mucus secretion, produce airway hyperresponsiveness, and result in epithelial shedding. Chemokines A variety of chemokines are secreted by the epithe lium (as well as other inflammatory cells) and attract inflammatory cells into the airways. Those of particular interest include eotaxin (an eosinophil chemoattractant), TARC and MDC (which attract TH2 cells), and RANTES (which has pluripotent pro-phlogistic effects). ETIOLOGIC MECHANISMS, RISK FACTORS, TRIGGERS, AND COMPLICATING COMORBIDITIES As illustrated in Fig. 298-1, the development of asthma involves an interplay between risk factors and exposures (see Table 298-1) and genetic predisposition. ■ ■HERITABLE PREDISPOSITION Asthma has a strong genetic predisposition. Family and twin stud ies suggest a 25–80% degree of heritability. Genetic studies sug gest complex polygenic inheritance complicated by interaction with environmental exposures. Further, epigenetic modifications related

to environmental exposures may also produce heritable patterns of asthma. Many of the genes related to asthma have been associated with risk for atopy. However, there appear to be genetic modifications that predispose to asthma and its severity. Association studies have identi fied multiple candidate genes. In many cases, these genes vary from population to population. The most consistently identified include ORMDL3/GSDMB (in the 17q21 chromosomal region), ADAM33, DPP-10, TSLP, IL-12, IL-33, ST2 (IL-33 receptor), HLA-DQB1, HLADQB2, TLR1, IL-13, and IL6R. Several of these genes have been identi fied in relation to the pathways involved in airway inflammation (Fig. 298-3). Regulation of ORMDL3 has been associated with altered TH2 cytokine levels. It is important to note that there is consider able evidence of ancestry heterogeneity (difference in the strength of genetic association by ancestry) so that, for example, an association with PYHIN1 (interferon inducible protein X) is only found among people of African descent. In many cases, association studies have iden tified polymorphisms in noncoding regions of the genome, suggesting that the majority of the currently identified traits act as “enhancers” of biologic processes.

PART 7 Disorders of the Respiratory System Genetic polymorphisms have also been associated with differential responses to asthma therapies. Variants in the β-receptor (Arg16Gly in ADRB2), the glucocorticoid-induced transcript 1 gene, and genes in the leukotriene synthesis and receptor pathways have been associated with altered response to the pharmacologic agents acting at those receptors or through those pathways. While genetic variation plays a key role in asthma susceptibility, it is important to understand that unraveling the complexities of the genetic contribution to asthma remains elusive. To wit, only 7.2% of asthma risk can be explained by the single nucleotide polymorphisms that have been associated with asthma. Recently, polygenic risk score analysis has been used as a tool to attempt to improve the prediction of asthma risk. A significant proportion of the heritability of asthma relates to the heritability of atopy. Atopy is the genetic tendency toward specific IgE production in response to allergen exposure. Serum levels of IgE correlate closely with the development of asthma. The National Health and Nutrition Examination Survey (NHANES) III found that half of asthma in patients aged 6–59 could be attributed to atopy with evidence of allergic sensitization. The allergens most associated with risk include house dust mites, indoor fungi, cockroaches, and indoor animals. ■ ■EXPOSURES AND RISK FACTORS Allergic Sensitization and Allergen Exposure Like asthma, the development of allergic sensitization involves an interplay between heritable susceptibility and allergen exposure. Allergen exposure during vulnerable developmental periods is believed to increase the risk of development of allergic sensitization in those with a tendency toward atopy. Allergic sensitization is increased in industrialized nations. Research comparing rural environments has suggested that early, varied microbiome exposure (exposure to bacteria and bacterial products) may reduce the development of atopy. Studies of the role of early allergen avoidance in reducing the risk of developing asthma have produced contradictory results. Tobacco Maternal smoking and secondhand smoke exposure are associated with increased childhood asthma. Childhood secondhand smoke exposure increased asthma risk twofold. Active smoking is estimated to increase the incidence of asthma by up to fourfold in ado lescents and young adults. Air Pollution Early life exposure to pollution increases the risk of development of asthma. Proximity to major roadways increases the risk of early childhood asthma, thought to be attributed to levels of nitro gen dioxide exposure. Decreasing nitrogen dioxide exposure has been found to decrease asthma incidence in children. Studies of exposure to mixed pollutants suggest that most risk lies with carbon monoxide and nitric dioxide, with marginal effects of sulfur dioxide. Indoor air pollution from

open fires and use of gas stoves has been associated

with increased risk of children developing asthma symptoms. Mecha nistically, pollutants are thought to cause oxidative injury to the air ways, producing airway inflammation and leading to remodeling and increased risk of airway sensitization. Infections Respiratory infections clearly can precipitate asthma deteriorations. However, the degree to which respiratory infections indicate susceptibility to asthma, represent a causal factor, or in some cases provide protection from asthma is unclear. Incidence and fre quency of human rhinovirus and respiratory syncytial virus infections in children are associated with development of asthma, but whether they play a causal role is unclear. Evidence of prior Mycoplasma pneu moniae infection has been associated with the development of asthma in Taiwanese adults. Occupational Exposures Occupational asthma is estimated to account for 10–25% of adult-onset asthma. The occupations associ ated with the most cases in European Community Health Surveys were nursing and cleaning. Two types of exposures are recognized: (1) an immunologic stimulus (further subdivided into high-molecularweight [e.g., proteins, flour] and low-molecular-weight [e.g., formal dehyde, diisocyanate] stimuli based on whether they act as haptens or can directly stimulate a response), and (2) an irritative stimulus. The immunologic form is associated with a latency period between time of exposure and development of symptoms. The irritative form, known as reactive airway dysfunction syndrome (RADS), will be discussed below. A combination of genetic predisposition (including atopy), tim ing, intensity of exposure, and co-exposure (e.g., smoking) influences whether an individual will develop occupational asthma. Diet There are suggestions that prenatal diet or vitamin deficiency may alter the risk of developing asthma. The evidence is not yet definitive, but vitamin D insufficiency may increase asthma risk in the progeny and supplementation may decrease such risk. Similarly, preliminary studies suggest that maternal supplementation with vita mins C and E and zinc may decrease asthma in children. One study suggested that maternal polyunsaturated fatty acid supplementation may decrease childhood asthma risk. Observational studies have sug gested that increased maternal sugar intake may increase childhood asthma risk. Obesity Multiple studies suggest that obesity may be a risk factor for development of childhood and adult asthma. Adipokines and IL-6 have been thought to play a pathobiologic role. Some have argued that the risk is overestimated, and a study from NHANES II found an asso ciation with dyspnea but not with airway obstruction. Medications There are conflicting data regarding prenatal and early childhood risk for asthma posed by certain classes of medica tions. Use of H2 blockers and proton pump inhibitors in pregnancy has been associated with an increased risk of asthma in children (relative risk, 1.36–1.45); however, another study found a small risk for H2 blockers only. Conflicting data have been presented on the risk of perinatal acetaminophen and early childhood acetaminophen use. In a prospective study, the use of acetaminophen was not associated with an increased risk of exacerbations in young children with asthma, when compared to ibuprofen. Prenatal and Perinatal Risk Factors Preeclampsia and pre maturity have been associated with increased risk of asthma in the progeny. Babies born by cesarean section are at higher risk for asthma. Those with neonatal jaundice are also at increased risk. Breast-feeding reduced early wheezing but has a less clear effect on later incidence of asthma. Endogenous Developmental Risk Factors Asthma is more prevalent among boys than girls, with the difference receding by age 20 and reversing (with increased prevalence among women) by age 40. Atopy is more prevalent among boys in childhood, and they have reduced airway size compared with girls. Both factors are thought to contribute to the sex discrepancy. A subset of women develop asthma

around menopause. Such asthma tends to involve non–type 2 mecha nisms. Pregnancy may precipitate or aggravate asthma as well. High-Concentration Irritant Exposure and RADS A solitary exposure to a high concentration of irritant agents that rapidly (usually within hours) produces bronchospasm and bronchial hyperactivity is known as RADS. Causative agents include oxidizing and reducing agents in an aerosol or high levels of particulates. The acute pathol ogy usually involves epithelial injury with neutrophilia. There is little evidence of type 2 inflammation. This syndrome differs from occupa tional asthma in that these patients have not become sensitized to the provocative agent and can return to work in that environment once they have recovered. However, the course of the disease may be vari able, with some series showing documented abnormalities and persis tent symptoms 10 years after exposure. Fungi and Allergic Airway Mycoses One to 2% of patients with asthma may have an IgE-mediated sensitization to colonization of the airway by fungi, with the most common fungus causing such a reac tion being Aspergillus fumigatus. So-called allergic bronchopulmonary aspergillosis (ABPA) is characterized by a type 2 airway inflammatory response to aspergillus with IgE >1000 IU/mL, eosinophils >500/μL, positive skin test to Aspergillus, and specific IgE and IgG antibodies to Aspergillus. Patients may have intermittent mucus plugging and central bronchiectasis. Up to two-thirds of patients will grow Aspergillus from the sputum. Treatment involves systemic antifungal treatment with itraconazole or voriconazole and oral corticosteroids. A role for biolog ics has also been suggested. Exercise-Induced Symptoms in Elite Athletes Exerciseinduced airway narrowing in elite athletes undertaking extreme exercise in strenuous condition. These athletes may have little, or no, airway hyperreactivity or asthma risk factors. The condition may involve additional mechanisms including direct epithelial injury. Such a syndrome has also been reported in swimmers possibly related to pool chlorination. ■ ■TRIGGERS OF AIRWAY NARROWING The risk factors and exposures reviewed above lead to increased airway reactivity and a propensity to react to factors that trigger airway narrowing (see Fig. 298-1). Almost all asthmatics can iden tify triggers that will make their asthma worse. The major triggers are listed in Table 298-2. Many of them overlap with the risk factors and etiologic factors reviewed above. In some cases, elimination of these triggers may dramatically reduce the impairment caused by asthma. In a minority, abatement can lead to “remission” so that these patients no longer require asthma medications and do not experience bronchospasm with their daily activities and routines. While acute exposures to these triggers generally cause short-lived bronchospasm, the bronchospasm may be severe enough that treat ment for an exacerbation is required. Chronic exposure may lead to permanent deterioration in asthma control, although this does not appear to be true for exercise or stress. It should be noted that evidence suggests that severe asthma exacerbations (those requiring systemic corticosteroids) may, in and of themselves, accelerate lung function decline. Allergens In patients with sensitization to particular allergens through production of allergen-specific IgE, exposure to those aller gens by inhalation can result in activation of mast cells and basophils with acute production of bronchoactive mediators (see Fig. 298-3). Such exposure can produce immediate bronchospasm (early response) and a late response (2–24 h after exposure) with bronchial narrowing and inflammation. These mechanisms can account for reactions to inhalation of pollens, mold, or dust; insects (especially cockroaches); animals; occupational materials; seasonal worsening of asthma; and socalled “thunderstorm asthma.” Chronic exposure may lead to persistent symptoms. While food allergies can produce bronchospasm through anaphylaxis, food allergies are generally not etiologically linked to asthma.

Irritants Many asthmatics report increased symptoms on expo sure to strong odors, smoke, combustion products, cleaning fluids, or perfumes. In general, the effects are short-lived, although

chronic exposure (see “Occupational Exposures” above) and large-quantity exposures (see discussion of RADS above) can lead to long-lasting or permanent symptoms.

Viral Infections Most asthmatics report that asthma exacerba tions can be triggered by upper respiratory infections. The inflamma tion that occurs may be neutrophilic as well as eosinophilic. There is some evidence that IgE generation may reduce production of inter feron, possibly predisposing to the effects of upper respiratory viruses. Increased airway reactivity after viral infections generally persists for 4–6 weeks but, in some cases, may be associated with permanent changes and impairment. The almost 50% reduction in exacerbations during the COVID-19 pandemic has been attributed to decreased viral infections. Asthma CHAPTER 298 Exercise and Cold/Dry Air Exercise may be a trigger to asth matic bronchoconstriction in patients with asthma. Hyperventilation that occurs with exercise dries the airway lining, changing the tonicity of lining cells and causing release of bronchoconstrictive mediators. This effect is more prominent the lower the moisture content of the air, and since cold air has a lower absolute moisture content, the lower the temperature of the inspired air, the less exercise is required to induce bronchoconstriction. In addition, cold air may produce airway edema during airway wall rewarming. At routine levels of exercise, these effects are short-lived. Air Pollution Increased rates of exacerbations have been associ ated with increased ambient ozone, sulfur dioxide, and nitrogen diox ide, among other air pollutants. Drugs Beta blockers may trigger bronchospasm even when used solely in ophthalmic preparations. While the more selective beta block ers are safe for most asthmatics, beta blocker use may be a cause of difficult-to-control asthma. Aspirin may precipitate bronchospasm in those with aspirin-exacerbated respiratory disease (see “Special Con siderations”). Angiotensin-converting enzyme (ACE) inhibitors (and to a lesser extent angiotensin receptor blockers) may cause cough that may be attributed to poorly controlled asthma. Occupational Exposures In addition to RADS (see above), epi sodic and/or recurrent exposures to workplace irritants and/or sub stances to which one has become sensitized can produce symptoms. These symptoms are usually reduced when patients are away from such exposures on weekends or vacation. Stress Asthmatics may report increased symptoms with stress. The mechanisms are poorly understood. Hormonal Factors A small proportion of women report a regu lar increase in perimenstrual symptoms, and symptoms may worsen during perimenopause. This may be related to rapid fluctuations in estrogen levels. Pregnancy can precipitate worsening of asthma in approximately one-third of pregnant patients. ■ ■COMORBIDITIES Comorbidities may make asthma difficult to manage, and the common comorbidities are listed in Table 298-3. Obesity Obese adults with asthma have more severe asthma symp toms than lean adults and are two to four times more likely to be hos pitalized with an asthma exacerbation. Nonrandomized studies have shown an improvement and significant reduction in exacerbations after bariatric surgery. Gastroesophageal Reflux Disease The presence of gastroesoph ageal reflux disease (GERD) predicts poor quality of life and is an inde pendent predictor of asthma exacerbations. Treatment of symptomatic reflux disease has been shown to produce modest improvements in airway function, symptoms, and exacerbation frequency. Treatment of asymptomatic patients has not shown a benefit.

TABLE 298-3 Differential Diagnosis and Comorbidities That May Make Asthma Difficult to Control Differential Diagnosis of Diseases with Overlapping Symptoms That Can Present with Obstructive Pulmonary Function Tests

1. Heart failure

2. Chronic obstructive pulmonary disease (COPD)
3. α1 Antitrypsin deficiency
4. Airway obstruction from mass or foreign body
5. Inducible laryngeal dysfunction (vocal cord dysfunction)
6. Bronchiolitis obliterans
7. Bronchiectasis
8. Tracheobronchomalacia PART 7 Disorders of the Respiratory System Comorbidities That Can Make Asthma Difficult to Control
9. Chronic rhinosinusitis +/– nasal polyposis
10. Obesity
11. Gastroesophageal reflux disease
12. Inducible laryngeal obstruction (vocal cord dysfunction)
13. COPD
14. Anxiety/depression
15. Obstructive sleep apnea Rhinosinusitis and/or Nasal Polyposis Rhinosinusitis may be a manifestation of the eosinophilic inflammation in the lower airway in asthma. In addition, poorly controlled rhinosinusitis is believed to aggravate asthma by several potential mechanisms including inflam matory and irritant effects of the secretions on the lower airway, neural reflexes, and production of inflammatory mediators and cells that pro duce systemic inflammation. Treatment with intranasal corticosteroids has been shown to decrease airway reactivity and emergency depart ment visits and hospitalizations. Evidence for the benefit of surgical therapy is inconclusive. There is increasing evidence that biologics tar geted at type 2 inflammation may also be particularly useful for asthma associated with rhinosinusitis and polyposis in particular. Nasal polyposis is rare in children, and its presence in adults with asthma should raise suspicions of aspirin-exacerbated respiratory dis ease (see “Special Considerations”). Inducible Laryngeal Obstruction Previously known as vocal cord dysfunction, this process involves inappropriate narrowing of the larynx, producing resistance to airflow; it can complicate asthma as well as mimic it, and it is more commonly seen in women and patients with anxiety and depression. Definitive diagnosis involves laryngos copy during symptomatic episodes or during induced obstruction. Chronic Obstructive Pulmonary Disease (COPD) See “Asthma-COPD Overlap” under “Special Considerations.” Anxiety/Depression Increased rates of asthma exacerbations occur in asthmatics with anxiety, depression, or chronic stress. Some patients may be unable to distinguish anxiety attacks from asthma. DIAGNOSIS AND EVALUATION ■ ■APPROACH A presumptive diagnosis of asthma can usually be made based on a compatible history of recurrent wheezing, shortness of breath, chest tightness, or cough related to common bronchoconstrictor precipi tants when appropriate components of the differential diagnosis have been considered and/or eliminated. In some cases, a therapeutic trial of low-dose inhaled corticosteroid (ICS) may be considered. In all but the mildest cases, the diagnosis should be confirmed with pulmonary function testing or demonstration of airway hyperresponsiveness. Unfortunately, the diagnosis may be difficult to confirm after initia tion of therapy since airway obstruction and hyperresponsiveness may be mitigated with therapy. A trial of tapering medications may be necessary. Studies have shown that more than one-third of patients with a physician diagnosis of asthma do not meet the criteria for the diagnosis.

Adjunctive evaluation, as outlined below, should be undertaken to identify precipitating factors and underlying mechanisms that may be amenable to specific therapies (e.g., allergen avoidance). Cases that require more than a daily moderate-dose ICS combined with a long-acting β2-agonist (LABA) (together known as ICS/LABA) should undergo more formal evaluation to assess comorbidities that may make asthma difficult to control and a reassessment of any pos sible confounding diagnoses that may mimic asthma symptoms (see Table 298-3). ■ ■PRIMARY ASSESSMENT TOOLS FOR ESTABLISHING A DIAGNOSIS History Patients with asthma most commonly complain of episodes of wheezing, shortness of breath, chest tightness, mucus production, or cough upon exposure to triggers listed in Table 298-2. Symptoms may be worse on arising in the morning. Some may have nocturnal symptoms alone. The latter such patients should be evaluated for post nasal drip or GERD if that is their sole presenting symptom. Patients frequently complain of symptoms with rapid changes of temperature or humidity. Exercise-induced symptoms are common and frequently reported with increased sensitivity to cold air. As compared to cardiac sources of dyspnea, exercise symptoms tend to develop more slowly after initiation of exercise and tend to resolve more slowly unless a β2agonist is administered after the onset of symptoms. A careful exposure history should be obtained for home (e.g., pets, molds, dust, direct or secondhand smoke), work (work environment and exposure to occupational sensitizers), and recreational (e.g., hobbies, recreational inhalants) exposures. Allergen-sensitized patients may complain of symptoms on exposure to known allergens such as animals and may complain of increased symptoms during specific pollen seasons. Up to two-thirds of patients with asthma will be atopic (as opposed to half of the U.S. population), and almost half will have a history of rhinitis, with many complaining of intermittent sinusitis. In patients with adultonset asthma, a careful occupational history should be obtained and a history of reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) or use of new medications, such as beta blockers (including ophthalmic preparations) and ACE inhibitors (due to potential cough), should be elicited. Physical Examination In between acute attacks, physical findings may be normal. Many patients will have evidence of allergic rhinitis with pale nasal mucus membranes. Five percent or more of patients may have nasal polyps, with increased frequency in those with more severe asthma and aspirin-exacerbated respiratory disease. Some patients will have wheezing on expiration (less so on inspiration). During an acute asthma attack, patients present with tachypnea and tachycardia, and use of accessory muscles can be observed. Wheezing, with a prolonged expiratory phase, is common during attacks, but as the severity of airway obstruction progresses, the chest may become “silent” with loss of breath sounds. Pulmonary Function Tests Effective reduction of the airway lumen in asthma produces increased resistance to airflow, which can be detected as a reduction in expiratory airflow during forced expiratory maneuvers. The peak expiratory flow rate (PEFR), forced expiratory volume in 1 s (FEV1), and the FEV1/forced vital capacity (FVC) ratio are reduced below the lower limit of normal. The flow-volume loop may show a characteristic scalloping (see Chap. 297). These findings may not be present during acute attacks or on therapy (especially after recent use of bronchodilators). Reversibility has been newly defined as ≥10% increase in the FEV1 percent of predicted (e.g., 60% predicted to 70% predicted) at least 15 min after administration of a β2-agonist or after several weeks of corticosteroid therapy. Many continue to use the prior definition of a 12% increase in the baseline FEV1 with a minimum 200-mL change. Diurnal peak flow variability of >20% has also been proposed as an indicator of reversible airways disease, but it is less reliable due to difficulties with quality control and variability of home assessments. Lung volumes and diffusing capacity should be normal in uncomplicated asthma. In more severe asthma with severe

airway obstruction, lung volumes may indicate air trapping, and total lung capacity may be under- or overestimated depending on whether body box or gas dilution methods, respectively, are utilized. Oscillom etry, which does not require forced expiratory maneuvers, is gaining increased use and can be particularly useful for diagnosing large airway and variable tracheal obstruction. Assessment of Airway Responsiveness In cases where pulmo nary function tests are nonconfirmatory and the diagnosis remains in doubt, testing to demonstrate increased reactivity to provocative stim uli in the laboratory can be undertaken. Methacholine, a cholinergic agonist, inhaled in increasing concentrations is most commonly used. A provocative dose producing a 20% drop in FEV1 (PD20) is calculated, with a cumulative value ≤400 μg indicative of airway reactivity. Man nitol is used as well, and occasionally, hypertonic saline may be used. Challenge with exercise and/or cold, dry air can be performed, with a positive response recorded if there is a ≥10% drop in FEV1 from base line. In the case of suspected environmental/occupational exposures, specific allergen challenges may be undertaken in specialized labs. ■ ■ADJUNCTIVE ASSESSMENT TOOLS Eosinophil Counts A large proportion of asthma patients not treated with oral or high-dose ICSs will have eosinophil counts ≥300 cells/μL. Eosinophil counts correlate with severity of disease in population studies. Their presence in patients with severe asthma indicates a likelihood that the patient would respond to medications targeted at type 2 inflammation. Extremely elevated levels should prompt consideration of eosinophilic granulomatosis with polyangiitis or primary eosinophilic disorders. IgE, Skin Tests, and Radioallergosorbent Tests Total serum IgE levels are useful in considering whether patients with severe asthma would be eligible for anti-IgE therapy. Levels >1000 IU/mL should prompt consideration of ABPA. Skin tests, or their in vitro counterparts that detect IgE directed at specific antigens (radioallergosorbent test [RAST]), can be useful in confirming atopy and suggesting allergic rhi nitis, which can complicate asthma management. Allergy investigations may be useful, when correlated with a history of reactions, in identifying environmental exposures that may be aggravating asthma. Exhaled Nitric Oxide Fraction of exhaled nitric oxide (FeNO) in exhaled breath is an indicator of type 2 inflammation (particularly IL-13 induced) in the airways. It is easily suppressed by ICSs and, thus, can be used to assess adherence in patients in whom it was initially elevated. Elevated levels (>35–40 ppb) in untreated patients are indica tive of type 2 inflammation. Levels >20–25 ppb in patients with severe asthma on moderate- to high-dose ICS indicate either poor adherence or persistent type 2 inflammation despite therapy. ■ ■ADDITIONAL EVALUATION IN SEVERE/POORLY RESPONSIVE ASTHMA In patients with poorly responsive asthma, additional evaluations for comorbidities (see Table 298-3) may be necessary, including sinus radiographic studies (even in those who have no symptoms of sinus disease) and esophageal studies in those who have symptoms of reflux. In patients with nonreversible disease, many obtain a serum α1 anti trypsin level. Additionally, the following evaluations may be of utility in poorly responsive asthma. Chest CT Chest CT can be useful to assess for the presence of bron chiectasis and other structural abnormalities that could produce airway obstruction. New image analysis tools are being used in the research setting to assess airway properties such as airway wall thickness, airway diameter, mucus plugging, and evidence of air trapping. Sputum Induced sputum may be used in more specialized centers to help characterize type 2 and non–type 2 inflammation by detection of eosinophils and neutrophils, respectively. In severe asthma, there is some evidence that some patients may have localized persistent eosino philic airway inflammation despite lack of peripheral eosinophils on blood analysis.

TABLE 298-4 Goals of Asthma Therapy

1. Reduction in symptom frequency to ≤2 times/week
2. Reduction of nighttime awakenings to ≤2 times/month
3. Reduction of reliever use to ≤2 times a week (except before exercise)
4. No more than 1 exacerbation/year
5. Optimization of lung function
6. Maintenance of normal daily activities
7. Satisfaction with asthma care with minimal or no side effects of treatment Asthma CHAPTER 298 TREATMENT Asthma GOALS OF ASTHMA THERAPY AND

ASSESSMENT OF CONTROL Goals of asthma therapy in terms of achieving control of symptoms and reducing risk (as reflected in frequency of asthma exacerba tions) are listed in Table 298-4. The therapeutic agents used in treatment are discussed below, and an integrated approach to care is discussed subsequently. A comprehensive treatment approach involves avoiding and reducing asthma triggers and, if necessary, the adjunctive use of medications. Asthma medications are primarily divided into those that relax smooth muscle and produce a fairly rapid relief of acute symptoms and those that target inflammation or mediator produc tion. The former medications are commonly referred to as reliever medications, and the latter are known as controller medications. REDUCING TRIGGERS Mitigation As shown in Tables 298-1 and 298-2, triggers and exposures can cause asthma and make it difficult to control. In the case of those with occupational exposures, removal from the offending environment may sometimes result in complete resolu tion of symptoms or significant improvement. Secondhand smoke exposure and frequent exposure to combustion products of can nabis are remediable environmental exposures as well. The removal of pets that are clearly associated with symptoms can reduce symp toms. Pest control at home and in the school in those with evidence of IgE-mediated sensitivity (skin test or IgE RAST) may also be beneficial. The effect of dust or mold control in reducing asthma symptoms has been more variable. There is moderate evidence that dust control (impermeable mattress and pillowcase covers) in those patients with symptoms and sensitization may be effective in reduc ing symptoms only when conducted as part of a comprehensive allergen mitigation strategy. Allergen Immunotherapy Allergen immunotherapy reduces IgEmediated reactions to the allergens administered. It clearly reduces the symptoms of allergic rhinitis and thus may be helpful in reduc ing this comorbidity. The evidence for its effectiveness in isolated asthma in those who are sensitized and have clinical symptoms is variable. Due to the risk of anaphylaxis, guidelines generally rec ommend immunotherapy only in patients whose asthma is under control and who have mild to moderate asthma. The evidence base for the effectiveness of sublingual allergen immunotherapy in the treatment of asthma is not substantial. Vaccination Respiratory infections are a major cause of asthma exacerbations. Adult patients with asthma are strongly advised to receive the currently available pneumococcal vaccines (regardless of age) and yearly influenza vaccines. COVID-19 vaccination and the respiratory syncytial virus vaccines are advised, as well. MEDICATIONS Bronchodilators Bronchodilators relax airway smooth muscle. There are three major classes of bronchodilators, β2-agonists, anti cholinergics, and theophylline. a2-Agonists Available in inhaled or oral form, these agents acti vate β2-receptors present on airway smooth muscle. Such receptors

are also present on mast cells, but they contribute little to the effi cacy of these agents in asthma. β2-receptors are G protein–coupled receptors that activate adenyl cyclase to produce cyclic AMP, which results in relaxation of smooth muscle. Use β2-Agonists are primarily used in inhaled forms

to provide relief of bronchospasm or to reduce the degree of bronchospasm anticipated in response to exercise or other provocative stimuli. Regular use has been associated with tachyphylaxis of the bron choprotective effect and possible increased airway reactivity. This may be more common in patients with a polymorphism at the 16th amino acid position of the β2-receptor. Frequent short-acting β2agonist use has been associated with increased asthma mortality, resulting in decreased enthusiasm for their use in isolation without inhaled corticosteroids. Short-Acting a2-Agonists (SABAs) Albuterol (also known as salbutamol) is the most commonly used agent. Bronchodila tion begins within 3–5 min of inhalation, and effects generally last 4–6 h. It is most commonly administered by metered-dose inhaler. Solutions for nebulization are also used, especially for relief of bronchospasm in children. Oral forms are available but are not commonly used.

PART 7 Disorders of the Respiratory System Long-Acting a2-Agonists Salmeterol and formoterol are the two available LABAs. They have an ~12-h duration of action. For moterol has a quick onset comparable to the SABAs. Salmeterol has a slower onset of action. These agents can be used for prophylaxis of exercise-induced bronchospasm. In contrast to their use in chronic obstructive pulmonary disease (COPD), these agents are not rec ommended for use as monotherapy in the treatment of asthma. Their use in asthma is generally restricted to use in combination with an ICS. Ultra-Long-Acting a2-Agonists These agents (indacaterol, olo daterol, and vilanterol) have a 24-h effect. They are only used in combination with ICSs in the treatment of asthma. Safety β2-Agonists are fairly specific for the β2-receptors, but in some patients and especially at higher doses, they can produce tremor, tachycardia, palpitations, and hypertension. They promote potassium reentry into cells, and at high doses, they can produce hypokalemia. Type B (nonhypoxic) lactic acidosis can also occur and is thought to be secondary to increased glycogenolysis and gly colysis and increased lipolysis, leading to a rise in fatty acid levels, which can inhibit conversion of pyruvate to acetyl-coenzyme A. Increased asthma mortality was associated with high-potency β2-agonists in Australia and New Zealand. Increased use of β2agonists for relief of bronchospasm is a clear marker of poor asthma control and has been associated with increased mortality. Questions had been raised as to whether adding LABAs to ICS might be associated with severe adverse asthma outcomes, but several studies have not detected such outcomes in comparison to maintaining the ICS dose. Anticholinergics Cholinergic nerve–induced smooth-muscle constriction plays a role in asthmatic bronchospasm. Anticholiner gic medications can produce smooth-muscle relaxation by antago nizing this mechanism of airway narrowing. Agents that have been developed for asthma have been pharmacologically designed to be less systemically absorbed so as to minimize their systemic anticho linergic effects. The long-acting agents in this class are known as long-acting muscarinic antagonists (LAMAs). Use The short-acting agents in this class can be used alone for acute bronchodilation. They appear to be somewhat less effective than β2-agonists and have a slower onset of action as well. Safety Dry mouth may occur. At higher doses and in the elderly, acute glaucoma and urinary retention have been reported. There was a numerical (but not significant) difference in mortality in African Americans treated with ICS/LAMA versus ICS/LABA for asthma.

Theophylline Theophylline, an oral compound that increases cyclic AMP levels by inhibiting phosphodiesterase, is now rarely used for asthma due to its narrow therapeutic window, drug-drug interactions, and reduced bronchodilation as compared to other agents. Controller (Anti-Inflammatory/Antimediator) Therapies So-called “controller” therapies reduce asthma exacerbations and improve long-term control, decreasing the need for intermittent use of

bronchodilator therapies. None of these therapies have yet been shown to prevent progression of airway remodeling or the more rapid decline in lung function that can occur in a subset of asthma patients. Corticosteroids Corticosteroids are particularly effective in reducing type 2 inflammation and airway hyperresponsiveness. Corticosteroids bind to a cytoplasmic glucocorticoid receptor to form a complex that translocates to the nucleus. The complex binds to positive and negative response elements that result in inhibition of T-cell activation; eosinophil function, migration, and prolifera tion; and proinflammatory cytokine elaboration and activation of nuclear factor-κB. It also attaches to other transcription factors, resulting in deactivation of other proinflammatory pathways. Use Corticosteroids reduce airway hyperresponsiveness, improve airway function, prevent asthma exacerbations, and improve asthma symptoms. Corticosteroid use by inhalation (ICSs) minimizes sys temic toxicity and represents a cornerstone of asthma treatment. ICS ICSs are the cornerstone of asthma therapy. They take advantage of the pleiotropic effects of corticosteroids to produce salutary impact at levels of systemic effect considerably lower than oral corticosteroids. Their use is associated with decreased asthma mortality. They are generally used regularly twice a day as first-line therapy for all forms of persistent asthma. Doses are increased, and they are combined with LABAs to control asthma of increasing severity (see next section "ICS/LABA and ICS/SABA"). European guidelines now recommend their intermittent use even in the mildest forms of asthma to reduce the likelihood of exacerbations. Longer-acting preparations permitting once-a-day use are avail able. Their effects can be noticeable in several days, but continued improvement may occur over months of therapy, with the major ity of improvement evident within the first month of regular use. Adherence to regular therapy is generally poor, with as few as 25% of total annual prescriptions being refilled. Very high doses are sometimes used to reduce oral corticosteroid requirements. Not all patients respond to ICS. Increasing evidence suggests that the most responsive patients are those with significant type 2–medi ated asthma. ICS/LABA and ICS/SABA ICSs are available in combination with a LABA. The combination produces asthma control using a lower dose of ICS. Guidelines suggest that they be considered for daily maintenance therapy once more than low-dose ICS are required for control. The World Health Organization Global Initiative for Asthma (GINA) Guidelines now suggest that Anti-Inflammatory Reliever (AIR) (a combination of a quick onset LABA (formoterol only) or a short acting beta-agonist, either of these agents combined with an inhaled corticosteroid (ICS/formoterol or ICS/SABA), be used instead of albuterol alone at ALL levels of severity (see Table 298-5 and "Approach to the Patient"). In the case of longacting beta-agonist, ONLY formoterol can be used in this manner since it acts quickly, whereas the other LABAs have a slower onset of action and therefore have not been evaluated. Currently, ICS/SABA is only available in the United States. Oral Corticosteroids Chronic oral corticosteroids (OCSs) at the lowest doses possible (due to side effects) are used in patients who cannot achieve acceptable asthma control without them. Alternateday dosing may be preferred. OCSs are also used to treat asthma exacerbations, frequently starting at a dose of 40–60 mg/d of pred nisone or equivalent with a rapid taper over 1–2 weeks. Since they

TABLE 298-5 Step Therapy for the Treatment of Asthma Ages 12+ (Modified from GINA and NAEPP) Address exposures and comorbidities (see Tables 298-2 and 298-3) Confirm inhaler technique and optimize adherence Move up or down steps based on control (see Table 298-3) STEP 1 STEP 2 STEP 3 STEP 4 STEP 5 Preferred regular therapy None Nonea or low-dose ICSb Low-dose ICS/formoterol Medium-dose ICS/formoterol High-dose ICS/LABA + add-on LAMA Alternative regular therapy None LTRA Medium-dose ICS High-dose ICS Anti-IgE or anti–IL-5 or anti–IL4-Rα or anti-TSLP Adjunctive therapy LTM, azithromycin, OCSc As-needed (PRN) reliever therapy ICS/formoterol

(low dose) or SABAb or ICS/SABAf ICS/formoterol (low dose)a, or PRN concomitant ICS and SABAa,b or SABAe,b or ICS/SABAf aIf using as-needed ICS/formoterol or PRN concomitant ICS and SABA, this is an option in which no regular daily therapy is prescribed. bNational Asthma Education and Prevention Program (NAEPP) recommendation. cTo be avoided as much as possible. dPRN ICS/formoterol only suggested for steps 3 and 4 by NAEPP. eIf using low-dose ICS as regular therapy. fAlternative GINA recommendation. Abbreviations: GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; ICS/LABA, combined ICS and LABA in one device; ICS/SABA, combined ICS and SABA in one device; IL, interleukin; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; LTM, leukotriene modifier; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PRN, as needed; SABA, short-acting β-agonist. are well absorbed, they may also be used for managing hospitalized patients. Intravenous Corticosteroids Intravenous preparations are fre quently used in hospitalized patients. Patients are rapidly transi tioned to OCS once their condition has stabilized. Intramuscular Corticosteroids In high-risk, poorly adherent patients, intramuscular triamcinolone acetonide has been used to achieve asthma control and reduce exacerbations. Safety Chronic administration of systemic corticosteroids is associated with a plethora of side effects including diabetes, osteo porosis, cataracts and glaucoma, bruising, weight gain, truncal obesity, hypertension, ulcers, depression, and accelerated cardiac risk, among others. Appropriate monitoring and infectious (pneu mocystis pneumonia prophylaxis for those treated chronically with ≥20 mg prednisone/d) and bone health prophylaxis are necessary. Intermittent “bursts” of systemic corticosteroids to treat asthma exacerbations are associated with reduced side effects, but observa tional studies have suggested that the cumulative dose over time is associated with deleterious side effects. ICSs have dramatically reduced side effects as compared to OCSs. At higher doses, bruising occurs and osteoporosis can accel erate. There is a small increase in glaucoma and cataracts. Local effects include thrush, which can be reduced by use of a spacer and gargling. Hoarseness may be the result of a direct myopathic effect on the vocal cords. Rare patients exhibit side effects even at mod erate doses of ICS. Children may experience growth suppression. Leukotriene Modifiers Agents that inhibit production of leu kotrienes (through inhibition of 5-lipoxygenase) or the action of leukotrienes at the CysLT1 receptor are moderately effective in asthma. They are also effective in reducing symptoms of allergic rhinitis. Montelukast, a CysLT1 antagonist, is frequently used in children with mild asthma due to concerns of ICS-related growth suppression. Leukotriene modifiers are effective in preventing exerciseinduced bronchoconstriction without the tachyphylactic effects that occur with regular use of LABAs. They are particularly effective in aspirin-exacerbated respiratory disease, which is characterized by significant leukotriene overproduction. They have also shown modest effect as add-on therapy in patients poorly controlled on high-dose ICS/LABA. CysLT1 Antagonists Montelukast and zafirlukast are administered orally once or twice daily, respectively. The onset of effect is rapid (hours), with the majority of chronic effectiveness seen within 1 month.

Asthma CHAPTER 298 ICS/formoterol (low or medium dose)d or ICS/SABAf 5-Lipoxygenase Inhibition Zileuton in its extended form is administered orally twice a day. Safety Montelukast is well tolerated, but has been associated with suicidal ideation. Zileuton increases liver function tests (transami nases) in 3% of patients. It inhibits CYP1A2. Cromolyn Sodium Cromolyn sodium is an inhaled agent believed to stabilize mast cells. It is only available by nebulization and must be administered two to four times a day. It is mildly to modestly effective and appears to be helpful for exercise-induced broncho spasm. It is used primarily in pediatrics in those concerned about ICS side effects. Anti-IgE Omalizumab, a monoclonal antibody to the Fc por tion of the IgE molecule,

prevents the binding of IgE to mast cells and basophils and thus blocks antigen-related signaling, which is responsible for production or release of many of the mediators and cytokines critical to asthma pathobiology. Over time, reduc tion in IgE production occurs as well. Anti-IgE has been shown to increase interferon production in rhinovirus infections, decrease viral-induced asthma exacerbations, and reduce the duration and peak viral shedding, probably due to interference with IgE's ability to reduce interferon γ production in response to viral infections. Use In asthma, anti-IgE has been tested in patients with a circulating IgE ≥30 IU/mL and a positive skin test or RAST to a perennial allergen. It is generally used in patients not responsive to moderate- to high-dose ICS/LABA. It reduces exacerbations by 25–50% and can reduce asthma symptoms, but has minimal effect on lung function. Anti-IgE is dosed based on body weight and cir culating IgE and is administered subcutaneously every 2–4 weeks depending on the calculated dose. In the United States, the maxi mum dose is 300 mg every 2 weeks, which generally restricts the drug to those with a body weight ≤150 kg. Most effects are gen erally seen in 3–6 months. Retrospective studies have suggested that patients with an exhaled nitric oxide approximately ≥20 ppb or circulating eosinophils ≥260/μL have the greatest response as ascertained by reduction in exacerbations. FeNO is slightly reduced by treatment, but circulating IgE, as measured by available clinical tests, is not affected since these tests measure total circulating IgE, not free IgE. Anti-IgE has also been found to be effective in patients with chronic idiopathic urticaria and nasal polyposis. Safety The incidence of side effects is low. Anaphylaxis has been reported in 0.2% of patients receiving the drug. IL-5–Active Drugs Mepolizumab and reslizumab are monoclonal antibodies that bind to IL-5, and benralizumab binds to the IL-5 receptor. They rapidly (within a day) reduce circulating eosinophils.

Use In patients symptomatic on moderate- to high-dose ICS/ LABA, generally with two or more exacerbations that require OCS per year and with an eosinophil count of ≥300/μL (unless they are on chronic OCS), IL-5–active drugs reduce exacerbations by about half or more. FEV1 and symptoms improve moderately as well. In patients who are not on chronic OCSs, these drugs are less effective in those with eosinophil counts <300/μL. In patients on chronic OCS, they reduce the need for OCSs regardless of circulating eosinophil count (presumably due to the fact that many of those patients have type 2 inflammation but their circulating eosinophils have been suppressed by the systemic OCS). FeNO and IgE are relatively unaffected by these drugs. Most clinical effects are usually seen within 3–6 months. Mepolizumab has been approved for treat ment of nasal polyposis. Safety These drugs are associated with minimal side effects.

PART 7 Disorders of the Respiratory System Anti–IL-4/13 The IL-4 and IL-13 receptors are heterodimers that share a common subunit, IL-4 receptor α. Dupilumab is an antibody that binds to this subunit and, thus, blocks signaling through both receptors. Use In addition to effectiveness in the phenotype of patients who respond to anti–IL-5 therapies, poorly controlled patients on moderate- to high-dose ICS/LABA with an FeNO of 20–25 ppb also appear to respond to dupilumab even if their peripheral eosino phils are not elevated. Dupilumab reduces exacerbations by ≥50%, decreases symptoms, and may produce more of an effect on FEV1 than anti–IL-5 drugs. It has been shown to be effective for patients requiring oral corticosteroids regardless of biomarker levels. It gradually reduces FeNO and IgE levels. Paradoxically, circulating eosinophil counts may initially temporarily increase. Most effects are seen by 3–6 months of therapy. It is also approved for nasal polyposis atopic dermatitis, eosinophilic esophagitis, and lupus pernio also approved for patients with COPD with exacerbations and elevated eosinophils. Safety Side effects are minimal, but cases

of serious systemic eosinophilia, most frequently associated with the reduction of oral corticosteroids, have been noted. Anti-TSLP Tezepelumab binds to TSLP, a proximal alarmin in the epithelial response cascade (Fig. 298-3). As a result, it affects multiple pathways and decreases blood eosinophils, FeNO, and IgE levels. Use In addition to effectiveness in patients who qualify for and respond to anti–IL-5 therapies and anti–IL-4/13, tezepelumab has some degree of effectiveness in patients with asthma who have recurrent exacerbations without evidence of elevated levels of FeNO or blood eosinophils. This agent reduces exacerbations by 50–70% and improves lung function and symptoms. Available studies have not been able to demonstrate effectiveness in atopic eczema or in reducing OCS dose. Most effects are seen within 3–6 months of therapy, and biomarker levels may continue to fall over time. Safety Minimal side effects have been reported. Bronchial Thermoplasty, Alternative Therapies, and Therapies Under Development • Bronchial Thermoplasty This proce dure involves radiofrequency ablation of the airway smooth muscle in the major airways administered through a series of three bron choscopies for patients with severe asthma. There is some evidence that it may reduce exacerbations in very select patients. The pro cedure may be accompanied by significant morbidity, and most guidelines do not recommend it other than in the context of clinical trials or registries. The manufacturer has discontinued production of the devices necessary for this procedure and it may no longer be available. Alternative Therapies Macrolides appear to be effective in a subset of asthmatics with poor response to other therapies and are suggested as possible adjunctive therapies in step 5 asthma (Table 298-5). Alternative therapies such as acupuncture and yoga

have not been shown to improve asthma in controlled trials. Stud ies with placebo have demonstrated that there may be a significant response to placebo. Therapies in Development Trials are underway targeting path ways and receptors shown in Fig. 298-3. Those in more advanced stages of development include therapies targeting IL-33, OX-40, and mediators involved in mucin production. Studies targeting IL-17 and TNF-α have not shown efficacy, but it is unclear if patients with appropriate endotypes were targeted. Proof-of-concept studies targeting mast cells via inhibition of tyrosine kinase have suggested efficacy in severe asthma. APPROACH TO THE PATIENT Asthma U.S. (National Asthma Education and Prevention Program [NAEPP]) and World Health Organization (Global Initiative for Asthma [GINA]) guidelines advise a symptomatic approach to asthma treatment assuming that appropriate measures have been taken to address asthma triggers, exposures, and comorbidities enumerated in Tables 298-2 and 298-3. Additionally, adherence and inhaler techniques need to be addressed. Poor adherence or poor inhaler technique has been identified as the cause of poor asthma control in up to 50% of patients referred for poorly controlled asthma. The stepwise approach to intensifying and reducing asthma therapy is outlined in Table 298-5. It involves “stepping” therapy up or down based on assessment of whether asthma is controlled by the criteria listed in Table 298-4. Assuming comorbidities have been addressed, adherence has been evaluated, education regard ing avoiding triggers has been performed, and inhaler technique is verified, the cornerstone of preferred therapy is the intensification of ICS therapy in conjunction with the use of a LABA to achieve greater control at lower ICS doses. A major change in the stepwise approach, advocated for more than two decades, has occurred. Evidence has accumulated that as-needed ICS can be used instead of regular ICS in milder asthma and that the trigger for such use could be patient perception of the need to use a reliever inhaler. This approach is now labeled AIR for Antiinflammatory Reliever. Since formoterol is a LABA with a rapid onset, combination ICS/formoterol has been used as a single agent in multiple studies: as needed without background therapy in milder asthma, and as needed in addition to twice-daily ICS/

formoterol in more severe asthma. Since asthma mortality can occur even in mild asthma (albeit at lower rates than more severe asthma), GINA, as part of a comprehensive strategy of asthma management, recommends ICS/formoterol be used as the reliever in all steps of asthma severity, including intermittent asthma (step 1). With recent introduction of a combination ICS/SABA in the United States, GINA recognizes use of this preparation as alternative antiinflammatory reliever that can be used in place of albuterol. NAEPP guidelines utilizing evidence-based studies recommend that ICS/ formoterol be used as the reliever medication in patients requiring step 3 and 4 therapy (see Table 298-5) and that as-needed concomi tant ICS and SABA can be used as a therapy in step 2. For the sake of simplicity, an adapted GINA approach is outlined in Table 298-5 with footnotes identifying the major differences from the NAEPP. Leukotriene receptor antagonists (LTRAs) are alternative medica tions in step 2, which may be used in those concerned about the minimal ICS side effects. However, recent warnings about suicidal ideation associated with montelukast may make this approach less appealing. Leukotriene modifiers and long-acting anticholinergics are possible add-on (adjunctive) therapies in those requiring step 4 and/or 5 therapies. Biologics are incredibly effective in their specific endotypes (type 2 with exacerbations and specific biomarkers, as previously described), but their high cost currently relegates them to step 5 therapy or beyond.

SPECIAL CONSIDERATIONS ■ ■ASTHMA ATTACKS Asthma deteriorations of mild to moderate severity can be initially treated with a β2-agonist administered up to every 1 h. Increasing the dose of ICSs by four- to fivefold may be helpful as well. If patients fail to achieve adequate control and continue to require β2-agonists hourly for several hours, they should be referred for urgent care. In the urgent care setting, PEFR or FEV1 should be assessed, and patients are usu ally treated with nebulized β2-agonists up to every 20 min. Those with PEFR >60% of predicted will frequently respond to β2-agonists alone. If they fail to respond in 1–2 h, intravenous corticosteroids should be administered. Supplemental oxygen is usually administered to correct hypoxemia. An LTRA and magnesium are sometimes given as well. Nebulized anticholinergics can be administered to produce additional bronchodilation. Failure to achieve PEFR >60% or persistent severe tachypnea over 4–6 h should prompt consideration of admission to the hospital. In-hospital treatment may include continuous bronchodilator nebulization. Noninvasive positive-pressure ventilation to assist with respiratory exhaustion is sometimes used to prevent a need for intuba tion, and helium-oxygen mixtures may be used to decrease the work of breathing. Antibiotics should be administered only if there are signs of infection. Most patients with asthma attacks present with hypocapnia due to a high respiratory rate. Normal or near-normal Pco2 in a patient with asthma in respiratory distress should raise concerns of impending respiratory failure and need for mechanical ventilation. Mechanical ventilation may be difficult in patients with status asthmaticus due to high positive pressures in the setting of high resistance to airflow due to airway obstruction. Mechanical ventilation should aim for low respiratory rates and/or low ventilation volumes to decrease peak airway pressures. This can frequently be achieved by “permissive hypercapnia”—allowing the Pco2 to rise and, if necessary, temporar ily correcting critical acidosis with administration of bicarbonate to increase the pH. Neuromuscular paralysis may sometimes be beneficial. Bronchoscopy to clear mucus plugs has been described but may be dangerous in the setting of difficulties with mechanical ventilation. ■ ■HIGH-RISK ASTHMA PATIENTS Three to four thousand people die from asthma in the United States each year. Table 298-6 lists characteristics of patients at high risk for asthma death. These characteristics should be considered in evaluating and treating patients who present with asthma. ■ ■EXERCISE-INDUCED SYMPTOMS In many cases, the degree of exercise intolerance may reflect poor asthma control. Treatment involves step therapy of asthma as

outlined in Table 298-5. In other cases, however, asthma may be well controlled in all other respects, but patients may report that they cannot under take the level of exercise they desire. Some increase in exercise capacity can be achieved by starting at lower levels of exercise (warming up) and by using a mask in colder weather to condition the air. Pretreat ment with a SABA can increase the threshold of ventilation required to induce bronchoconstriction. LABAs may extend the period of protec tion, but their use alone in asthma is to be discouraged. For occasional exercise, ICS/LABA can be used, but regular use may expose the patient to unnecessary doses of ICS. If regular exercise is undertaken, TABLE 298-6 Patients at Greater Risk for Asthma Mortality

1. History of intensive care unit admission for asthma
2. History of intubation for asthma
3. Illicit drug use
4. Depression
5. New diagnosis within past year
6. ≥2 emergency unit visits in past 6 months
7. Severe psychosocial problems
8. Lower socioeconomic status
9. On daily prednisone prior to admission

then LTRAs may provide protection and can be used regularly. A SABA (or ICS/formoterol) should always be available for quick relief.

Exercise-induced airway narrowing in elite athletes may be related to direct epithelial injury. In addition to the above, conditioning of incoming air may be of major assistance. Ipratropium has been reported to be of utility as well. ■ ■PREGNANCY Asthma may improve, deteriorate, or remain unchanged during preg nancy. Poor asthma control, especially exacerbations, is associated with poor fetal outcomes. The general principles of asthma management and its goals are unchanged. Avoidance of triggers, especially smoking environments, is critical in view of the risk of loss of control and, in the case of smoking, its clear effects on risk of development of asthma in the child. There is extensive experience suggesting the safety of inhaled albuterol, beclomethasone, budesonide, and fluticasone, with reassuring information on formoterol and salmeterol in pregnancy. Animal studies have not suggested toxicity for montelukast, zafirlu kast, omalizumab, and ipratropium. Antibodies cross the placenta, and there are few human data on the safety of the asthma biologics. Chronic use of OCS has been associated with neonatal adrenal insuf ficiency, preeclampsia, low birth weight, and a slight increase in the frequency of cleft palate. However, it is clear that poorly controlled asthma during pregnancy carries greater risk to the fetus and mother than these effects. There should be no hesitancy in administering routine pharmacotherapy for acute exacerbations. Initiation of aller gen immunotherapy during pregnancy is not recommended. In cases where prostaglandins are needed to manage pregnancy, PGF2-α should be avoided since it is associated with bronchoconstriction. Asthma CHAPTER 298 ■ ■ASPIRIN-EXACERBATED RESPIRATORY DISEASE A subset of patients (5–10%) present in adulthood with difficult-tocontrol asthma and type 2 inflammation with eosinophilia, sinusitis, nasal polyposis, and severe asthma exacerbations that are precipitated by ingesting inhibitors of cyclooxygenase, with aspirin being the most prominent of such inhibitors. Such patients, classified as having aspirin-exacerbated respiratory disease, overproduce leukotrienes in response to inhibition of cyclooxygenase-1, probably secondary to inhibition of PGE2. These patients should avoid inhibitors of cyclooxy genase-1 (aspirin and NSAIDs) but can generally tolerate inhibitors of cyclooxygenase-2 and

acetaminophen. They should be treated with leukotriene modifiers. Aspirin desensitization can be undertaken to decrease upper respiratory symptoms and to allow chronic adminis tration of aspirin or NSAIDs for those that require it. Dupilumab and the IL-5–active biologics appear to be particularly helpful (some have been approved to treat nasal polyposis in this setting) and appear to be superseding aspirin desensitization in management except when chronic administration of aspirin or NSAIDs is required for another therapeutic indication. ■ ■SEVERE ASTHMA Severe and difficult-to-treat asthma, which composes ~5–10% of asthma, is defined as asthma that, having undergone appropriate evalu ation for comorbidities and mimics, education, and trigger mitigation, remains uncontrolled on step 5 therapy or requires step 5 therapy for its control. Severe asthma can account for almost 50% of the cost of asthma care in the United States. A significant proportion of these patients have trouble with adherence and/or inhaler technique, and these factors need to be investigated vigorously. More than half of these patients have evidence of persistent eosinophilic inflammation as evidenced by peripheral blood eosinophils and/or induced sputum. Those with recurrent exacerbations have a substantially increased likelihood of responding to the type 2 targeted biologics. Tezepelumab has been shown to have some degree of effectiveness in those without elevated type 2 biomarkers. Treatment for those with mixed inflam mation, isolated neutrophilic inflammation, or pauci-granulocytic inflammation remains to be determined. Some data suggest that many of these patients may have aberrations in the pathways responsible for resolution of inflammation. A rare patient may have biochemical

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