Prevalence, Burden, Epidemiology, and Pathophysiology of Asthma

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Asthma Epidemiology, Burden, and Pathophysiology
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Asthma is a chronic inflammatory disorder of the airways characterized by airflow obstruction, heightened bronchial response, and underlying inflammation.\textsuperscript{1,2} The acute manifestations of the disorder, often called "asthma attacks," are periodic, recurrent episodes caused by chronically hyperactive and inflamed airways, leading to airflow obstruction.\textsuperscript{2}

For most patients, asthma onset begins in childhood, with patterns of inflammation and disease persistence determined by early, recognizable risk factors, including parental history of asthma and atopy (a genetic predisposition toward allergic hypersensitivity reactions).\textsuperscript{3,4}

During an acute exacerbation, individuals may experience wheezing, coughing, chest tightness, chest pain, or shortness of breath. The severity of asthma attacks varies from mild to moderate to severe. In extreme cases, attacks may be life-threatening and require immediate medical attention.\textsuperscript{1,2,5}

There is no known cure for asthma.\textsuperscript{6} However, it can be controlled with appropriate medical care, and by avoiding exposures (particularly environmental exposures that may trigger an attack), exacerbations can be lessened and severe exacerbations should be rare.\textsuperscript{7}

Epidemiology and Risk Factors
Asthma is a significant public health issue, affecting about 300 million people worldwide.\textsuperscript{8} In 2009, it was estimated that 1 in 12 people (approximately 25 million) had asthma in the United States alone.\textsuperscript{9} Asthma prevalence has been on the rise, increasing from 3.1\% in 1980 to 5.5\% in 1996 and 7.3\% in 2001 to 8.4\% in 2010.\textsuperscript{10}

Race and ethnicity may play a role in asthma prevalence, as evidenced by data from 2001 through 2010. Higher rates of asthma were observed among blacks than whites and Hispanics, whereas Hispanics had lower rates than either group (Figure 1).\textsuperscript{10}

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In addition to race/ethnicity, asthma prevalence varies by a number of modifiable and nonmodifiable risk factors, including weight, tobacco use, age, socioeconomic status, and geography.\textsuperscript{11} Overall, it is more prevalent in children than adults. In terms of gender, asthma is more prevalent in women than men; however, among children, boys have a higher prevalence (11.3\%) than girls (7.9\%). Not surprisingly, the prevalence of asthma is higher among families living in poverty compared with those who have incomes above the federal poverty level.\textsuperscript{1}

Asthma prevalence also varies from state to state, as shown by Behavioral Risk Factor Surveillance System data (Figure 2).\textsuperscript{12}

Obesity has been receiving increasing attention as a risk factor for asthma. In a study published last year, Zhang and colleagues reported a high prevalence of asthma among obese (10.2\%, 95\% confidence interval [CI], 10.0-10.3) and morbidly obese (18.2\%, 95\% CI, 17.7-18.7) persons, concluding that the ongoing obesity epidemic could be contributing to an increased prevalence of asthma among adults in some states.\textsuperscript{11}

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Economic Burden of Asthma
In 2007, the total societal cost of asthma was estimated at $56 billion. Most of this total ($50.1 billion) was attributed to medical expenses, whereas loss of productivity resulting from missed school days or workdays and premature death accounted for the remainder.\textsuperscript{13} By 2008, working adults who experienced 1 or more asthma attacks during the previous 12 months missed

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Figure 1. Asthma prevalence by race/ethnicity in the United States (2001-2010).

![Figure 1. Asthma prevalence by race/ethnicity in the United States (2001-2010).](image)

a combined total of 14.2 million days of work due to asthma.1

In 2010, asthma accounted for 3404 deaths; 439,400 hospitalizations; 1.8 million emergency department visits; and 14.2 million physician office visits.14 It was estimated that from 2002 to 2007, the value of productivity loss attributable to asthma was $2.03 billion because of morbidity and $2.37 billion because of mortality, per year. In addition, asthma was responsible for incremental direct medical costs of $3259 per person per year.13 In terms of healthcare utilization, asthma is responsible for an estimated 15.0 million outpatient visits per year.15

Pathophysiology

Although the root causes of the inflammatory process leading to asthma are yet to be fully explained, the development of asthma appears to involve the interaction between genetic and environmental factors that take place at a critical point in the development of the immune system.2,16

The pathophysiology of asthma is complex and involves mechanisms of adaptive and nonadaptive immunity that result in airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness.2,17 Evidence indicates that patterns of inflammation vary according to phenotypic differences, which are identifiable clusters of demographic, clinical, or pathophysiological characteristics, including allergic asthma, nonallergic asthma, late-onset asthma, asthma with fixed airflow limitation, and asthma with obesity.3 Although some phenotype-guided treatments are available for patients with severe asthma, thus far, phenotypes have not correlated strongly with specific pathological processes or treatment responses.1

In allergic asthma—the most common form of the disease—T helper type 2 (TH2) lymphocytes produce interleukin (IL)-4, IL-5, IL-9, and IL-13 in response to airborne allergens. These cytokines regulate the allergen-specific synthesis of immunoglobulin E (IgE) from B cells, promote the growth and differentiation of mast cells and eosinophils and the recruitment and activation of basophils, and directly cause airway hyperreactivity, a hallmark characteristic of asthma.17,18

Airway Inflammation

In asthma, the mechanism of inflammation varies from acute to subacute to chronic.19 Most patients have chronic inflammation, which persists over many years. In addition to ongoing chronic inflammation, patients may also experience acute inflammatory episodes, or exacerbations, of asthma.19,20

Airway inflammation is characterized by varying degrees of mucus hypersecretion, desquamation of the epithelium, smooth muscle hyperplasia, and airway remodeling.19 The degree of airway hyperresponsiveness is usually correlated with the clinical severity of asthma.21

Chronic inflammation of the airways is associated with increased bronchial hyperresponsiveness, which leads to bronchospasm and typical symptoms of wheezing, shortness of breath, and coughing following exposure to triggers such as allergens, environmental irritants, or viruses. In some patients with chronic asthma, airflow limitation may be only partially reversible because of airway remodeling, which is characterized by hypertrophy and hyperplasia of smooth muscle, subepithelial fibrosis, injury to epithelial cells, and angiogenesis.2

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Several cell types are involved in the inflammatory process, including mast cells, macrophages, eosinophils, epithelial cells, endothelial cells, and activated T lymphocytes. Patients with asthma have elevated numbers of mast cells in the smooth muscle lining the airways. Mast cells play a role in initiating the acute bronchoconstrictor responses to allergens and other stimuli, and are thought to be an important con-
Structural cells of the airways, including epithelial and endothelial cells, are thought to be an important source of inflammatory mediators, such as cytokines and lipid mediators.

Two additional cell types, invariant natural killer T (iNKT) cells and innate lymphoid cells (ILCs), have been found to produce cytokines that mediate the inflammatory process in asthma, independently of adaptive immunity and conventional antigens. Although the specific roles of iNKT cells and ILCs in immunity are still being defined, these cells respond to environmental triggers important in clinical asthma and may function independently and in conjunction with adaptive immunity to shape immunity environmental triggers, including specific allergens, microbes, and foods.17

Airflow Obstruction
Airflow obstruction can be caused by a variety of changes, including bronchoconstriction, edema, mucus plug formation, and airway remodeling (Figure 3).15 Acute bronchoconstriction, which is the primary manifestation of the early asthmatic response, takes place when IgE-dependent mediators are released upon exposure to airborne allergens. Airway edema, which typically occurs 6 to 24 hours following an allergen challenge, constitutes late asthmatic response. Chronic mucus plug formation, which consists of serum proteins and cell debris that accumulate in the airways, may take weeks to resolve. The structural changes associated with chronic inflammation may limit the reversibility of airflow obstruction, resulting in permanent tissue impairment.26

Airway obstruction causes resistance to airflow and decreased expiratory flow rates. Over time, patients may experience irreversible decline in lung function because of persistent, chronic pathology that results in thickening of airway walls.26

Bronchial Hyperresponsiveness
Bronchial hyperresponsiveness is an exaggerated response to stimuli, leading to excessive bronchial narrowing.27 Although it is recognized as an important feature in asthma, it does not occur in all patients with the disease.28 Moreover, bronchial hyperresponsiveness is not specific to asthma, and may also be caused by endogenous pathologies such as chronic obstructive pulmonary disease (COPD), viral respiratory infection, and cystic fibrosis as well as exogenous stimuli, including atopy, tobacco smoking, smoke inhalation, and near-drowning.27

Although the precise biochemical mechanisms have not been fully elucidated, the pathogenesis of bronchial hyperresponsiveness depends on the underlying pathological process.
As a result, there are important differences in the pathogenesis of bronchial hyperresponsiveness in patients with asthma, COPD, or allergic rhinitis.25-27 Bronchial hyperresponsiveness is associated with the influx of inflammatory cells.28 In asthma, epithelial shedding and subsequent loss of barrier function can contribute to bronchial hyperresponsiveness by allowing allergens to penetrate the epithelial barrier. Epithelial damage also results in the loss of enzymes that break down inflammatory mediators, which may exacerbate the inflammatory process.32

The precise pathological mechanisms involved in bronchial hyperresponsiveness are currently being explored. Researchers have found that the TH2 cytokines IL-4, IL-5, and IL-13 are each associated with worsening of bronchial hyperresponsiveness in animal models. Specific interventions to block each of these cytokines in humans with asthma may allow even greater specificity, to tailor treatment to the individual patient’s needs and circumstances.33 Emerging research that seeks to identify more targeted therapies for asthma will be discussed in more detail in the next issue of this series.

References
The prevalence and cost of asthma are considerable. In 2010, an estimated 25.7 million Americans had asthma, and direct and indirect costs related to the care of this disorder totaled a staggering $56 billion in 2007. According to the 2012 Behavioral Risk Factor Surveillance System, 49% of patients with asthma reported an attack in the past year, 11% reported no symptoms in the past year, and 43% reported no physician visits in the past year. Furthermore, only 27% of patients reported having an asthma management plan, and 33% reported missing work or days of reduced activity. Clearly, there is room for improvement when it comes to the management of asthma in the United States.

One of the most important questions facing practitioners when a patient presents with symptoms of cough, wheezing, nocturnal signs, and sleep disruption, is whether the individual has asthma. To establish a diagnosis, practitioners should access patient history, and inquire about symptoms to determine if they are consistent with recurrent episodes of airflow obstruction.

The key signs of asthma include recurrent wheezing, shortness of breath, chest tightness, and cough that vary over time and intensity. Variable expiratory airflow limitation is noted if measurements of peak expiratory flow rates are made. Typically, symptoms are worse at night or in the early morning, and may be triggered by infections, exercise, allergens, weather, and irritants.

Obesity is an important risk factor for asthma, as it often results in an altered pulmonary physiology and increased airway resistance. In addition, obesity is associated with more asthma exacerbations, especially in women. Patients with asthma who are obese tend to have more airway symptoms and airway inflammation. These patients also respond differently to asthma medications. Therefore, it is imperative to manage obesity in order to improve airway hyperresponsiveness and inflammation.

Various tools can be used to assess and monitor asthma, such as spirometry, which provides an objective measure of lung function; the forced expiratory volume in 1 second (FEV1)/forced vital capacity ratio of >0.75 to 0.80 is considered normal in adult patients. Other asthma assessment tools include asthma control questionnaires, asthma control tests, and peak flow meters.

The clinical symptoms of asthma may vary greatly in terms of severity. Some of the characteristics of severe asthma include chronic airflow obstruction, eosinophilic and/or neutrophilic asthma, corticosteroid insensitivity, and recurrent exacerbations. Given the fact that asthma is heterogenous in terms of the underlying clinical and inflammatory phenotypes involved, the care of patients is moving toward a more personalized, targeted approach.

In the future, we will have phenotype-targeted treatments based on the pathophysiology and biomarkers of asthma. Phenotyping patients with asthma with links to pathophysiological mechanisms will lead to a more precise, rational way of providing specific treatments to the individual patient. For example, patients with recurrent exacerbations who have sputum or blood eosinophils may be candidates for anti-interleukin-5 antibody treatment; and patients with chronic airflow obstruction, airway wall remodeling, low FEV1 levels, and high serum periostin levels may be candidates for anti-interleukin-13 antibody treatment. In addition, patients with neutrophils in the sputum may be more responsive to macrolide antibiotics, and patients with eosinophilic asthma may be more responsive to an anti-interleukin-4 receptor.

References
Managed care organizations (MCOs) allocate resources to improve the quality of asthma care while controlling asthma-related drug costs. MCOs that are accredited by the National Committee for Quality Assurance (NCQA) focus on Healthcare Effectiveness Data and Information Set (HEDIS) measures to develop management strategies for drugs. NCQA-accredited MCOs strive to create and maintain a drug formulary that offers value to the member; value is defined as outcomes relative to costs.  

HEDIS measures are divided into 2 categories: (1) preventive care and (2) condition-specific care. The targeted areas for condition-specific care focus on asthma, cardiac conditions, chronic obstructive pulmonary disease, depression, diabetes, mental illness, rheumatoid arthritis, tobacco use, and alcohol and drug abuse. The 2015 HEDIS measures for asthma include the use of appropriate medications and medication management. The HEDIS quality metrics and the overall value of the drug are taken into consideration when managed care pharmacy teams develop utilization management strategies to address pharmacy costs.

The main article in this publication provides an excellent update for healthcare professionals regarding asthma and its prevalence, pathophysiology, and economic burden. The prevalence of asthma continues to rise along with treatment-related costs. The pathophysiology of asthma remains a complex subject, with treatment still focused on controlling symptoms rather than halting disease progression. Therefore, managing patients with asthma continues to focus on symptom control and avoidance of triggers of an exacerbation.

The economic burden of asthma is well known. Outpatient visits, emergency department visits, and hospitalizations are the key drivers of asthma-related costs. To reduce these costs and improve patient outcomes, MCOs have established disease state management programs that utilize case managers and drug formulary designs, such as Pitney Bowes’s value-based benefit design. In order to effectively manage asthma at the health plan level, multiple departments within the organization need to work together to achieve a common goal.

On the pharmacy side, a managed care’s annual drug spending and patient compliance to medication regimens are monitored, using formulary design and management techniques to provide cost-effective options for patients. Pharmacy departments work with medical management departments to identify patients who are over- or underutilizing medications in an effort to reduce exacerbations that lead to hospitalization. Using claims data on the pharmacy and medical side allows the health plan to apply resources in the most effective manner.

Asthma disease progression is based on genetic and environmental factors. By understanding the disease process and identifying allergens that trigger asthma attacks, patients can better manage their symptoms. As novel targeted therapies continue to be developed, health plans are monitoring pipeline drug development to prepare for potential new therapies that will target asthma disease progression. It is hoped that these advances will lead to improved outcomes for patients with this disorder.

References
Asthma continues to be an important chronic condition for public and private payers, especially given the fact that it ranks as the top pediatric condition for commercial and managed Medicaid plans. From a clinical perspective, asthma management has evolved considerably in the past 2 decades, leading to better self-management and more appropriate use of medications. Perhaps most notably, improvements in asthma control have resulted in improved outcomes and quality of life for patients and their families.

In terms of payer mix, asthma disproportionately affects Medicaid members for 2 reasons. First, asthma is more prevalent among children than among adults, and the managed Medicaid member base skews toward a younger demographic. Second, asthma disproportionately affects those at the lower socioeconomic end of the spectrum, again representing the group frequently served by Medicaid programs.

From a payer perspective, hospitalizations are the most important component of healthcare utilization in asthma, followed by emergency department (ED) visits. Hospitalizations and ED visits tend to occur more frequently in patients with uncontrolled severe disease who experience frequent exacerbations. Furthermore, these patients are frequently nonadherent to their prescribed chronic therapy.

In asthma, pharmacy management focuses on the appropriate use of controller medications to help limit acute exacerbations (ie, asthma attacks), which can be dangerous and even life-threatening to the patient. These efforts are closely aligned with the national quality initiatives led by the National Committee for Quality Assurance (NCQA), the main accrediting body for managed care health plans. NCQA evaluates payer performance on 2 core asthma quality measures: (1) use of appropriate medication for individuals with asthma, and (2) medication management for individuals with asthma. These measures provide specific criteria that allow payers to identify and to report appropriate medication use in patients diagnosed with persistent asthma. They also provide the tools needed to help payers proactively identify and intervene with members who have an elevated high risk of developing exacerbations as a result of the suboptimal use of asthma control medications.

In addition to targeted pharmacy-based programs, payers play an important role in promoting patient self-management and medication adherence through condition-management initiatives. In asthma, these population-based programs are designed to educate members about their disease, promote awareness of exacerbation triggers, and encourage appropriate use of medications.

Asthma management has also been facilitated by the adoption of ED observation units, which allow hospitals to monitor patients for up to 23 hours without inpatient admission. Typically, payers have been supportive of observation units for patients with acute asthma exacerbations under the assumption that close monitoring in the outpatient setting will lead to improved quality of care, less hospitalizations, and perhaps fewer recurrences. There is evidence to suggest that ED observation units have resulted in improved patient satisfaction and cost-savings; one study found that the cost of monitoring a patient in an observation setting is approximately half of the cost of monitoring the same patient in an inpatient setting.

Overall, advances in asthma management have been positive for payers as well as for patients. The appropriate prescribing of controller medications have led to substantially improved disease control and reduced daily burden for patients. Furthermore, improved adherence to asthma control medications has been shown to reduce healthcare-related utilization and costs.

Despite improvements in asthma care, however, a number of key unmet needs remain. First, in the clinical practice guidelines promulgated by the National Heart, Lung, and Blood Institute, which have not been revised since 2007 but are due to be updated in 2015, treatment recommendations are based on symptomatology rather than on diagnostic criteria. This is important because differential diagnoses of respiratory conditions continue to pose a challenge for clinicians, especially when trying to differentiate between asthma,
“chronic bronchitis,” and chronic obstructive pulmonary disease in adults.

In addition, a substantial number of patients are nonadherent to their controller medications—as prescribed or at all. This is surprising given the minimal financial barriers to drugs in the category because of generic availability; some payers that have implemented value-based insurance designs charge minimal or zero copays for generic asthma control medications.

Similar to other chronic conditions, the future of asthma care will likely bring new opportunities to personalize patient care as more gene-based targeted therapies are developed and commercialized.

Ultimately, however, asthma management is predominantly driven by the patient–provider relationship. Nevertheless, health plans seek to identify high-risk patients who take multiple rescue medications without a controller medication, often referring these patients to outreach programs by case management professionals. In addition, payers also engage in population health efforts, which may include the development and dissemination of asthma self-management tools for their members with asthma. They may also work with their network providers to raise awareness about validated patient assessment tools.

References

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