Asthma in adolescents and adults: Evaluation and diagnosis

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INTRODUCTION

The "classic" signs and symptoms of asthma are intermittent dyspnea, cough, and wheezing. Although typical of asthma, these symptoms are nonspecific, making it sometimes difficult to distinguish asthma from other respiratory diseases. The definitive diagnosis of asthma requires the history or presence of respiratory symptoms consistent with asthma, combined with the demonstration of variable expiratory airflow obstruction [1-3].

Tools used in the diagnosis of asthma include history, physical examination, pulmonary function testing, and other laboratory evaluations. This topic review describes these tools, followed by several specific strategies for making the diagnosis of asthma in adolescents and adults.

The diagnosis of asthma in children and older adults and an overview of asthma management are discussed separately. (See "Asthma in children younger than 12 years: Initial evaluation and diagnosis" and "Diagnosis and management of asthma in older adults" and "An overview of asthma management".)

DEFINITION

While asthma is readily recognized in its classic presentation, with intermittent cough, wheeze, and shortness of breath brought on by characteristic triggers and relieved by bronchodilating medications, it is difficult to provide a definition that distinguishes asthma from similar and overlapping conditions. In the absence of a definitive laboratory test or biomarker, asthma has defied precise definition, one acceptable to all disciplines (including clinicians, physiologists, and pathologists). Clinically, its symptoms are non-specific. Physiologically, asthma is characterized by bronchial hyperresponsiveness, the tendency of airways to narrow excessively in response to a variety of stimuli that provoke little or no bronchoconstriction in persons without airway disease, but bronchial hyperresponsiveness is not unique to asthma. Pathologically, asthma may be described broadly as "a chronic inflammatory disorder of the airways" [1]. However, this description omits the characteristic waxing and waning of airflow obstruction in asthma and fails to distinguish asthma from other inflammatory airways disorders, such as chronic bronchitis or bronchiolitis.

A more precise definition combines the central roles of inflammation and bronchial hyperresponsiveness with the characteristic clinical symptoms. Towards this end, asthma has been defined by the Expert Panel 3 of the National Asthma Education and Prevention Program as "a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment" [1]. This definition is descriptive of key features of the disease, but it lacks utility for patients and clinicians.

The Global Initiative for Asthma defines asthma as follows [2]: "Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation."

Many of the features described above for asthma overlap with chronic obstructive pulmonary disease (COPD). Sometimes the distinction between asthma and COPD is clear: chronic exercise limitation and persistent airflow obstruction in a middle-aged or older person with a history of more than 20 pack-years of cigarette smoking point to a diagnosis of COPD. In COPD, pre- and post-bronchodilator pulmonary function testing may confirm little or no reversibility of the airflow obstruction. At other times, however, the distinction is less clear, such as when patients with COPD exhibit episodic symptoms and a large reversible component to their airflow obstruction. Recognition of these overlapping features of both asthma and COPD in some patients has led to description of the condition, asthma-COPD overlap, discussed below. (See 'Differential diagnosis' below and "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging", section on 'Definitions' and "Asthma and COPD overlap (ACO)".)

"Reactive airways disease" is an imprecise term that has been used to describe transient symptoms of cough and wheeze when confirmation of a diagnosis of asthma is lacking. Although it may be appropriate as a description of intermittent wheezing in very young children in whom a diagnosis of asthma cannot yet be definitively ascertained, it should be avoided in adolescents and adults in whom additional testing is available to confirm or exclude a diagnosis of asthma [4]. "Reactive airways dysfunction syndrome (RADS)" refers to an airway disorder resulting from an intense exposure to an inhaled chemical irritant or noxious gas. It is characterized by asthma-like features of bronchial hyperresponsiveness and airflow obstruction. (See "Reactive airways dysfunction syndrome and irritant-induced asthma".)

CLINICAL FEATURES

Asthma is diagnosed before the age of seven years in approximately 75 percent of cases [5]. As a result, clinicians treating adolescents and adults will often encounter patients whose diagnosis of asthma was made years earlier. Many children experience a remission of asthma symptoms around the time of puberty, with potential recurrence years later. Asthma may develop at any age, although new-onset asthma is less frequent in older adults compared to other age groups. Occupational asthma, aspirin-sensitive asthma (aspirin-exacerbated respiratory disease), and eosinophilic asthma are distinct syndromes that typically have their onset in adulthood.

History — A pattern of respiratory symptoms that occur following exposure to triggers (eg, allergen, exercise, viral infection) and resolve with trigger avoidance or asthma medication is typical of asthma. Some patients will report all three of the classic symptoms of asthma, while others may report only one or two:

- Wheeze (high-pitched whistling sound, usually upon exhalation)
- Cough (often worse at night)
- Shortness of breath or difficulty breathing

"Wheezing" does not have a standard meaning for patients and may be used by those without a medical background to describe a variety of sounds, including upper airway noises emanating from the nose or throat. Cough may be dry or productive of clear mucoid or pale yellow sputum (made discolored by the presence of eosinophils). Asthma is a potential cause of unexplained chronic cough. (See "Evaluation of subacute and chronic cough in adults".)

Some patients describe chest tightness, a band-like constriction, or the sensation of a heavy weight on the chest. In contrast, sharp chest pain is rarely used to describe the sensation of asthma.

Because the symptoms of asthma are also seen in several other respiratory diseases, it is difficult to be certain of the diagnosis of asthma based upon history alone [6-8]. However, certain historical features heighten the probability of asthma:

- **Episodic symptoms** – Asthmatic symptoms characteristically come and go, with a time course of hours to days, resolving spontaneously with removal from the triggering stimulus or in response to anti-asthmatic medications. Patients with asthma may remain asymptomatic for long periods of time. Report of symptoms that occur or worsen at night is often a feature of asthma.

- **Characteristic triggers** – Respiratory symptoms triggered by exercise, cold air, and exposure to inhaled allergens (aeroallergens) are suggestive of asthma. A list of questions that can help elicit a history of asthma triggers is provided in the table (table 1).

  Exercise-triggered symptoms typically develop 5 to 15 minutes **after** a brief (eg, five minutes) period of exertion or about 15 minutes into prolonged exercise and resolve with rest over approximately 30 to 60 minutes. This time-course is distinct from simple exertional dyspnea, which typically begins shortly after the onset of exertion and abates within five minutes of stopping exercise. In asthma, exercise-induced symptoms occur more commonly and are more intense when the inhaled air is cold. (See "Exercise-induced bronchoconstriction", section on 'Clinical manifestations'.)

  Allergens that commonly trigger asthmatic symptoms include dust mites, molds, furry animals, cockroaches, and pollens (table 1) [1]. The acute onset of lower respiratory tract symptoms reliably precipitated by exposure to a cat or dog is virtually pathognomonic of asthma. Allergenic foods very rarely cause isolated asthma symptoms without other simultaneous allergic manifestations, such as angioedema, urticaria, hypotension, or gastrointestinal distress. Symptoms brought on by irritant-type exposures (eg, cigarette smoke, strong fumes, changes in weather, airborne chemicals or dusts) are non-specific and do not favor a diagnosis of asthma over other respiratory diseases. Viral infections are common triggers for asthma, although they can provoke exacerbations in other chronic respiratory conditions as well. Moreover, acute viral bronchitis in the absence of asthma may at least transiently cause respiratory symptoms that mimic asthma. Unique to asthma is the onset of cough, wheeze, and/or chest tightness 30 to 120 minutes following ingestion of aspirin or any cyclooxygenase-1 inhibitor (referred to as "aspirin-sensitive asthma" or "aspirin-exacerbated respiratory disease"), but this sensitivity occurs in only a small minority (an estimated 7 percent) of asthmatic patients and rarely before early adulthood. (See "Trigger control to enhance asthma management" and "Aspirin-exacerbated respiratory disease".)

  Other rare but characteristic sensitivities that may occasionally be reported by persons with asthma include symptoms triggered by ingestion of sulfites or certain food dyes. (See "Allergic and asthmatic reactions to food additives".)

- **Work-related exposures** - It is estimated that as many as 10 percent of cases of new-onset asthma in the adult are due to workplace-related exposures (occupational asthma). The diagnosis may be suspected based on a characteristic history of asthmatic symptoms temporally associated with work-related exposures, especially in occupations in which there is exposure to known sensitizing agents. The diagnosis can be confirmed by demonstration of variable airflow obstruction before and after a work shift, and in some cases the diagnosis is supported by identification of IgE-specific antibodies in the blood to the offending sensitizer [9]. (See "Occupational asthma: Clinical features, evaluation, and diagnosis".)

- **Personal or family history of atopy** – A strong family history of asthma and allergies or a personal history of atopic diseases (eg, atopic dermatitis, seasonal allergic rhinitis and conjunctivitis) favors a diagnosis of asthma in a patient with suggestive respiratory symptoms. (See "Risk factors for asthma", section on 'Atopy and allergens' and "Genetics of asthma".)

- **History of asthmatic symptoms as a child** – Recollection of childhood symptoms of chronic cough, nocturnal cough in the absence of respiratory infections, or a childhood diagnosis of "recurrent bronchitis" or "wheezy bronchitis" favors asthma, but may also be reported in someone with bronchiectasis or simply frequent childhood respiratory infections. A history of childhood asthma that abated in late childhood or early adulthood combined with “new onset” of asthmatic symptoms in adulthood favors a diagnosis of recurrent asthma.

Certain historic features lessen the prior probability of asthma. These include:

- Lack of improvement following anti-asthmatic medications – Patients who have tried an inhaled bronchodilator and obtained no relief of their symptoms are less likely to have asthma. Similarly, lack of dramatic improvement with a course of oral glucocorticoids suggests a diagnosis other than asthma. (See 'Differential diagnosis' below.)

- Onset of symptoms after age 50 – In middle-aged and older patients, other respiratory and cardiovascular diseases with overlapping manifestations become the more likely explanation for shortness of breath, cough, and wheeze, although the new onset of asthma remains a possibility. The evaluation of asthma in older adults is discussed separately. (See "Diagnosis and management of asthma in older adults".)

- Concomitant symptoms such as chest pain, lightheadedness, syncope, or palpitations suggest an alternate diagnosis such as pulmonary vascular disease, cardiomyopathy, early coronary artery disease, or pericardial disease. (See "Evaluation of the adult with dyspnea in the emergency department" and "Approach to the adult patient with syncope in the emergency department".)

- History of cigarette smoking – In patients with more than 20 pack-years of cigarette smoking, the likely etiology of cough, wheeze, and shortness of breath shifts away from asthma toward chronic obstructive pulmonary disease, although the two diseases can co-exist. (See "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging".)

Physical findings — Widespread, high-pitched, musical wheezes are a characteristic feature of asthma, although wheezes are not specific for asthma and are usually absent between asthma exacerbations. Wheezes are heard most commonly on expiration, but can also occur during inspiration. Asthmatic wheezing usually involves sounds of multiple different pitches, starting and stopping at various points in the respiratory cycle and varying in tone and duration over time. It is different from the monophasic wheezing of a local bronchial narrowing (eg, due to an aspirated foreign body or bronchogenic cancer), which has single pitch and repeatedly begins and ends at the same point in each respiratory cycle.

Expiratory noises transmitted from the upper airway (eg, larynx, pharynx) can mimic wheezing and are often described as wheezing by patients. However, these upper airway noises are typically loudest over the neck and greatly diminished over the chest in contrast to true wheezes that are typically louder over the chest. Patients may be able to identify respiratory noises as inspiratory rather than expiratory, a description generally favoring an etiology other than asthma. Clinicians can usually distinguish the low-pitched wheezes (also called "rhonchi") that clear with cough, a sign of increased airway secretions as may be seen in bronchitis or bronchiectasis, from the typical high-pitched expiratory wheezes of asthma. (See "Evaluation of wheezing illnesses other than asthma in adults".)

Physical findings that suggest **severe** airflow obstruction in asthma include tachypnea, tachycardia, prolonged expiratory phase of respiration (decreased I:E ratio), and a seated position with use of extended arms to support the upper chest ("tripod position") [1,2]. Use of the accessory muscles of breathing (eg, sternocleidomastoid) during inspiration and a pulsus paradoxus (greater than 12 mmHg fall in systolic blood pressure during inspiration) are usually found only during severe asthmatic attacks. However, these signs are insensitive manifestations of severe airflow obstruction; their absence does not exclude the possibility of a severe asthmatic attack. (See "Examination of the arterial pulse" and "Acute exacerbations of asthma in adults: Emergency department and inpatient management", section on 'Clinical findings'.)

Importantly, the presence or absence of wheezing on physical examination is a poor predictor of the severity of airflow obstruction in asthma. Wheezing may be heard in patients with mild, moderate, or severe airway narrowing, while widespread airway narrowing may be present in individuals without wheezing. Thus, the presence of wheezing alerts one to the likely presence of airway narrowing, but not its severity.

Extrapulmonary physical findings in patients with asthma that can provide evidence in support of or against a diagnosis of asthma include the following:

- Pale, swollen membranes on examination of the nasal cavities with an otoscope and a cobblestone appearance to the posterior pharyngeal wall suggest associated allergic rhinitis, a common condition among patients with allergic asthma. (See "Allergic rhinitis: Clinical manifestations, epidemiology, and diagnosis".)

- Nasal polyps, which appear as glistening, gray, mucoid masses within the nasal cavities, should prompt questioning about concomitant aspirin sensitivity, anosmia, and chronic sinusitis (picture 1). Since aspirin-exacerbated respiratory disease (asthma, nasal polyps, and aspirin sensitivity) is uncommon in childhood, the finding of nasal polyps in an adolescent with lower respiratory tract symptoms should lead to consideration of alternative diagnoses, specifically cystic fibrosis. (See "Aspirin-exacerbated respiratory disease" and "Cystic fibrosis: Clinical manifestations and diagnosis".)

- Atopic dermatitis with typical lichenified plaques in a flexural distribution, especially of the antecubital and popliteal fossae, volar aspect of the wrists, ankles, and neck (picture 2 and picture 3), may accompany asthma in adolescents and adults. In early childhood it is a risk factor for the later development of asthma, with as many as a third of children with atopic dermatitis progressing to asthma. (See "Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis" and "Risk factors for asthma", section on 'Atopy and allergens'.)

- Clubbing is not a feature of asthma; its presence should direct the clinician toward alternative diagnoses such as interstitial lung disease, lung cancer, and diffuse bronchiectasis, including cystic fibrosis. (See "Approach to the adult with interstitial lung disease: Clinical evaluation" and "Cystic fibrosis: Clinical manifestations and diagnosis".)

EVALUATION

The laboratory evaluation of a patient with suspected asthma is predominantly focused on pulmonary function testing. Other laboratory studies, including chest radiography, blood tests, and tests for allergy, are useful in selected patients but cannot of themselves establish or refute a diagnosis of asthma.

Pulmonary function testing — Tests of airflow limitation are critical tools in the diagnosis of asthma. A detailed discussion of a wider range of pulmonary function tests used in the diagnosis of asthma and other causes of shortness of breath is presented separately. (See "Pulmonary function testing in asthma".)

Spirometry — Spirometry, in which a maximal inhalation is followed by a rapid and forceful complete exhalation into a spirometer, includes measurement of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) [10]. These measurements provide information that is essential to the diagnosis of asthma [1]. We obtain baseline spirometry in virtually all patients with a suspected diagnosis of asthma. (See "Office spirometry" and "Pulmonary function testing in asthma".)

The results of spirometry can be used to determine the following:

- Determine whether baseline airflow limitation (obstruction) is present (reduced FEV_1/FVC ratio)
- Assess the reversibility of the obstructive abnormality by repeating spirometry after administration of a bronchodilator
- Characterize the severity of airflow limitation (based on the FEV_1 as a percentage of the normal predicted value)
- For patients with normal airflow (normal FEV_1/FVC ratio), identify a restrictive pattern as an alternate explanation for dyspnea (eg, FVC <80 percent predicted)

An obstructive pattern on spirometry is identified numerically by a reduction in the ratio of FEV_1 to FVC [11]. When FEV_1/FVC is reduced below normal (less than 0.70 or less than the lower limit of normal [LLN], which is the cut-off at the fifth percentile of

the confidence interval provided electronically by modern computerized spirometers), airflow obstruction is present. When the FEV_1/FVC ratio is normal or increased, there is no expiratory airflow obstruction. (See "Pulmonary function testing in asthma" and "Selecting reference values for pulmonary function tests".)

Having identified the presence of airflow obstruction by a reduction in FEV_1/FVC, the severity of airflow obstruction is then categorized by the degree of reduction of the FEV_1 below normal. The severity of airflow obstruction based on spirometry is graded as borderline, mild, moderate, and severe as shown in the figure (figure 1), although other grading systems can be used [11,12]. These categories are used for pulmonary function interpretation and are NOT the same as categories used by the National Asthma Education and Prevention Program (NAEPP) guidelines to stage asthma severity (table 2) [1].

An obstructive pattern can also be identified visually by inspection of the shape of the expiratory flow-volume curve that is often provided by modern spirometry equipment. A scooped, concave appearance to the expiratory portion of the flow-volume loop signifies diffuse intrathoracic airflow obstruction, typical of asthma and many other obstructive lung diseases (figure 2). Inspection of the inspiratory and expiratory portions of the flow-volume loop can also be useful in identifying the characteristic patterns seen in upper airway obstruction (figure 3). (See "Overview of pulmonary function testing in adults", section on 'Flow-volume loop' and "Flow-volume loops".)

Bronchodilator response — We assess bronchodilator reversibility in almost all adult and adolescent patients with airflow limitation on their baseline spirometry, as recommended by the NAEPP guidelines [1]. Acute reversibility of airflow obstruction is tested by administering 2 to 4 puffs of a quick-acting bronchodilator (eg, albuterol), preferably with a valved holding-chamber ("spacer"), and repeating spirometry 10 to 15 minutes later. Measurements can also be made before and after administration of nebulized bronchodilator. An increase in FEV_1 of 12 percent or more, accompanied by an absolute increase in FEV_1 of at least 200 mL, can be attributed to bronchodilator responsiveness with 95 percent certainty.

The presence of a bronchodilator response, in isolation, is not sufficient to make the diagnosis of asthma, however. Bronchodilator responsiveness may be seen with other conditions, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, non-cystic fibrosis bronchiectasis, and bronchiolitis. Asthma is typically distinguished from these other conditions by the capacity for a "large" increase in FEV_1. The definition of a large bronchodilator response is not standardized; investigators generally classify a large response as at least 15 or 20 percent. However, there is no precise cutoff value that defines an "asthmatic" bronchodilator response.

Occasionally, patients with asthma will have airflow obstruction on spirometry but fail to exhibit a 12 percent or greater increase in FEV_1 following bronchodilator (a "false negative" response). Reasons for false negatives include the following:

- Inadequate inhalation of the bronchodilator due to problems using the metered-dose inhaler correctly
- Recent use of a quick-acting bronchodilator or other anti-asthmatic medications (eg, long-acting bronchodilators), resulting in near-maximal bronchodilation prior to testing
- Minimal airflow obstruction at the time of testing (FEV_1 already close to 100 percent)
- In some patients with asthma, the presence of irreversible airways obstruction due to chronic airways inflammation or scarring

Changes in the forced expiratory flow between 25 and 75 percent of the vital capacity (FEF_{25-75}) observed over time or in response to bronchodilator are not used to diagnose asthma in adults; nor are decreases in the FEF_{25-75} used to characterize the severity of asthma.

Bronchoprovocation testing — Bronchoprovocation testing is available in most pulmonary function testing laboratories and is a useful tool for diagnosing asthma in patients with normal baseline airflow. Bronchoprovocation testing can be used to identify or exclude airway hyperresponsiveness in patients with atypical presentations (eg, normal baseline spirometry, no

variability in airflow limitation with serial spirometry or peak flow) or isolated symptoms of asthma, especially cough. (See 'History' above.)

A provocative stimulus (eg, inhaled methacholine, inhaled mannitol, exercise, or hyperventilation of dry air) is used to stimulate bronchoconstriction. People with asthma are more sensitive (hyperresponsive) to such stimuli than those without asthma (figure 4). When paradoxical vocal cord motion is being considered in the differential, an inspiratory and expiratory flow volume loop and sometimes also direct laryngoscopy are performed during bronchoprovocation testing to identify an upper airway response mimicking asthma. (See "Inducible laryngeal obstruction (paradoxical vocal fold motion)", section on 'Evaluation and diagnosis'.)

The technical aspects of performing this type of testing, interpreting the results, and identifying the causes of false positive and false negative results are presented separately. A positive test (indicating bronchial hyperresponsiveness) is not entirely specific for asthma. Using a cut point of 8 mg/mL of methacholine or less to indicate the presence of hyperresponsiveness, as many as 5 percent of the normal population and a greater percentage of non-asthmatic persons with rhinitis will exhibit positive results. However, false negative results are uncommon, and a negative test (no significant decline in FEV_1 at the highest dose of methacholine administered) performed in a patient off controller therapy for asthma reliably excludes the diagnosis of asthma. (See "Bronchoprovocation testing", section on 'Pharmacologic challenge'.)

Other specialized provocation testing can be used when evaluating the role of a specific precipitating factor. Typical examples include measuring lung function before and after exercise when a diagnosis of exercise-induced bronchoconstriction related to asthma is suspected, and evaluation of possible occupational asthma by FEV_1 or PEF measurements made before and after the work shift. (See "Exercise-induced bronchoconstriction" and "Bronchoprovocation testing", section on 'Exercise challenge' and "Occupational asthma: Clinical features, evaluation, and diagnosis".)

Peak expiratory flow — The peak expiratory flow (PEF) is measured during a brief, forceful exhalation, using a simple and inexpensive device (approximately $20). We typically use PEF measurements to monitor patients with a known diagnosis of asthma or to assess the role of a particular occupational exposure or trigger, rather than as a tool for the primary diagnosis of asthma [1]. In contrast to spirometry, applying quality control to peak flow measurements is difficult because of the lack of graphic display to ensure appropriate technique and maximal patient effort and the lack of ability to calibrate different peak flow meters.

- **Technique** – The PEF maneuver can be performed sitting or standing. Proper technique involves taking a maximally large breath in, putting the peak flow meter quickly to the mouth, sealing the lips around the mouthpiece, and blowing out as hard and fast as possible into the meter. For PEF, the effort does not need to be sustained beyond one to two seconds. The maneuver is performed three times and the highest of the three measurements is recorded (table 3 and figure 5). (See "Peak expiratory flow monitoring in asthma" and "Patient education: How to use a peak flow meter (Beyond the Basics)".)

- **Normal values** – Average normal values for men and women are based upon height and age (calculator 1 and calculator 2) (table 4A-B). Average normal values for adolescents are based upon height (table 5). The range of normal values around the mean is up to 80 to 100 L/min.

- **Interpretation of PEF –** A single peak flow determination made in the doctor's office at the time that a patient is experiencing respiratory symptoms, if reduced from the normal predicted value, is suggestive of asthma. However, it is not diagnostic because a reduced peak flow is not specific for airflow obstruction and can be seen with other pulmonary processes. On the other hand, a reduced peak flow that improves by more than 20 percent approximately 10 to 20 minutes after administration of a quick-acting bronchodilator (eg, inhaled albuterol) provides supportive evidence favoring the diagnosis of asthma.

Even with careful measurements, PEF may vary as much as 10 to 15 percent from one measurement to the next. PEF results that vary little over time (less than 10 percent of the maximal value) despite the presence of symptoms such as cough and shortness of breath argue against the diagnosis of asthma. In contrast, PEF values that repeatedly fall by more than 20 percent when symptoms are present and return to baseline as symptoms resolve are consistent with asthma.

- **Limitations of PEF** – PEF measurement has several shortcomings as a diagnostic tool for asthma, including [1,10,11,13-16]:
  - Peak flow values often underestimate the severity of airflow obstruction (figure 6). Significant airflow obstruction may be present on spirometry when the peak flow is within the normal range.
  - Reduced peak flow measurements may be seen in both obstructive and restrictive diseases. Spirometry and sometimes measurement of lung volumes are necessary to distinguish the two.
  - Peak flow measurements are not sufficient to distinguish upper airway obstruction (eg, vocal cord dysfunction) from asthma. Spirometry with a flow-volume loop is needed for evaluation of upper airway obstruction. (See "Overview of pulmonary function testing in adults", section on 'Flow-volume loop'.)
  - The validity of PEF measurements depends entirely upon patient effort and technique. Errors in performing the test frequently lead to underestimation of true values, and occasionally to overestimation.
  - Home PEF monitoring is unsupervised. Patients may produce higher values in the clinician's office with appropriate coaching to ensure a maximal effort.
  - Peak flow meters cannot be routinely calibrated, unlike spirometers. Thus, results will vary somewhat between different instruments and the accuracy of a particular peak flow meter may deteriorate over time.

Exhaled nitric oxide — The measurement of nitric oxide in a patient's exhaled breath can aid in the diagnosis of asthma in combination with other tests, but a normal level does not exclude asthma. The test is based on the observation that eosinophilic airway inflammation associated with asthma leads to up-regulation of nitric oxide synthase in the respiratory mucosa, which in turn generates increased amounts of nitric oxide gas in the exhaled breath. The concentration of nitric oxide (fraction of exhaled nitric oxide [FENO]) in the exhaled breath of some persons with asthma is elevated above the low levels of FENO in normal individuals and those with stable, well-controlled asthma. An elevated FENO (≥40 to 50 parts per billion) can help “rule in” asthma, although potentially confounding respiratory diseases (eg, allergic rhinitis, eosinophilic bronchitis) must be excluded. Treatment with oral and/or inhaled glucocorticoids reduces airway inflammation and levels of exhaled nitric oxide. The measurement of FENO and its potential role in asthma diagnosis and monitoring are discussed separately. (See "Exhaled nitric oxide analysis and applications".)

Blood tests — No blood tests are available that can determine the presence or absence of asthma or gauge its severity. However, a complete blood count (CBC) with differential white blood cell analysis to screen for eosinophilia or significant anemia may be helpful in certain cases. We typically obtain a CBC and differential when asthma symptoms are severe, the patient presents to the hospital with an exacerbation, nasal polyposis is present, the chest radiograph is abnormal (eg, suggestive of eosinophilic pneumonia or eosinophilic granulomatosis with polyangiitis [Churg Strauss]), or a parasitic infection is suspected.

- Markedly elevated eosinophil percentages (>15 percent) or counts (>1500 eosinophils/microL) may be due to allergic asthma, but should prompt consideration of alternative or additional diagnoses, including parasitic infections (eg, Strongyloides), drug reactions, and syndromes of pulmonary infiltrates with eosinophilia, including allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome. (See "Approach to the patient with unexplained eosinophilia" and "Overview of pulmonary eosinophilia".)

- Significant anemia can cause dyspnea that is unresponsive to asthma therapies and would require further evaluation to determine the causative process.

For the lifelong non-smoker with persistent and irreversible airflow obstruction, a one-time measurement of the serum alpha-1 antitrypsin level is recommended to exclude emphysema due to homozygous alpha-1 antitrypsin deficiency, which is in the differential of chronic and largely irreversible airflow limitation. (See "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency".)

Tests for allergy — Allergy tests are not useful for the diagnosis of asthma, but they can be helpful to confirm sensitivity to suspected allergic triggers of respiratory symptoms and to guide on-going management of asthma. We usually perform allergy testing in selected patients with a history of symptoms that occur upon exposure to particular aeroallergen(s) (table 1), persistent symptoms and suspicion of exposure to relevant allergens in the home environment (eg, pet animals, dust, cockroaches, or mice), and/or moderate-to-severe asthma symptoms despite conventional therapies. In addition to the peripheral blood eosinophil count mentioned above, the main tests for allergy are the total serum immunoglobulin E (IgE) level and the tests for specific allergic sensitization, which include blood testing for specific IgE antibody to inhalant allergens and skin testing with extracts of inhalant allergens.

Measurement of total serum IgE levels is indicated in patients with moderate-to-severe persistent asthma when considering treatment with anti-IgE monoclonal antibody (omalizumab) or when allergic bronchopulmonary aspergillosis is suspected on the basis of eosinophilia, a positive skin test to aspergillus, or radiographic evidence of mucus plugging or central bronchiectasis. An elevated total IgE level may occur in the absence of asthma (eg, in allergic rhinitis or eczema), and allergic asthma may be present in the absence of an elevated total IgE level, which may not fully reflect the levels of mast cell-bound IgE in airway tissue. Very high total IgE levels (>1000 IU/mL) are typically found in persons with allergic bronchopulmonary aspergillosis, certain parasitic infections, and sometimes eczema. (See "The biology of IgE", section on 'Increased total IgE' and "Clinical manifestations and diagnosis of allergic bronchopulmonary aspergillosis" and "Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis".)

Allergic sensitivity to specific allergens in the environment can be assessed using either of two methods: blood tests for allergen-specific IgE or allergy skin tests.

- Blood tests for allergen-specific IgE most commonly utilize enzyme-linked immunosorbent assays (ELISA) to measure minute quantities of IgE antibody specifically directed at particular allergens (as opposed to the total serum IgE discussed above). This type of blood test is often referred to as RAST, although the radioallergosorbent assay method has been replaced with a non-radioactive detection reagent, called an immunoassay. Based on the aeroallergens in the patient's geographic location and household, a panel of immunoassays is ordered. Aeroallergens (eg, house dust mite antigen, cat and dog danders, cockroach antigen, mouse and rat antigens, pollens, and mold spores) are the types of allergens most commonly implicated in asthma. Orally ingested food allergens rarely cause isolated asthmatic symptoms; inhaled food particles (eg, fish cooking, peanut dust in a closed space) occasionally trigger asthma symptoms. By asking relatively few specific questions, clinicians can often elicit a potential relationship between allergen exposure and asthmatic symptoms that will guide the choice of which antigens to assess by immunoassay (table 1). When ordering these blood tests, one can select specific antigens for testing or choose among pre-grouped panels of antigens. The technique and accuracy of immunoassays are discussed separately. (See "Overview of in vitro allergy tests", section on 'Immunoassays for allergen-specific IgE'.)

- Allergy skin tests are performed to a panel of indoor and outdoor aeroallergens. The negative predictive value of skin testing (using prick and intradermal techniques) is very high, such that skin testing can exclude allergy with relative certainty. Skin testing should be performed by a trained allergy technician and interpreted by an allergy specialist. The indications, contraindications, technique, and interpretation of allergy skin tests are presented in detail separately. (See "Overview of skin testing for allergic disease".)

The advantages of in vitro testing over skin testing are that no trained technician is needed to apply the test, antihistamines and other medications do not interfere with the results, and there is no risk of adverse reactions (eg, inducing asthmatic reactions or anaphylaxis). The disadvantages are the greater cost and somewhat lesser sensitivity of immunoassays compared with skin testing and lack of the immediate and often powerful visual feedback for the patient that occurs with a positive skin test reaction.

Imaging — In the absence of comorbid illness, the chest radiograph is almost always normal in patients with asthma. However, many clinicians, including ourselves, obtain a chest radiograph for new-onset, moderate-to-severe asthma in adults over age 40 to exclude the occasional alternative diagnosis that may mimic asthma (eg, the mediastinal mass with tracheal compression or heart failure). The cost-effectiveness of this approach has not been evaluated.

In contrast, chest radiographs are routinely recommended when evaluating severe or "difficult-to-control" asthma and when co-morbid conditions (eg, allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, or atelectasis due to mucus plugging) are suspected based on history, physical examination, and/or other laboratory data.

In addition, chest radiography is indicated in patients presenting with features that are atypical for asthma, including any of the following:

- Fever
- Chronic purulent sputum production
- Persistently localized wheezing
- Hemoptysis
- Weight loss
- Clubbing
- Inspiratory crackles
- Significant hypoxemia (eg, pulse oxygen saturation less than approximately 94 percent) in the absence of an acute asthmatic attack
- Moderate or severe airflow obstruction that does not reverse with bronchodilators

High resolution computed tomography (HRCT) scanning is performed when abnormalities seen on conventional chest radiography need clarification or when other processes are suspected, such as bronchiectasis, bronchiolitis obliterans, tracheomalacia, or vascular anomalies compromising central airways (eg, right sided aortic arch and aberrant left subclavian artery). (See 'Differential diagnosis' below and "Overview of bronchiolar disorders in adults" and "Clinical manifestations and diagnosis of bronchiectasis in adults" and "Vascular rings and slings", section on 'Right aortic arch with aberrant left subclavian artery and left-sided ductus arteriosus/ligamentum'.)

DIAGNOSIS

A history of intermittent symptoms typical of asthma plus the finding on physical examination of characteristic musical wheezing (present in association with symptoms and absent when symptoms resolve) strongly point to a diagnosis of asthma. Confirmation of the diagnosis of asthma is based on two key additional elements [1,2]:

- The demonstration of variable expiratory airflow limitation, preferably by spirometry
- Exclusion of alternative diagnoses (see 'Differential diagnosis' below)

Spirometry is the primary method for confirming variable airflow limitation; variability may be demonstrated by testing before and after bronchodilator, from one office visit to another, or before and after bronchoprovocation challenge. Use of pulmonary function testing in this manner helps to prevent both over- and under-diagnosis of asthma [17-19]. The importance of

confirming reversible airflow limitation was illustrated by a study of 701 randomly selected adults with a physician diagnosis of asthma in the previous five years [18]. Upon careful review by a panel of experts, the diagnosis of asthma was excluded in 33 percent and among these, less than half had had previous testing to confirm airflow limitation. (See 'Pulmonary function testing' above.)

The results of initial spirometry are used to guide the diagnostic approach, as described in the following sections.

Initial spirometry shows airflow limitation — A symptom pattern suggestive of asthma AND airflow limitation on initial spirometry, which completely reverses to normal following bronchodilator, virtually clinch the diagnosis of asthma. Likewise, typical symptoms and a large reversibility of airflow obstruction on spirometry (increase in FEV_1 >15 percent) generally confirm the diagnosis of asthma. (See 'Bronchodilator response' above.)

As an example, reversible airflow obstruction in the patient with chronic cough but without other chest symptoms or wheezing on examination would assist in making the correct diagnosis of asthma. On the other hand, finding little or no reversibility on a single test does not necessarily exclude asthma, as the airflow limitation can be caused by concomitant airway inflammation that will only reverse with anti-inflammatory medication (eg, inhaled or oral glucocorticoids) or removal from exposure to an aeroallergen. However, incomplete or absent reversibility should raise the possibility of an alternate diagnosis. (See 'Differential diagnosis' below.)

Initial spirometry is normal — Patients with asthma who are asymptomatic at the time of evaluation often have normal lung function. For these patients, the following strategies can be used to confirm the clinical diagnosis [2]:

- Repeat spirometry at subsequent office visits when the patient is symptomatic
- Patient-recorded serial measurements of PEF over time (eg, morning and evening, with symptoms, and after administration of bronchodilator)
- Bronchoprovocation testing, such as methacholine, mannitol, or exercise challenge (see 'Bronchoprovocation testing' above)

Serial measurements of lung function over time — One useful strategy for diagnosing asthma in patients with normal lung function on initial spirometry is to ask the patient to use a portable hand-held device to measure FEV_1 or PEF and record readings obtained twice a day for two weeks or with and without symptoms. The diagnosis of asthma is confirmed by a reliable series of recordings that document more than 20 percent variability in FEV_1 or PEF over time (especially when these reductions are associated with asthmatic symptoms). Individuals who experience little variability (10 percent or less) in their PEF, even when respiratory symptoms are present, likely do not have asthma [2].

Similar data collection can take place in the clinician's office by recording spirometry or PEF at each patient visit. This method is less dependent on the reliability of the patient independently making self-measurements, although multiple visits may be required.

Serial patient-recorded measurements of FEV_1 (using a small, electronic, hand-held device) or PEF can be combined with a "therapeutic trial" of a bronchodilator [20]. Significant decreases in PEF that reverse within minutes of use of an inhaled beta-adrenergic agonist typify asthma. In individuals without asthma or other chronic airway disease, the increase in PEF following bronchodilator administration would be expected to be less than 20 percent.

Bronchoprovocation — The presence of airways hyperresponsiveness, a key feature of asthma, can be confirmed with bronchoprovocation testing, usually in the form of a methacholine or mannitol inhalation challenge. This diagnostic strategy is particularly useful for patients with atypical symptoms or an atypical response to medications. Given the test's high negative predictive value, it is especially useful when exclusion of a diagnosis of asthma is helpful in patient management. Bronchoprovocation testing is a relatively costly diagnostic strategy and relies on the expertise of sophisticated pulmonary

function laboratories. (See 'Bronchoprovocation testing' above and "Bronchoprovocation testing", section on 'Diagnosis of asthma'.)

A positive methacholine provocation challenge (eg, a 20 percent decrease in FEV_1 at a methacholine concentration of 8 mg/mL or less) is indicative of airways hyperresponsiveness. While airways hyperresponsiveness is most commonly due to asthma, other diseases, such as COPD, cystic fibrosis, and allergic rhinitis, can cause a "false positive" methacholine challenge. (See "Bronchoprovocation testing", section on 'Interpretation'.)

Diagnosis based on history and clinical course — In some instances, the history and clinical course are strongly suggestive of asthma, and a treatment trial is initiated as part of the diagnostic process. The combination of a typical presentation (eg, repeated episodes of typical symptoms triggered by typical stimuli), musical wheezes on auscultation, and a prompt response to anti-asthma medication may be used to make a presumptive diagnosis, as might occur for new-onset asthma presenting in an acute care setting. However, we agree with the NAEPP guidelines that the clinical diagnosis of asthma should be validated with objective data, whenever possible. For patients with less typical or more persistent or refractory symptoms, formal spirometric data are essential to ensure that the correct diagnosis is identified [21].

DIFFERENTIAL DIAGNOSIS

Cough, wheeze, shortness of breath, and chest tightness, while characteristic of asthma, are also symptoms of a number of other respiratory diseases affecting both the upper and lower respiratory tracts. Some of these diseases can also result in airflow obstruction on spirometry. In addition, certain non-respiratory conditions (eg, heart failure, gastroesophageal reflux) may mimic asthma symptoms, and several common conditions (eg, chronic rhinosinusitis, laryngopharyngeal esophageal reflux) may coexist with asthma and increase its severity.

Conditions causing similar symptoms — Alternative diagnoses that may cause cough, wheeze, or shortness of breath include the following:

- **Wheeze** — Wheezing may be generated by luminal narrowing anywhere along the respiratory tract, including nares, pharynx, glottis, trachea, and bronchi. Inspiratory upper airway sounds, including stridor, are usually distinguishable from asthma. Expiratory wheezes emanating from the upper airway (eg, vocal cord dysfunction syndrome) are often readily audible without a stethoscope but sound distant on auscultation of the lower chest. However, at times these upper airway sounds may be transmitted widely throughout the chest, making differentiation from asthma difficult. A focal, monophonic wheeze (eg, bronchogenic carcinoma or foreign body aspiration) should not be confused with asthma. The full spectrum of disorders that can cause wheezing is presented elsewhere. (See "Clinical presentation, diagnostic evaluation, and management of central airway obstruction in adults" and "Evaluation of wheezing illnesses other than asthma in adults".)

- **Cough** — When persistent cough is the presenting complaint and lung function and chest radiograph are normal, the differential includes rhinitis or rhinosinusitis, gastroesophageal reflux disease (GERD), post-viral tussive syndrome, eosinophilic bronchitis, cough induced by angiotensin converting enzyme inhibitors, and infection with Bordetella pertussis ("whooping cough"). (See "Evaluation of subacute and chronic cough in adults".)

  A chronic cough with mucoid sputum production in a long-term cigarette smoker (generally more than 10 pack-years) points to a diagnosis of chronic bronchitis. Chronic bronchitis may develop in the presence or absence of airflow limitation on pulmonary function tests and may be partially alleviated by treatments for asthma.

- **Dyspnea** — Dyspnea has a broad differential, but common causes that are in the differential of asthma in the adult are COPD, heart failure, pulmonary embolism, and sarcoidosis. (See "Approach to the patient with dyspnea" and "Evaluation of the adult with dyspnea in the emergency department".)

Obesity can cause a pattern of dyspnea that mimics asthma [17]. In a study of patients with an elevated body mass index (BMI >30 kg/m^2) and a doctor diagnosis of asthma, formal testing for bronchial hyperresponsiveness was negative in 36 percent [22]. This observation underscores the need for a definitive initial diagnosis of asthma. Obesity can also add to the severity of dyspnea in patients with asthma. (See "Risk factors for asthma", section on 'Obesity'.)

In patients with asthma-like symptoms, the diagnostic considerations vary in part by age:

- In adolescents and young to middle-aged adults, the principal considerations include recurrent bouts of bronchitis, bronchiolitis, bronchiectasis, paradoxical vocal cord motion, pulmonary embolism, GERD, panic disorder, and sarcoidosis. (See "Overview of bronchiolar disorders in adults" and "Clinical manifestations and diagnosis of bronchiectasis in adults" and "Inducible laryngeal obstruction (paradoxical vocal fold motion)" and "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism" and "Gastroesophageal reflux and asthma" and "Clinical manifestations and diagnosis of pulmonary sarcoidosis".)

- In older-aged patients, especially cigarette smokers, additional considerations include COPD, left-ventricular heart failure, interstitial lung disease, tumors involving central airways, and recurrent oropharyngeal aspiration. (See "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging" and "Heart failure: Clinical manifestations and diagnosis in adults".)

Conditions producing obstructive patterns on spirometry

- COPD typically presents in patients with a substantial smoking history (eg, >20 pack years). The symptoms of dyspnea on exertion and cough with or without sputum production can mimic adult-onset asthma. Variable airflow obstruction over time and an improvement on post-bronchodilator spirometry can be seen, similar to asthma, although the improvement in postbronchodilator spirometry is generally less pronounced in COPD and does not achieve normal values. (See "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging".)

- Asthma-COPD overlap (ACO) is characterized by persistent airflow limitation (may be partially reversible) in patients with features of both asthma (atopy and large variability in airflow limitation) and COPD (history of cigarette smoking and a component of irreversible airflow obstruction) [2,23]. Patients are typically age 40 or older with a long history of cigarette smoking, and in addition they may have had asthma symptoms since childhood. Aeroallergen sensitivity is common, as is a family history of asthma and allergy. Symptoms are typically persistent, but variable. Research suggests a distinct natural history and perhaps genetic predisposition compared to COPD without asthmatic features. (See "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging" and "Asthma and COPD overlap (ACO)".)

- Bronchiectasis, a condition of abnormal widening of the bronchi due to airway wall injury associated with chronic or recurrent infection, shares many clinical features with asthma, including inflamed airways, obstruction to airflow, and exacerbations characterized by increased dyspnea and sputum production. Bronchiectasis is suspected on the basis of prominent symptoms of cough with mucopurulent sputum production, recurrent chest infections, and sometimes hemoptysis. The diagnosis is usually established radiographically based on characteristic findings of bronchial wall thickening and luminal dilation seen on chest computed tomographic (CT) scans. (See "Clinical manifestations and diagnosis of bronchiectasis in adults".)

- Constrictive bronchiolitis, also known as bronchiolitis obliterans, is characterized by submucosal and peribronchiolar fibrosis that causes concentric narrowing of the bronchiolar lumen. Constrictive bronchiolitis is most commonly seen following viral illness, inhalation injury, transplantation (eg, bone marrow, lung), or in the context of rheumatoid lung or inflammatory bowel disease (table 6). Symptoms include progressive onset of cough and dyspnea associated with hypoxemia at rest or with exercise. Crackles may be present. Pulmonary function tests show a progressive and

irreversible airflow limitation. Findings on CT scan may include centrilobular bronchial wall thickening, bronchiolar dilation, tree-in-bud nodularity, and a mosaic pattern of attenuation of lung tissue density. (See "Overview of bronchiolar disorders in adults" and "Overview of bronchiolar disorders in adults", section on 'Diagnosis'.)

- Central airway obstruction can be caused by numerous benign and malignant processes and can mimic asthma with dyspnea on exertion that may progress to dyspnea with minimal activity. Monophonic wheezing or stridor may be present. Symptoms are minimally, if at all, improved by inhaled bronchodilator. A high index of suspicion is needed as conventional chest radiographs are rarely diagnostic. Flow-volume loops can show the characteristic changes of flow limitation due to upper airway obstruction (figure 3 and figure 7). A high resolution CT scan with three-dimensional airway reconstruction can be helpful when structural lesions (eg, stenosis, airway tumors, vascular rings) are suspected. Dynamic chest CT imaging at end inspiration and during forced expiration can be used to diagnose tracheobronchomalacia. The gold standard for diagnosis of central airway obstruction is direct visualization via bronchoscopy. (See "Flow-volume loops" and "Clinical presentation, diagnostic evaluation, and management of central airway obstruction in adults", section on 'Diagnostic evaluation and initial management' and "Tracheomalacia and tracheobronchomalacia in adults", section on 'Computed tomography'.)

Coexistent conditions — Certain illnesses commonly coexist with asthma and may exacerbate its course. These illnesses are discussed separately. (See "Evaluation of severe asthma in adolescents and adults", section on 'Assessing comorbid conditions'.)

- Allergic rhinitis is present in most patients with allergic asthma and in at least 50 percent of those with non-allergic asthma [24]. The frequency with which rhinitis and asthma co-exist has prompted formation of the "integrated airway hypothesis," which proposes that the two conditions are essentially one disorder, involving both the upper and lower airways in most patients [25]. Post-nasal drip associated with any form of chronic rhinitis or sinusitis can also worsen asthma symptoms. (See "Chronic rhinosinusitis: Clinical manifestations, pathophysiology, and diagnosis".)

- Both obesity and GERD can mimic asthma and can worsen pre-existent asthma. (See "Gastroesophageal reflux and asthma".)

- Patients with obesity and mild asthma may perceive more severe dyspnea than would be anticipated on the basis of spirometry. (See "Risk factors for asthma", section on 'Obesity'.)

INDICATIONS FOR REFERRAL

Consultation with an asthma specialist, either a pulmonologist or an allergist, is warranted when the diagnosis of asthma is uncertain, when the asthma is difficult-to-control, medication side effects are intolerable, or when a patient has frequent exacerbations. Pulmonologists may be most helpful if alternative pulmonary diseases are suspected or if further pulmonary testing or bronchoscopy may be needed. Referral to an allergist may be most helpful if allergic triggers need further evaluation or if concomitant nasal and ocular allergy symptoms are difficult-to-control.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Asthma in adolescents and adults" and "Society guideline links: Exercise-induced bronchoconstriction".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Asthma treatment in adolescents and adults (Beyond the Basics)" and "Patient education: Trigger avoidance in asthma (Beyond the Basics)" and "Patient education: How to use a peak flow meter (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Asthma may develop at any age, although the majority of people with asthma are diagnosed in childhood. Obtaining the clinical history in an adult should include questions about the presence of symptoms earlier in life. Other historic clues that are highly suggestive of asthma include recurring, episodic symptoms, the presence of typical triggers (especially exercise, cold air, or allergen exposure), and personal or family history of allergic disease (table 1). (See 'History' above.)

- The physical examination may be normal in asthma. The presence of abnormal findings (such as wheezing) is suggestive of asthma, although not specific. Asthmatic wheezing is typically composed of multiple high-pitched sounds audible most prominently during expiration. Nasal examination should be included to check for the pale, swollen mucosa of associated allergic rhinitis and for nasal polyps, which raise the possibility of aspirin-exacerbated respiratory disease. (See 'Physical findings' above.)

- The pulmonary function tests most helpful in diagnosing asthma are spirometry pre- and post-bronchodilator, bronchoprovocation testing (usually with methacholine), and peak expiratory flow (PEF) monitoring. Expiratory airflow obstruction with a reversible reduction in the forced expiratory volume in one second (FEV_1), heightened sensitivity to bronchoprovocative agents such as methacholine or exercise, and variability over time of >20 percent in PEF are findings consistent with asthma. (See 'Pulmonary function testing' above.)

- Other laboratory studies are sometimes indicated to identify potential asthma triggers and exclude alternative diagnoses, including blood tests (eg, complete blood count with white blood cell differential, total serum immunoglobulin E, and allergen-specific immunoassays), skin testing for environmental allergies, and a chest radiograph. (See 'Evaluation' above.)

- The diagnosis of asthma is based upon the presence or history of symptoms consistent with asthma (most commonly episodic cough, wheezing, or dyspnea provoked by typical triggers), combined with the demonstration of variable expiratory airflow obstruction. The strategies for using pulmonary function testing vary based on the results of initial spirometry. (See 'Definition' above and 'Diagnosis' above.)

- The preferred approach to the diagnosis of asthma is the use of spirometry to identify reversible airflow obstruction. An obstructive pattern with an increase in FEV_1 of more than 12 percent from the baseline measurement following administration of 2 to 4 puffs of a quick-acting bronchodilator, is suggestive of asthma, especially if post-bronchodilator spirometry is normal. (See 'Spirometry' above.)

- An alternative approach is to obtain serial measurements of FEV_1 or PEF over time at home or in the office. Patients can track the results in a peak flow diary (figure 5). A variability of >20 percent that corresponds to symptoms is strongly suggestive of asthma. PEF measurement can be combined with a therapeutic trial of inhaled bronchodilator. (See 'Peak expiratory flow' above and 'Serial measurements of lung function over time' above.)

- Bronchoprovocation testing, such as with a methacholine, mannitol, or exercise challenge, is typically reserved for patients in whom the baseline spirometry is normal and the diagnosis remains uncertain. (See 'Bronchoprovocation testing' above and "Bronchoprovocation testing".)

- For clinical settings in which neither spirometry nor peak flow measurement is available, a diagnosis of **probable** asthma can be made based upon history alone, provided the patient has typical symptoms that respond promptly and completely to therapy. History-based diagnosis is also appropriate for urgent care settings when patients respond to asthma therapies as expected. Peak flow measurements are appropriate in these office-based and urgent care settings to supplement history and exam. (See 'Diagnosis based on history and clinical course' above.)

- The differential diagnosis of asthma includes respiratory and non-respiratory conditions that may cause similar symptoms, wheezing on examination, and/or an obstructive pattern on spirometry. Evaluation should include assessment for conditions that may co-exist with asthma and worsen its severity. (See 'Differential diagnosis' above.)

- The classification of asthma severity (table 2) and a step-wise approach to asthma management are provided separately. (See "An overview of asthma management".)

Topic 543 Version 30.0

GRAPHICS

Questions to help identify asthma triggers*

Allergen exposures
Do you have asthma symptoms year-round or only certain times of year?
Do you have pets? Or birds? Are they indoors or outdoors most of the time?
Have you seen cockroaches at home/school/work in the past month? How about rodents?
Is there moisture, dampness, moldy odor, or visible mold in your home?¶
For patients who live in dry climates, do you use an evaporative cooler (also known as a swamp cooler)? These coolers are associated with increased humidity and increased mold/dust mites.
Do your asthma symptoms get worse during pollen seasons (eg, tree pollen in early spring in New England) or more humid times of year (suggests molds and dust mites)?
Have you ever had allergy skin or IgE testing? If so, do you have the results?
Irritant exposures
Do you smoke cigarettes? If so, how many/day and how long have you smoked?
Does anyone at home/work/daycare smoke?
Do you smoke cannabis (marijuana), use electronic cigarettes, or vape?
Do you use a wood-burning stove or fireplace at home?
Do you have any unvented/open fire stoves or heaters at home?
Are you exposed regularly to smells or fumes from perfumes, cleaning agents, or sprays?
Work and school
Do you cough, wheeze or need your inhaler more during the week at work/school than on weekends or times away from work/school?
Do your eyes or nose itch or feel irritated at work/school?
Do coworkers or other students have similar symptoms?
Are you exposed to fumes, dusts, or vapors at work? If so, what?
Nasal problems
Do you have seasonal or persistent nasal congestion, runny nose, postnasal drip, or decreased sense of smell?
Are your nasal symptoms worse at home/school/work?
Gastroesophageal reflux
Do you have heartburn (burning sensation in the chest); does food come back up into your mouth; or do you sense/taste sour stomach acid coming

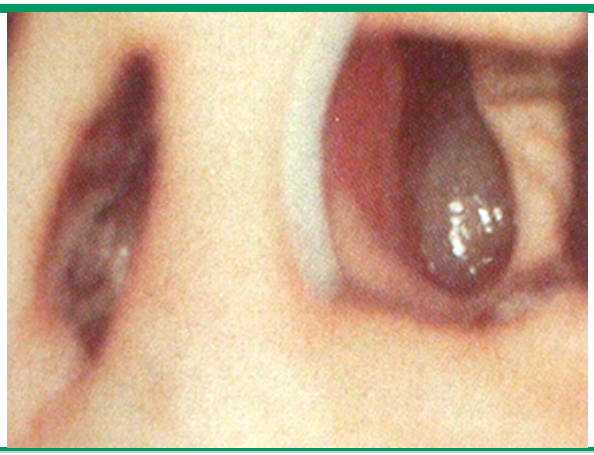
up into your throat?
Medications that can worsen asthma
Do you use eye drops? If so, which? Do your asthma symptoms worsen after taking them?
Do you use any medications that contain beta-blockers or ACE inhibitors? Has your asthma worsened since you started taking this medication?
Do you take aspirin or other NSAIDs? Do your asthma symptoms flare when you take them?
Possible sulfite sensitivity[Δ]
Do you have wheezing, coughing, or shortness of breath after eating shrimp, dried fruit, or processed potatoes or after drinking beer or wine?

IgE: immunoglobulin E; ACE: angiotensin-converting enzyme; NSAID: nonsteroidal anti-inflammatory drug.
* These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.
¶ Higher humidity makes mold and mite exposure more likely. Visible mold suggests significant mold exposure.
Δ Rare issue in children.

Adapted from: National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication no. 08-4051, 2007.

Graphic 80507 Version 12.0

Nasal polyps in nostril



Nasal polyps appear as glistening, gray or white, mucoid masses in the nasal cavities.

Courtesy of Glenis Scadding, MD and Peter Andrews, BSc, FRCS.

Graphic 50105 Version 4.0

Adult atopic dermatitis

Chronic atopic dermatitis with lichenification (skin thickening and enhancement of skin markings) of the knee flexures in a 22-year-old woman.

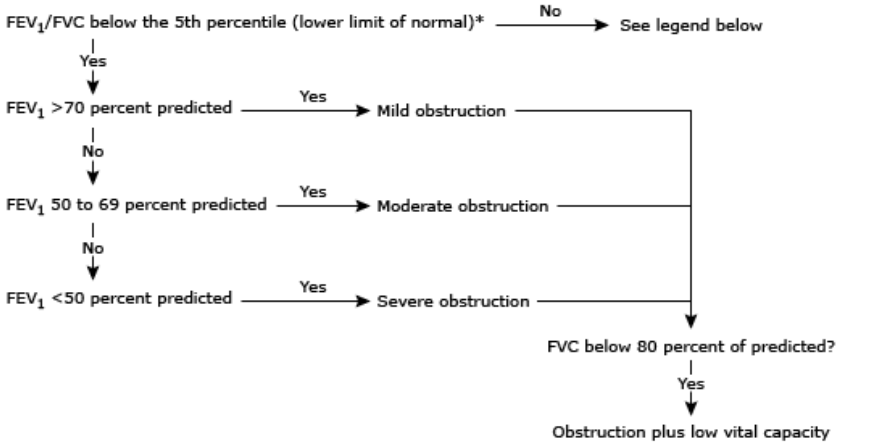
Graphic 64525 Version 4.0

Adult chronic atopic dermatitis

Lichenified, hyperpigmented plaque in the elbow flexure of a 35-year-old woman with atopic dermatitis.

Graphic 55375 Version 5.0

Interpretation of office spirometry: Obstructive pattern



If the FEV_1/FVC ratio is normal AND the FEV_1 is greater than 80 percent of predicted, then the spirometry is normal.
If the FEV_1/FVC is reduced and the FEV_1 is >80 percent predicted, spirometry may be normal; this finding may be due to a prolonged exhalation phase leading to overestimation of the FVC.
If the FEV_1/FVC ratio is normal, but the FVC is mildly reduced (70 to 80 percent of predicted), the cause may be abdominal obesity or poor technique.
If the FEV_1/FVC ratio is normal, but the FVC is below 80 percent of predicted, consider referring the patient to a pulmonary function laboratory for measurement of lung volumes and diffusing capacity (DLCO) to assess for a possible restrictive ventilatory defect (eg, interstitial lung disease or respiratory muscle weakness).

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.
* The FEV_1 decreases with age, so the lower limit of normal (LLN) should be used to detect airway obstruction rather than the absolute value of FEV_1/FVC.

Adapted from: Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26:948.

Graphic 72469 Version 2.0

Classifying asthma severity in youths 12 years of age or older and adults

Components of severity		Classification of asthma severity (youths ≥12 years of age and adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8 to 19 years – 85% 20 to 39 years – 80% 40 to 59 years – 75% 60 to 80 years – 70%	Symptoms	≤2 days/week	>2 days/week, but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2 times/month	3 to 4 times/month	>1 time/week, but not nightly	Often 7 times/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week, but not >1 time/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60 but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	**Exacerbations requiring oral systemic corticosteroids**	**0 to 1/year (see footnote)**	**≥2/year (see footnote)**		
		Consider severity and interval since last exacerbation			
		Frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV_1			

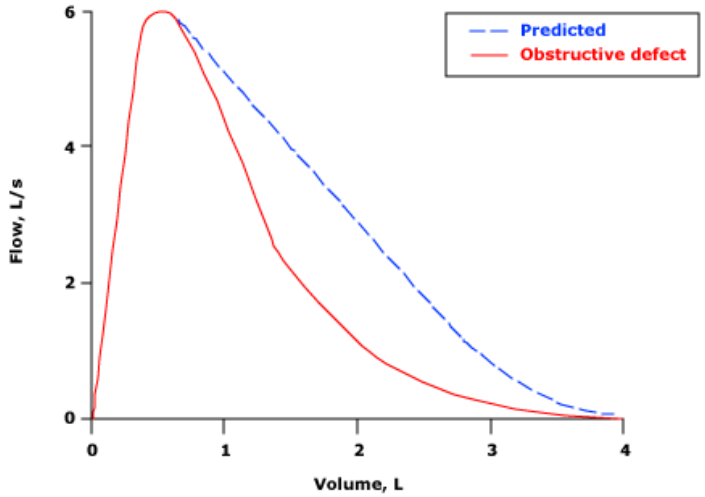
Classifying severity for patients who are not currently taking long-term control medications. Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous two to four weeks and spirometry. Assign severity to the most severe category in which any feature occurs. At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; EIB: exercise-induced bronchoconstriction; ICU: intensive care unit.

Reproduced from: National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication no. 08-4051, 2007.

Graphic 71425 Version 3.0

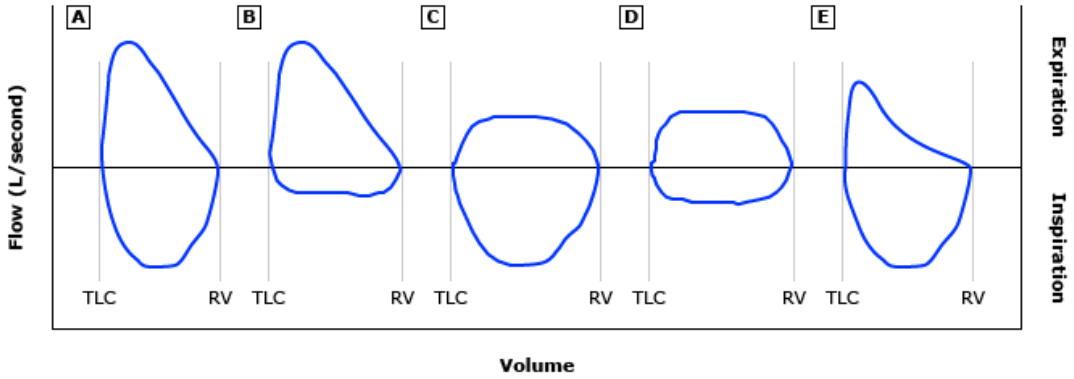
Obstructive defect



The flow-volume curve in a patient with an obstructive defect (red, solid line) demonstrates scooping of the expiratory portion of the flow-volume curve compared with the predicted curve (blue, dashed line). The expiratory flow rate is reduced over most of the vital capacity.

Graphic 58092 Version 4.0

Flow-volume loops in upper airway obstruction



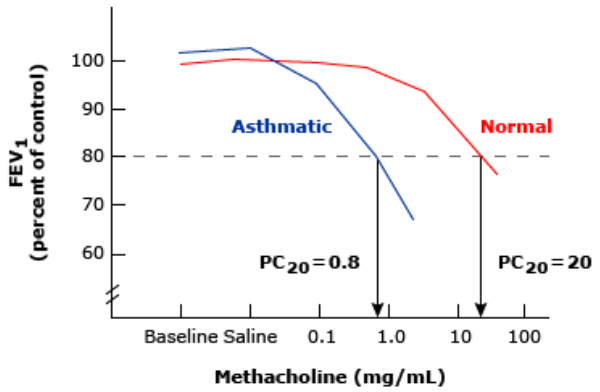
The configuration of the flow-volume loop can help distinguish the site of airway narrowing. The airways are divided into intrathoracic and extrathoracic components by the thoracic inlet.
(A) Normal flow-volume loop: the expiratory portion of the flow-volume curve is characterized by a rapid rise to the peak flow rate, followed by a nearly linear fall in flow. The inspiratory curve is a relatively symmetrical, saddle-shaped curve.
(B) Dynamic (or variable, nonfixed) extrathoracic obstruction: flow limitation and flattening are noted on the inspiratory limb of the loop.
(C) Dynamic (or variable, nonfixed) intrathoracic obstruction: flow limitation and flattening are noted on the expiratory limb of the loop.
(D) Fixed upper airway obstruction (can be intrathoracic or extrathoracic): flow limitation and flattening are noted in both the inspiratory and expiratory limbs of the flow-volume loop.
(E) Peripheral or lower airways obstruction: expiratory limb demonstrates concave upward, also called "scooped-out" or "coved" pattern.

TLC: total lung capacity; RV: residual volume.

Adapted from: Stoller JK. Spirometry: a key diagnostic test in pulmonary medicine. Cleve Clin J Med 1992; 59:75.

Graphic 76811 Version 7.0

Bronchoprovocation testing



The effect of increasing the inhaled dose of methacholine in a healthy subject (red) and an asthmatic patient (blue). The provocative concentration is the amount of inhaled agonist required to drop the FEV_1 by 20 percent from the baseline (PC_{20} FEV_1) and is much less in the asthmatic than in the normal subject: 0.8 mg/mL versus 20 mg/mL. In general, a PC_{20} ≤8 mg/mL is consistent with asthma; and a PC_{20} >16 mg/mL is considered a negative test. Thus, an increase in airway responsiveness is characterized by a decrease in the PC_{20}.

Graphic 82365 Version 2.0

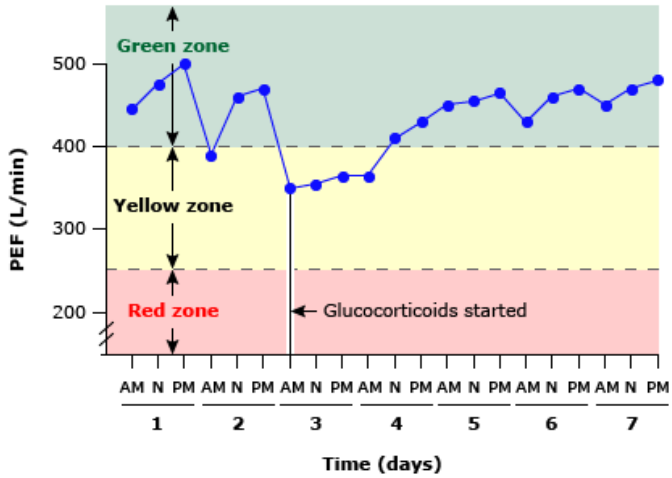
Technique for peak flow measurement in asthma

Move peak flow meter indicator to zero.
Sit or stand up straight.
Take in a deep breath, as deep as you can.
Place peak flow meter in your mouth and close your lips around the mouthpiece*.
As soon as your lips are sealed around mouth piece, blow out as hard and fast as you can using your chest and belly muscles¶. This should take no more than 2 seconds.
Write down the result.
Repeat two more times (three total).
Record the highest of the three values.

* Nose clips are not necessary.
¶ Make sure to use all of your breathing muscles, not just your mouth muscles. This needs a lot of force, like blowing out a candle several feet away.

Graphic 53856 Version 5.0

Peak flow diary in asthma



Diary record of peak expiratory flow (PEF) from an asthmatic patient over a one week period. The patient recorded PEF three times a day at waking (AM), noon (N) and upon retiring (PM). The red zone is set at 50 percent of the personal best, whereas the yellow is from 50 to 80 percent and the green zone is >80 percent. Notice the reproducible morning (AM) falls in PEF characteristic of the patient with nocturnal asthma. Also note the improvement in PEF as glucocorticoids are added to the treatment regimen.

Graphic 79373 Version 2.0

Predicted peak expiratory flow (PEF; liters/minute) for males age 20 to 70 years

Age (years)	Height				
	60 inches/152 cm	65 inches/165 cm	70 inches/178 cm	75 inches/191 cm	80 inches/203 cm
20	477	539	606	678	748
25	484	546	613	685	756
30	488	550	616	688	759
35	487	549	616	688	758
40	483	545	611	683	754
45	474	536	603	675	746
50	462	436	591	663	733
55	446	508	575	646	717
60	426	488	554	626	697
65	402	464	530	602	673
70	374	436	503	574	645

For patients who do not know their personal best PEF, this table can help estimate an expected "personal best." This table uses a prediction equation for White males, age 20 to 70 years. Refer to UpToDate calculator for values for additional age, height, and race/ethnicity parameters.

Reference:

1. *Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159(1):179.*

Graphic 57257 Version 10.0

Predicted peak expiratory flow (PEF; liters/minute) for females age 20 to 70 years

Age (years)	Height				
	55 inches/140 cm	60 inches/152 cm	65 inches/165 cm	70 inches/178 cm	75 inches/190 cm
20	333	372	418	468	517
25	340	379	425	475	524
30	344	383	429	479	528
35	344	383	430	479	529
40	342	381	427	477	526
45	336	376	422	471	521
50	328	367	413	463	512
55	316	323	401	451	501
60	301	341	387	436	486
65	283	323	369	419	468
70	263	302	348	398	447

For patients who do not know their personal best PEF, this table can help estimate an expected "personal best." This table uses a prediction equation for White females age 20 to 70 years. Refer to UpToDate calculator for values for additional age, height, and race/ethnicity parameters.

Reference:

1. *Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159(1):179.*

Graphic 62839 Version 10.0

Predicted average peak expiratory flow values for normal children

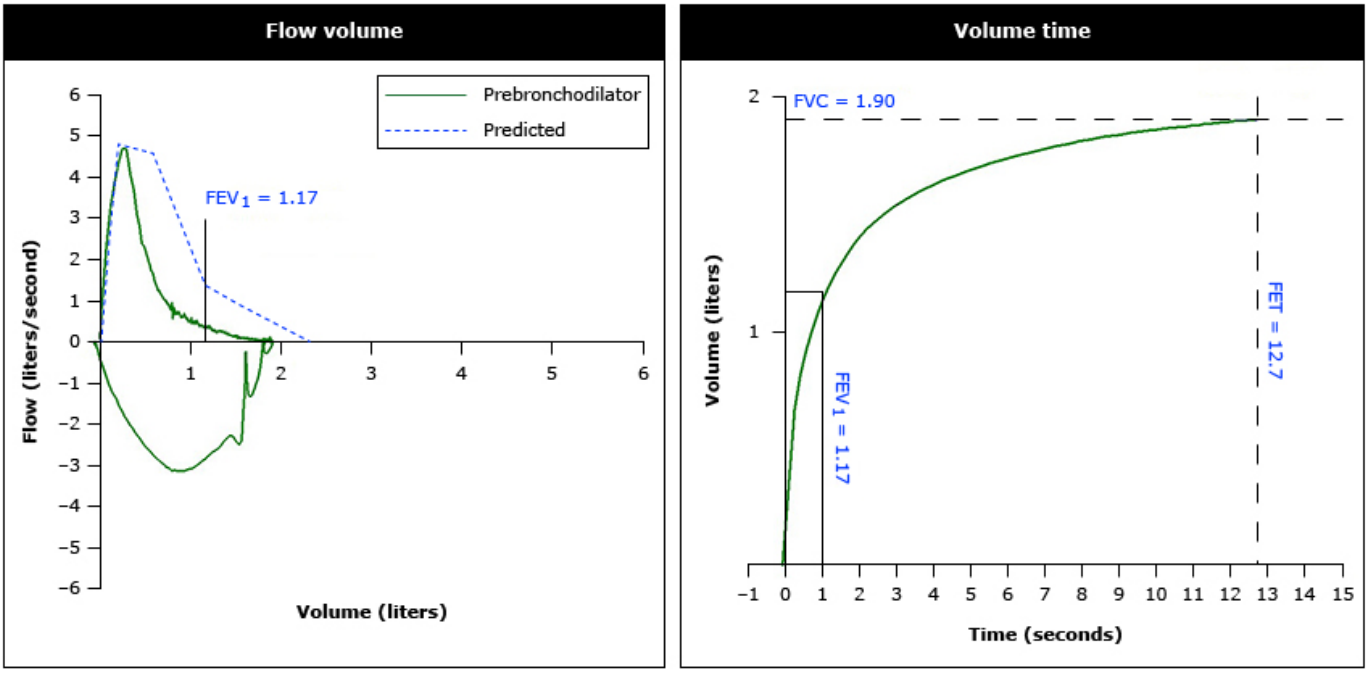
Height		PEFR	Height		PEFR
(inches)	(cm)	(L/min)	(inches)	(cm)	(L/min)
43	109	147	56	142	320
44	112	160	57	145	334
45	114	173	58	147	347
46	117	187	59	150	360
47	119	200	60	152	373
48	122	214	61	155	387
49	124	227	62	157	400
50	127	240	63	160	413
51	130	254	64	163	427
52	132	267	65	165	440
53	135	280	66	168	454
54	137	293	67	170	467
55	140	307			

PEFR: peak expiratory flow rate.

Graphic 64420 Version 5.0

Spirometry and peak expiratory flow in asthma

Spirometry		Predicted range		Prebronchodilator	
		Mean	95%	Actual	% predicted
FVC effort time		----	----	11:46	----
FEV_1	liters	1.77	1.21	1.17	66
FVC	liters	2.32	1.64	1.90	82
FEV_1/FVC	%	77	68	61	79
PEF	liters/second	4.79	3.30	4.97	104



Flow-volume loop (flow-volume plot) and spirometry (volume-time plot) in a patient with moderate airflow limitation (reduced FEV_1/FVC ratio and reduced FEV_1) on spirometry, but normal PEF. This discrepancy reflects rapid emptying of gas from the trachea and central bronchi, but slowed expiratory flow from the remainder of the bronchial tree.

95%: the low end of the 95% confidence intervals around the mean; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; FET: forced expiratory time; PEF: peak expiratory flow.

Graphic 111849 Version 1.0

Clinical syndromes associated with bronchiolitis

Inhalation injury
Toxic fume inhalation (eg, silo fillers, welders, mustard gas)
Mineral dusts
Irritant gases (eg, chlorine, ammonia, paraquat)
Volatile flavoring agents (popcorn factory)
Electronic cigarettes ("vaping" or "dabbing")
Postinfectious
Viruses
Respiratory syncytial virus
Adenovirus or rhinovirus
Influenza or parainfluenza
Measles or mumps
Varicella zoster
Cytomegalovirus
Human immunodeficiency virus (HIV)
Other infectious agents
Bordetella pertussis
Mycoplasma pneumoniae
Nocardia
Drug-induced reactions
Busulfan
Free-base cocaine
Gold
Nimesulide
Penicillamine
Rituximab
Sauropus androgynus leaf (papaverine)
Sulfasalazine
Sulfamethoxypyridazine

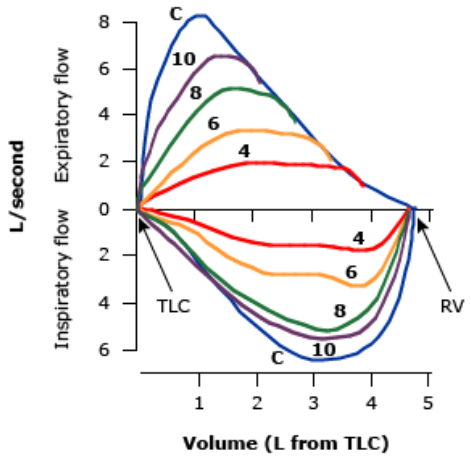
Associated diseases
Organ transplantation
Bone marrow
Heart-lung
Lung
Rheumatic disease
Rheumatoid arthritis
Sjögren syndrome
Systemic lupus erythematosus
Polymyositis/dermatomyositis
Rare associations
Acute respiratory distress syndrome (ARDS)
Ataxia telangiectasia
Lysinuric protein intolerance
Malignant histiocytosis
Paraneoplastic pemphigus
Primary biliary cholangitis
Ulcerative colitis
Vasculitis, especially granulomatosis with polyangiitis
Idiopathic
Cryptogenic bronchiolitis obliterans

References:

1. *Galateau F. [Pulmonary lesions in Wegener's disease. Report of the French Anatomo-clinical Research Group. Study of 40 pulmonary biopsies]. Rev Mal Respir 1992; 9:431.*
2. *Chatté G, Streichenberger N, Boillot O. Lymphocytic bronchitis/bronchiolitis in a patient with primary biliary cirrhosis. Eur Respir J 1995; 8:176.*

Graphic 70650 Version 7.0

Flow-volume loop and degree of upper airway narrowing



Volume (as liters [L] from total lung capacity [TLC]) is plotted against inspiratory and expiratory flows. The blue line (C) is the control effort; the number on each curve refers to the orifice diameter in mm. Lesions must narrow the tracheal lumen to less than 8 mm before abnormalities can be detected by spirometry.

TLC: total lung capacity; RV: residual volume.

Redrawn from Miller RD, Hyatt RE. Obstructing lesions of the larynx and trachea: clinical and physiologic characteristics. Mayo Clin Proc 1969; 44:145.

Graphic 73686 Version 4.0

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