37 Wheezing and Asthma

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Definition

A *wheeze* is a high-pitched, musical, adventitious lung sound produced by airflow through an abnormally narrowed or compressed airway(s). A wheeze is synonymous with a high-pitched or sibilant rhonchus.

Asthma is a heterogeneous syndrome characterized by variable, reversible airway obstruction and abnormally increased responsiveness (hyperreactivity) of the airways to various stimuli. The syndrome is characterized by wheezing, chest tightness, dyspnea, and/or cough, and results from widespread contraction of tracheobronchial smooth muscle (bronchoconstriction), hypersecretion of mucus, and mucosal edema, all of which narrow the caliber of the airways. The resulting airflow obstruction may be chronic or episodic, with respiratory symptoms resolving either spontaneously or as a result of therapy (bronchodilators or corticosteroids). A generally accepted definition of asthma does not yet exist because the syndrome has different causes, mechanisms, clinical features, and responses to therapy.

Technique

Wheezing is a subjective complaint that may be described in various ways. Some patients report noisy, difficult breathing (wheezy dyspnea), whereas others describe a whistling type of breathing or rattling secretions in the throat. The majority of asthmatic patients who report active wheezing generally have this finding documented by the examining physician. Nevertheless, wheezing is not always present during active asthma, and its absence should not exclude the diagnosis. Some patients with chronic asthma may become accustomed to wheezing and do not volunteer this information unless specifically asked. Most patients with asthma complain more frequently about chest tightness (in combination with shortness of breath or cough) than wheezing. Thus, any patient with chronic or episodic respiratory symptoms or who presents with a history of asthma or other chronic airway disease should be asked about wheezing.

The diagnosis of asthma is usually obvious from the patient's history. It should be highly suspected from a description of episodic and variable respiratory symptoms (with or without wheezing) or recurrent chest colds and bronchitis (productive cough). A careful, thorough history is fundamental not only in arriving at an accurate diagnosis but also in determining the severity of an individual's asthma and its appropriate therapy. The clinician should inquire about the following:

General (relating to the overall course of asthma in an individual):

- Age of onset of asthma
- Continuous or intermittent, with or without medications
- Usual precipitating factors (Table 37.1)
- Environmental survey (e.g., allergens, occupational or home exposures, smoking, air pollution)
- Medications, past and present, for asthma, noting the name or type of drugs, dosages, frequency, side effects, and compliance
- Related disability (e.g., time lost from work, school, or recreation)
- Frequency of visits to a physician or emergency room for asthma
- Frequency of hospitalizations, including any intubation and mechanical ventilation
- Associated medical conditions, (e.g., nasal polyps, sinusitis, allergies, gastroesophageal reflux, infection, psychological stress, and disorders that may simulate asthma)
- Personal and family history of asthma, atopy (allergic rhinitis, hay fever, eczema), positive skin tests for allergens, immunotherapy

Specific (relating to acute episode in an individual):

- Frequency, duration, intensity of attacks
- Time of onset (e.g., morning or night, following exposure to a medication, food, or other substances)
- Possible causes (e.g., viral upper respiratory tract infection, exercise, emotional stress)
- Presence of complicating factors (e.g., fever, chest pain, sputum production, vomiting)
- Use of medications during attacks and symptomatic response, if any

Basic Science

Wheezing may result from localized or diffuse airway narrowing or obstruction from the level of the larynx to the

Table 37.1
Contributing or Precipitating Factors in Asthma

Respiratory infections
Changes in humidity or temperature
Exercise
Noxious fumes or odors
Air pollution (e.g., ozone, sulfur dioxide)
Allergens (e.g., pollen, animals, foods)
Drugs
Occupational agents (e.g., cotton dust, isocyanates, acids, enzymes)
Gastroesophageal reflux
Sinusitis
Psychological factors
Noncompliance with prescribed therapy or lack of education regarding asthma and its therapy
Idiopathic

small bronchi. The airway narrowing may be caused by bronchoconstriction, mucosal edema, external compression, or partial obstruction by a tumor, foreign body, or tenacious secretions. Wheezes are believed to be generated by oscillations or vibrations of nearly closed airway walls. Air passing through a narrowed portion of an airway at high velocity produces decreased gas pressure and flow in the constricted region (according to Bernoulli's principle). The internal airway pressure ultimately begins to increase and barely reopens the airway lumen. The alternation of the airway(s) between nearly closed and nearly open produces a "fluttering" of the airway walls and a musical, "continuous" sound. The flow rate and mechanical properties of the adjacent tissues that are set into oscillation determine the intensity, pitch, composition (monophonic or polyphonic notes), duration (long or short), and timing (inspiratory or expiratory, early or late) of this dynamic symptom and sign. Wheezes are heard more commonly during expiration because the airways normally narrow during this phase of respiration. Wheezing during expiration alone is generally indicative of milder obstruction than if present during both inspiration and expiration, which suggests more severe airway narrowing. However, most asthmatic patients are unable accurately to correlate their wheezing (or other respiratory symptoms) to the severity of airway obstruction as measured objectively by pulmonary function tests.

In contrast, the absence of wheezing in an asthmatic may indicate either improvement of the bronchoconstriction or severe, widespread airflow obstruction. The latter suggests that the airflow rates are too low to generate wheezes or the viscous mucus is obstructing large regions of the peripheral airways. Increasing exhaustion and a "silent chest" are ominous signs of respiratory muscle fatigue and failure, leading to status asthmaticus.

In asthma, the markedly increased airway resistance (airflow obstruction) contributes to the characteristic physiologic and clinical changes observed during active or symptomatic periods. The airway obstruction is diffuse and nonuniform in distribution, resulting in ventilation–perfusion inequalities and hypoxemia. Airways tend to close early during expiration, and hyperinflation results. Although breathing at high lung volumes tends to maintain open airways, this response demands increased muscular work of breathing to provide adequate ventilation, which is increased secondary to stimulation of airway receptors and hypoxia. Most asthmatics complain of greater difficulty during inspiration than expiration, due to the uncomfortable work of breathing necessary to ventilate hyperinflated, abnormally stiff, or noncompliant lungs.

Several hypotheses have been proposed to explain the pathogenesis of bronchoconstriction and other airway abnormalities in asthma. None completely accounts for all the clinical forms of asthma. The proposed mechanisms probably overlap and interrelate even in the same individual.

The immediate, type I immunologic reaction occurs primarily in "allergic" asthma and involves biochemical reactions between an antigen and a specific antibody (immunoglobulin E, IgE) bound to sensitized airway mast cells and basophils. This immunologic reaction results in the release of potent biochemical mediators that contract bronchial smooth muscle, increase vascular permeability and mucus secretion, and attract inflammatory cells.

Preformed histamine, neutrophil and eosinophil chemotactic factors, and platelet-activating factors are released. In addition, membrane-associated oxidative metabolism of arachidonic acid generates prostaglandins ($PGF_2\alpha$ and PGD_2) and leukotrienes (LTC_4, D_4, E_4), which are potent bronchoconstrictors. Type III (arthus) immunologic reactions have also been implicated in some cases of asthma and in the related allergic bronchopulmonary aspergillosis.

A neurogenic or reflex mechanism is observed in "nonallergic" asthma provoked by nonspecific stimuli (e.g., exercise, infection, air pollution) that apparently do not initiate type I immunologic responses. This nonimmunologic hypothesis stresses the importance of the parasympathetic nervous system (vagus nerve) in regulating airway caliber. Chemical or mechanical inflammation stimulates cholinergic irritant receptors in the airway mucosa to hyperreact, leading to vagally mediated reflex bronchoconstriction. This reflex is produced by either direct mediator release or secondary stimulation of irritant receptors by smooth muscle constriction.

A partial beta-adrenergic blockade or deficiency has also been proposed to explain some types of "nonallergic" asthma (e.g., propranolol-induced asthma) because bronchial smooth muscle tone appears to be modulated by beta-adrenergic receptors and alterations in the metabolism of intracellular cyclic nucleotides. Beta-adrenergic stimulation increases cyclic 3,5-adenosine monophosphate (AMP) and decreases cyclic 3,5-guanosine monophosphate (GMP), resulting in smooth muscle relaxation (bronchodilation). Beta-adrenergic inhibition produces opposite effects, resulting in bronchoconstriction. Therefore, asthmatics may have relative beta-adrenergic hyporesponsiveness and an imbalance between adrenergic and cholinergic regulation that favor the latter, resulting in greater than normal mediator generation and unopposed bronchoconstriction.

Clinical Significance

Although most patients presenting with acute asthma can be readily recognized and diagnosed, the clinician must always be cognizant that "all that wheezes is not asthma." Almost any respiratory disorder that leads to airway narrowing or obstruction can be associated with wheezing. The differential diagnosis of wheezing is long (Table 37.2) and, at times, complicated, particularly if asthma coexists with another pulmonary disease.

Wheezing may be acute or chronic (recurrent) in chil-

Table 37.2
Differential Diagnosis of Wheezing

Asthma
Acute and chronic bronchitis
Emphysema
Acute left ventricular failure with pulmonary edema ("cardiac asthma")
Aspiration
Sarcoidosis
Extrinsic allergic alveolitis (hypersensitivity pneumonitis)
Acute pulmonary embolism
Carcinoid syndrome
Systemic mastocytosis
Central airway obstruction
a. Structural: tumors, foreign body, stricture, goiter
b. Functional: laryngeal spasm or edema
Bronchiolitis
Cystic fibrosis
Syndromes with pulmonary infiltrates and eosinophilia, including allergic bronchopulmonary aspergillosis
Factitious asthma

dren with nonasthmatic disorders. *Acute wheezing* in small children suggests bronchiolitis, particularly if the child was well prior to an upper respiratory tract infection (frequently respiratory syncytial virus) and has relatively irreversible airway obstruction without evidence of atopy. Many children with acute bronchiolitis may develop asthma; the long-term course of the illness may be the best diagnostic determinant because bronchiolitis does not usually recur. In a child, wheezing that is most prominent during inspiration suggests laryngotracheobronchitis (croup), epiglottitis, aspiration of a foreign body, or congenital laryngeal or tracheal narrowing. Wheezing occurs during both inspiration and expiration as the airway caliber becomes increasingly smaller. Wheezing may become confused with stridor, which is a high-pitched musical or "crowing" sound localized in the larynx or trachea. *Chronic wheezing* and respiratory infections in a child should raise the possibility of cystic fibrosis, with or without gastrointestinal complaints.

Adults with a new onset of wheezing generally have different nonasthmatic disorders from those in children. In adults, stridor or localized wheezing may be caused by mechanical obstruction of a central airway, such as by a tumor, foreign body (especially food), goiter, or stenosis. In addition to laryngeal edema (resulting from angioedema or anaphylaxis) and vocal cord paralysis, some individuals may have spastic adduction of the vocal cords due to functional or psychological factors. Wheezing in combination with productive cough and/or exertional dyspnea is not infrequent in chronic bronchitis or emphysema. Some patients may have increased wheezing during the early morning hours ("nocturnal asthma") as a result of congestive heart failure with pulmonary edema ("cardiac asthma"), gastric aspiration, or sinusitis in which the recumbent position during sleep promotes pulmonary sequelae. Transient wheezing occurs in some patients with pulmonary embolism, the carcinoid syndrome, and systemic mastocytosis as a result of the release of bronchoactive amines or mediators. Parenchymal lung disorders such as sarcoidosis, extrinsic allergic alveolitis, and the adult respiratory distress syndrome (noncardiogenic pulmonary edema) can occasionally produce wheezing due to airway compromise by granulomas or edema fluid, release of mediators, or underlying asthma. A large group of diseases characterized by pulmonary infiltrates and peripheral blood eosinophilia may produce asthma-like wheezing: Loeffler's syndrome, chronic eosinophilic pneumonia, tropical eosinophilia, hypereosinophilic syndrome, various vasculitides, and allergic bronchopulmonary aspergillosis.

The heterogeneity and complexity of asthma are most apparent when one attempts to classify the various forms of this syndrome (Table 37.3). Different categories of asthma represent a clinical spectrum, and the majority of patients have features of several forms. For example, although "extrinsic" and "intrinsic" asthma are popular conceptual terms, many asthmatics do not conform to either category, and some may develop intrinsic asthma after many years with extrinsic features.

Extrinsic (allergic) *asthma* commonly occurs in young patients who have other allergic or atopic disorders, as well as a family history of asthma and/or atopy. A specific, often seasonal antigen characteristically produces a type I hypersensitivity reaction, resulting in paroxysmal bronchoconstriction. Eosinophils in the sputum, eosinophilia, increased IgE, and positive skin tests for immediate hypersensitivity are common findings.

Intrinsic (nonallergic or infective) *asthma* occurs primarily in adulthood (more than 30 years of age) and is not usually associated with atopy, seasons, eosinophilia, increased IgE, or positive skin tests. These patients are hyperreactive to a wide variety of stimuli and have some intrinsic abnormality of bronchomotor tone. In many patients the onset of asthma is preceded by an upper respiratory infection, and asthmatic symptoms tend to persist for years with variations in severity rather than asymptomatic remissions.

Table 37.3
Classification of Asthma

Extrinsic (allergic) asthma
Intrinsic (nonallergic) asthma
Asthmatic bronchitis
Exercise-induced asthma
Drug-induced asthma
Occupational asthma
Variant or atypical asthma

Asthmatic bronchitis occurs in elderly, nonatopic patients who have a long or heavy smoking history and active chronic cough and sputum production with superimposed hyperreactive airways. The latter is supported by partial reversal of airway obstruction by bronchoconstriction during inhalation challenge with methacholine or histamine. Sinusitus and sputum rich in polymorphonuclear leukocytes (rather than eosinophils) are frequently present. Allergy evaluation is negative.

Exercise-induced asthma occurs in the majority of asthmatic patients who exercise (e.g., running, cycling). Wheezing and dyspnea characteristically develop shortly after completion of a sustained physical activity and may be the only symptoms of asthma. The severity of the symptoms depends on the duration and type of exercise and how recently the individual previously exercised. This phenomenon is caused by respiratory heat or water loss, which then releases mast cell mediators.

Drug-induced asthma occurs in patients shortly after exposure to certain medications (e.g., propranolol, timolol, aspirin, nonsteroidal anti-inflammatory agents, cholinergic drugs), additives (e.g., tartrazine, metabisulfite, alcohol), or certain medical procedures (e.g., studies using iodinated radiographic contrast dyes, hemodialysis). A patient with wheezing temporally related to aspirin ingestion, rhinitis, and nasal polyps suggests aspirin hypersensitivity. Foods may also contain potentially asthmagenic chemicals, such as monosodium glutamate and bisulfite preservative. In general, asthma related to these agents does not appear to have an immunologic mechanism and is more frequent in adult, nonatopic asthmatic patients.

Occupational asthma may be provoked in susceptible individuals following exposure to irritants present in a work setting or at home. The list of occupations and related asthmagenic substances used or generated is long and continually expanding. A further discussion is presented in Chapter 41, Environmental Inhalation.

Variant or *atypical asthma* occurs in some patients who present without wheezing but with acute or chronic cough or dyspnea as the sole symptom of asthma. Paroxysms of cough or dyspnea may or may not be related to a specific stimulus, season, time of day, activity, postnasal drip, or respiratory infection. Asthmatic patients with cough as the major or only symptom develop bronchoconstriction localized primarily in the central or large airways where subepithelial cough receptors abound and reflex broncho-

constriction occurs following exposure to various stimuli. Patients complaining of episodic dyspnea have involvement predominantly in the peripheral airways where bronchoconstriction, mucosal edema, and secretion contribute to the airway obstruction. Although most patients with atypical asthma are adults, the physical examination and routine pulmonary functions tests are not helpful (usually normal), making the diagnosis difficult and confusing. The diagnosis must begin with a high index of suspicion. It is supported by the patient's response during an inhalation challenge with methacholine or histamine and/or an empirical trial of bronchodilators. This subgroup of asthmatics emphasizes the fact that wheezing is not always a cardinal manifestation of asthma.

References

American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987;136:225–44.

Boushey HA, Holtzman MH, Sheller JR, et al. Bronchial hyperreactivity. Am Rev Respir Dis 1980;121:389–413.

Edelson JD, Rebuck AS. The clinical assessment of severe asthma. Arch Intern Med 1985;145:321–23.

Forgacs P. Lung sounds. London: Bailliæere Tindall, 1978;44–54.

Lawlor GJ Jr, Tashkin DP. Asthma. In: Lawlor GJ Jr, Fischer TJ, eds. Manual of allergy and immunology: diagnosis and therapy. Boston: Little, Brown, 1981;113–56.

McFadden ER Jr, Ingram RH Jr. Exercise-induced airway obstruction. Ann Rev Physiol 1983;45:453–63.

Shim CS, Williams H Jr. Relationship of wheezing to the severity of obstruction in asthma. Arch Intern Med 1983;143:890–92.

Statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Disease. Chronic bronchitis, asthma, and pulmonary emphysema. Am Rev Respir Dis 1962;85:762–68.

Szczeklik A, Gryglewski RJ. Asthma and anti-inflammatory drugs. Mechanisms and clinical patterns. Drugs 1983;25:533–43.

*Weiss EB, Segal MS, Stein M, eds. Bronchial asthma. Mechanisms and therapeutics, 2d ed. Boston: Little, Brown, 1985.

Williams MH Jr, Shim CS. Asthma. In: Simmons DH, ed. Current pulmonology. Chicago: Medical Year Book Publishers, 1985:6:267–305.