CHAPTER

5

DIAGNOSIS

AND

CLASSIFICATION

KEY POINTS:

- Asthma is underdiagnosed throughout the world.
- Asthma can often be diagnosed on the basis of symptoms. However, measurements of lung function, and particularly the reversibility of lung function abnormalities, greatly enhance diagnostic confidence.
- Lung function measurements that are most helpful for the diagnosis of asthma (in patients over 5 years of age) include forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and airway hyperresponsiveness.
- Asthma severity is classified by the presence of clinical features before treatment is started and/or by the amount of daily medication required for optimal treatment.
- Measurements of allergic status add little to the diagnosis of asthma but can help in the identification of risk factors so that appropriate environmental control measures can be recommended.
- Special care should be given to diagnosing asthma in children, in individuals with recurrent cough, in the elderly, and in individuals exposed to occupational agents known to cause asthma.

Epidemiological studies both in children and adults (especially the elderly) consistently suggest that asthma is underdiagnosed and as a consequence undertreated[1]. Part of the problem is that many patients tolerate intermittent respiratory symptoms (though not, for example, chest pains) before obtaining a medical opinion. The transient nature of asthma symptoms serves to reinforce the acceptance of symptoms. Another important factor resulting in underdiagnosis of asthma is the nonspecific nature of the symptoms, which can lead to alternative diagnoses by the attending health care professional. It should be remembered that establishing a correct diagnosis of asthma is essential if appropriate drug therapy is to be given. Not infrequently asthma in children is diagnosed as variant forms of bronchitis[2] and, as a consequence, treated inappropriately and ineffectively with successive courses of antibiotics and cough medications[3]. Although the adage “all that wheezes is not asthma” is frequently cited, asthma as a cause of wheeze and related symptoms is so common that a more appropriate view might be “all that wheezes is asthma until proven otherwise.”

CLINICAL DIAGNOSIS

History and Measurements of Symptoms

A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, and chest tightness. Seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides.

Figure 5-1 highlights questions that are useful when considering a diagnosis of asthma. **Figure 5-2** presents a questionnaire that has been used and validated for the diagnosis of asthma in epidemiological studies[4,5]. Measurements of symptoms and lung function are important parameters for assessing the characteristics of the patient's asthma. Various symptom scores have been developed and validated in order to quantify asthma control[6] and quality of life[7,8]. Symptom scores should be adapted to the age and the cultural background of the patient.

Physical Examination

Because asthma symptoms are variable, the physical examination of the respiratory system may be normal. The most usual abnormal physical finding is wheezing on auscultation. However, some people with asthma may

Figure 5-1. Questions to Consider in Diagnosis of Asthma

- Has the patient had an attack or recurrent attacks of wheezing?
- Does the patient have a troublesome cough at night?
- Does the patient have a wheeze or cough after exercise?
- Does the patient have wheeze, chest tightness, or cough after exposure to airborne allergens or pollutants?
- Do the patient’s colds “go to the chest” or take more than 10 days to clear up?
- Are symptoms improved by appropriate antiasthma treatment?

Figure 5-2. International Union Against Tuberculosis and Lung Disease (IUATLD) Asthma Questionnaire[4,5]

- Have you had wheezing or whistling in your chest at any time?
- Have you had an attack of shortness of breath that came on following strenuous activity at any time?
- Have you woken up with an attack of wheezing at any time?
- Have you woken up with an attack of coughing at any time?
- Have you had an attack of shortness of breath that came on during the day when you were at rest at any time?

have normal auscultation but significant airflow limitation when measured objectively.

Clinical signs such as dyspnea, airflow limitation (wheeze), and hyperinflation are more likely to be present if patients are examined during symptomatic periods. During an exacerbation of asthma, contraction of airway smooth muscle, edema, and hypersecretion tend to close the smaller (noncartilaginous) airways. To compensate, the patient breathes at a higher lung volume to increase outward retraction of the airways, thereby helping to maintain their patency. Thus the more severe the airflow limitation, the greater the tendency for airway closure to occur, and the higher the lung volume must be to keep airways open. The combination of hyperinflation and advanced airflow limitation in an asthma exacerbation also markedly increases the work of breathing.

Although wheezing is the most typical physical finding in asthma, this sign may be absent in severe asthma exacerbations. However, patients in this state usually have other physical signs reflecting severity, such as cyanosis, drowsiness, difficulty speaking, tachycardia, hyperinflated chest, use of accessory muscles, and intercostal recession.

Measurements of Lung Function

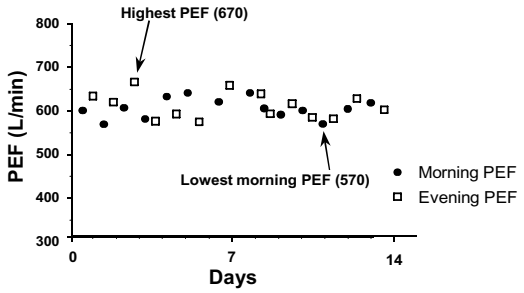
Patients with asthma frequently have poor recognition of their symptoms and poor perception of the severity, especially if their asthma is severe and longstanding[9]. Assessment of symptoms such as dyspnea and wheezing by physicians may also be inaccurate. Measurements of lung function, particularly the reversibility of lung function abnormalities, provide a direct assessment of airflow limitation. Measuring the variability in lung function provides an indirect assessment of airway hyperresponsiveness. However, although some relationship has been established between laboratory indices of airway hyperresponsiveness and peak expiratory flow (PEF) variability[10], they are not interchangeable. For example, PEF variability may respond rapidly to glucocorticosteroid treatment[11], whereas histamine or methacholine airway responsiveness improves over a slower time course[12]. Nevertheless, measurements of airflow limitation, its reversibility (**Figure 1-5** and **Figure 1-7**), and its variability (**Figure 1-6**) are considered critical in establishing a clear diagnosis of asthma. These measurements underlie the new asthma management strategies advocated in established asthma guidelines. Measurement of lung function for diagnosing and monitoring asthma is analogous to measurement in other chronic diseases. For example, blood pressure measured with a sphygmomanometer is used for diagnosing and monitoring hypertension, and blood glucose measured with reagent strips or digital read-out meters is used for diagnosing and monitoring diabetes.

A wide range of different methods to assess the level of airflow limitation exists, but two methods have found widespread acceptance for use in patients over 5 years of age. These are the measurement of forced expiratory volume in 1 second (FEV_1) and its accompanying forced vital capacity (FVC), and the measurement of peak expiratory flow (PEF). Both of these measurements depend on the concept of airflow limitation relating directly to the luminal size of the airways (airway caliber) and the elastic properties of the surrounding lung tissue (alveoli).

Spirometry. Measurement of FEV_1 and FVC is undertaken during a forced expiratory maneuver using a spirometer. Recommendations for the standardization of spirometry have been published[13,14]. The procedure is repeatable, but effort dependent; therefore, proper instructions on how to perform the forced expiratory maneuver must be given to patients, and the highest values of two or three recordings taken. The test begins to lose its reliability at values of FEV_1 less than 1 liter. Predicted values of FEV_1, FVC, and PEF based on age, gender, and height have been obtained from population studies, and although these are being continually revised, they form some useful bases against which to judge whether a given value is abnormal or not. It is important that predicted values of FEV_1, FVC, and PEF take into account ethnic characteristics and extremes of age. Because diseases other than those causing airflow limitation may result in reduced FEV_1, a useful assessment of airflow limitation can be obtained as the ratio of FEV_1 to FVC. In the normal lung, flow limitation on forced expiration results in FEV_1/FVC ratios of greater than 80 percent and in children possibly greater than 90 percent. Any values less than these are suggestive of airflow limitation.

Spirometry is helpful for the diagnosis of asthma, where at least a 12 percent improvement in FEV_1 either spontaneously, after inhalation of a bronchodilator, or in response to a trial of glucocorticosteroid therapy favors a diagnosis of asthma[15]. Spirometry is also helpful for monitoring the activity of the asthma, although primarily in a clinic health care setting because the apparatus is cumbersome and moderately expensive. Small electronic spirometers have been developed for portable use, but expense is likely to limit their widespread acceptance. Nevertheless, spirometry recordings are helpful in diagnosing asthma and assessing its severity, and

Figure 5-3. A Simple Index of PEF Variation[25]



(Minimum morning PEF (% recent best) = 570/670 = 85%)

recordings at regular intervals (dependent upon the severity of the disease) assist in monitoring the long-term progress of asthma and its long-term response to therapeutic interventions. Spirometry, as opposed to PEF monitoring, is particularly helpful in assessing progress in patients with greatly compromised lung function (e.g., the elderly person with asthma and chronic obstructive pulmonary disease) because PEF measurements can be relatively well preserved in such patients in the presence of greatly reduced spirometric values.

Peak expiratory flow. An important aid in the diagnosis and subsequent treatment of asthma is the PEF meter. In some countries, PEF meters are becoming available on health service prescription. Recent versions of the PEF meter are relatively inexpensive (at least in affluent countries), portable, plastic, and ideal for patients to use in home settings for day-to-day objective monitoring of asthma.

PEF meters are useful in clinic and primary health care settings to help in the diagnosis of asthma, where at least a 15 percent improvement after inhalation of a bronchodilator or in response to a trial of glucocorticosteroid therapy favors a diagnosis of asthma[16]. PEF meters are also useful for ongoing supervision of asthma if spirometry is impractical (**Figure 1-6**). Finally, regular home monitoring of PEF is sometimes useful because it can help patients detect early signs of asthma deterioration. Several studies have demonstrated that patients' symptom reports are unreliable indicators of airflow limitation[17,18]. Poor perception of the severity of asthma on the part of the patient and health care professional has been cited as a major factor causing delay in treatment and thus may contribute to increased severity and mortality from asthma exacerbations[19]. However, this is not the case with all patients. One study showed that symptoms preceded the onset of declines in lung function[20].

It is important to note that measurements of PEF do not always correlate with other measurements of lung function in asthma and are not necessarily interchangeable in evaluating asthma severity[21]. For example, in children with asthma, PEF can be normal as airflow obstruction and gas trapping worsens. Therefore PEF can underestimate the degree of airflow obstruction[22]. Also, in children, measurements of PEF do not always correlate with symptoms or other measures of disease severity[23]. For these reasons, PEF measurements are ideally compared to the patient's own previous best measurements.

Careful instruction is required if patients are to reliably measure PEF because PEF measurements, like FEV_1 and FVC measurements, are effort dependent. A PEF meter may be used regularly throughout the day and over weeks and months to aid in the assessment of asthma severity and monitor the response to treatment. The severity of asthma is reflected not only in the level of baseline airflow limitation, but also in its variability, particularly across 24 hours (**Figure 1-6**). Ideally PEF should be measured first thing in the morning when values are usually close to their lowest and last thing at night when values are usually at their highest.

One method of describing diurnal PEF variability is as the amplitude (the difference between the prebronchodilator morning value and the postbronchodilator value from the evening before), expressed as a percentage of the mean daily PEF value[24]. Another method is the minimum morning prebronchodilator PEF over 1 week, expressed as a percent of the recent best (Min%Max)[25] (**Figure 5-3**). This latter method has been suggested to be the best PEF index of airway lability because it requires only a once-daily reading, it correlates better than any other index with airway hyperresponsiveness, and the calculation is simple[25].

A diurnal variation in PEF of more than 20 percent is considered to be diagnostic of asthma, the magnitude of the variability being broadly proportional to disease severity (**Figure 1-6**)[24]. However, it should be noted that in mild intermittent asthma or in severe intractable disease, variability in PEF may not be present or may be lost. In more severe asthma, diurnal variation and reversibility may not be a feature until after a trial of glucocorticosteroids. Even then, the more severe intransigent forms of the disorder may take many weeks of treatment before reversibility becomes apparent.

By using a combination of regular symptom recording and PEF measurement, patients can be provided with

treatment plans that are responsive to asthma severity, and the course of asthma can be effectively monitored[26]. Furthermore, it is conceivable that a patient's adherence to treatment may be enhanced by observing objectively his/her responses to therapy.

Although long-term PEF monitoring for most patients with persistent asthma can be valuable and may be ideal, this is not always possible for reasons of cost, cooperation, and availability of peak flow meters. However, short-term monitoring is particularly recommended for establishing a diagnosis, identifying possible environmental triggers, and evaluating changes in therapy. Long-term monitoring is particularly recommended for those patients with severe asthma, for those with poor perception of severity, and for those who have ever been hospitalized.

PEF measurement may be of use not only in establishing a diagnosis of asthma and assessing its severity but also in uncovering an occupational cause for asthma. When used in this way, PEF should be measured more frequently than twice daily and special attention paid to changes occurring inside and outside the workplace[27].

If, in the presence of infrequent symptoms, these tests fail to support a diagnosis of asthma, it is usually advisable to maintain surveillance with periodic reevaluation until the diagnostic situation becomes clearer. In these circumstances, the health care professional should take special consideration of the patient's family history, age, and asthma triggers before deciding on a diagnostic or therapeutic course of action. When there is doubt, a trial of treatment with short-acting β_2-agonists as needed and inhaled glucocorticosteroids is considered one of the surest ways of establishing a diagnosis of asthma, especially if combined with PEF monitoring. A clear knowledge of the degree of lung dysfunction (such as with daily measurements of PEF) over a period of time not only offers the opportunity for detecting environmentally related causes of the asthma but also provides the criteria for assessing asthma severity and environmental influences, and for observing the response to treatment.

The clinician must always feel confident that the diagnosis of asthma is fully established because the consequences for the patient are considerable and frequently lifelong. The requirements for diagnostic confirmation in patients presenting with severe symptoms and gross lung dysfunction differ from those for asymptomatic patients.

Airway hyperresponsiveness. For patients with symptoms consistent with asthma, but normal lung function, measurements of airway responsiveness to methacholine, histamine, or exercise challenge may help establish a diagnosis of asthma[28]. These measurements are sensitive for a diagnosis of asthma, but have low specificity[29]. This means that a negative test can be useful to exclude a diagnosis of persistent asthma, but a positive test does not always mean that a patient has asthma. This is because airway hyperresponsiveness has been described in patients with allergic rhinitis[30] and in those with airflow limitation caused by conditions other than asthma, such as cystic fibrosis[31], bronchiectasis, and chronic obstructive pulmonary disease[32].

Measuring Noninvasive Markers of Airway Inflammation

The evaluation of airway inflammation associated with asthma may be undertaken by examining spontaneously produced or hypertonic saline-induced sputum for eosinophils and metachromatic cells[33]. In addition, levels of exhaled nitric oxide (NO)[34] or carbon monoxide (CO)[35] have been suggested as noninvasive markers of airway inflammation in asthma. Levels of exhaled NO and CO are elevated in people with asthma (who are not taking inhaled glucocorticosteroids) compared to people without asthma, yet these findings are not specific for asthma. Neither sputum eosinophilia nor exhaled gases has yet been evaluated prospectively as an aid in asthma diagnosis. There is a need to develop further noninvasive discriminate measurements of airway inflammation.

Measurements of Allergic Status

The presence of an allergic component in asthma can be identified by skin testing or measurement of specific IgE in serum. While these tests add little to the diagnosis of asthma, they can help in identifying its risk factors or triggers so that appropriate environmental control measures can be recommended. Deliberate provocation of the airways with a suspected allergen or sensitizing agent may also be helpful in establishing causality, especially in the occupational setting[27], but is not routinely recommended, because it is not often useful in establishing a diagnosis and on the grounds of safety.

Skin tests with allergens represent the primary diagnostic tool in determining atopic status. Prick tests are the most commonly used for diagnostic purposes. Their characteristics–simplicity, rapidity of performance, low cost, and high sensitivity–explain their key position. However, when improperly performed, skin tests can lead to falsely positive or negative results. Measurement of specific IgE in serum does not surpass skin tests and is more expensive. The main limitation of methods to assess allergic status is that a positive test does not necessarily

mean that the disease is allergic in nature, as some individuals have specific IgE antibodies without any symptoms. The relevant exposure and its relation to symptoms must be confirmed by the patient history. Measurement of total IgE in serum has no value as a diagnostic test for atopy.

PARTICULARLY DIFFICULT DIAGNOSTIC GROUPS

In this section emphasis is given to the difficult problems in diagnosing asthma in children, in the elderly, in relation to occupational exposure to risk factors, in seasonal asthma, and in cough variant asthma. For these patient groups measurements of airflow limitation and variability are extremely useful for establishing a diagnosis of asthma.

Childhood Asthma

Diagnosis of asthma in children can present a particularly difficult problem, largely because episodic wheezing and cough are among the most common symptoms encountered in childhood illnesses, particularly in children under 3 years old[3]. Although health care professionals are increasingly encouraged to make a positive diagnosis of asthma whenever recurrent wheezing, breathlessness, and cough occur (particularly if these symptoms occur at night and in the early morning), the disorder's underlying process may be different in infants than in older children and adults[36]. The use of the label "asthma" to describe such children has important clinical consequences. It implies a syndrome in which there is airway inflammation and for which there is a specific protocol of management.

The younger the child, the greater the likelihood that an alternative diagnosis may explain recurrent wheeze. Alternative causes of recurrent wheezing in infancy include cystic fibrosis, recurrent milk inhalation, primary ciliary dyskinesia syndrome, primary immune deficiency, congenital heart disease, congenital malformation causing narrowing of the intrathoracic airways, and foreign body aspiration. Features such as a neonatal onset of symptoms, associated failure to thrive, vomiting-associated symptoms, and focal lung or cardiovascular signs all suggest an alternative diagnosis and indicate the need for further investigations, such as a sweat test to exclude cystic fibrosis, measurements of immune function, and reflux studies. Chest radiography is an important diagnostic test to exclude such alternative causes of wheezing.

Among those children in whom an alternative diagnosis has been excluded, there is the possibility that recurrent wheezing does not have a uniform underlying pathogenesis[3]. Nonetheless, there are two general patterns of wheezing in infancy. Some infants who have recurrent episodes of wheeze associated with acute viral respiratory infections, often with a first episode in association with respiratory syncytial virus bronchiolitis, come from nonatopic families and have no evidence of atopy themselves[37,38]. These infants usually outgrow their symptoms in the preschool years and have no evidence of subsequent asthma, though they may have minor defects of lung function and airway hyperresponsiveness. This syndrome may have more to do with airway geometry than airway inflammation[39], and thus may differ mechanistically from the more established chronic inflammatory condition that underlies asthma in older children and adults.

Other infants with asthma have an atopic background often associated with eczema and develop symptoms later in infancy that persist through childhood and into adult life[40]. In these children, characteristic features of airway inflammation can be found even in infancy. However, there are no practical, clinical tests that can be done to establish the presence of airway inflammation. Also, there are no clear markers to predict the prognosis for an individual child. However, in young children with frequent wheezing, a parental history of asthma along with the presence of other atopic manifestations in the child are significantly associated with the presence of asthma at age 6[41]. The onset of wheeze at an early age (under 2 years) is a poor predictor of whether asthma will persist in later childhood[3,37,38].

It is likely that the relationship between wheezing associated with recurrent viral infections and the later development of persistent asthma requires further study. Not only are the etiological mechanisms of asthma in childhood unclear, but there is also considerable reluctance on the part of doctors to establish a diagnosis and, therefore, to initiate appropriate therapy. Because lower respiratory tract symptoms similar to symptoms of asthma are so common in childhood (and frequently occur in association with upper respiratory tract symptoms), often either a correct diagnosis is not made or an inappropriate diagnosis is given, thereby depriving the child of antiasthma medication. Although in these young children there is the possibility of overtreatment, the episodes of wheezing may be foreshortened and reduced in intensity by the effective use of anti-inflammatory medications and bronchodilators rather than antibiotics. It is for this reason that health care professionals are encouraged to use the word "asthma" rather than other terminology to describe recurrent viral-associated wheezing in early childhood.

Asthma in all age groups may present only as repeated coughing, especially at night, with exercise, and with viral illness, but these are particularly common patterns of presentation of the disease in childhood. The presence of recurrent nocturnal cough in an otherwise healthy child should raise asthma as a probable diagnosis.

In children under the age of 5, the diagnosis of asthma has to be based largely on clinical judgment and an assessment of symptoms and physical findings. Because the measurement of airflow limitation and airway hyper-responsiveness in infants and small children requires complex equipment and is difficult[42], these measurements can only be recommended as a research tool. A trial of treatment is probably the most confident way to make a diagnosis of asthma in children (and in many adults as well). Prognostic features include a family history of asthma or eczema and the presence of eczema in a young child with respiratory symptoms[38]. Children 4 to 5 years old can be taught to use a PEF meter and obtain reliable readings. However, unless there is careful parental supervision of when and how the measurements are made, PEF recording in childhood can be unreliable[43]. The use of diary cards to record symptoms, PEF, and treatment has proved an invaluable part of asthma management strategies.

Some children with asthma present only with exercise-induced symptoms. In this group, or when there is doubt over the presence of mild asthma in a child, exercise testing is helpful. A 6-minute running protocol is easily performed in clinical practice. When used in conjunction with measurements of airflow limitation (FEV_1 or PEF), this can be most helpful in establishing a firm diagnosis of asthma[44], especially if the cough produced by the exercise is similar to that occurring spontaneously at night.

Asthma in the Elderly

A group of patients in which the diagnosis of asthma is often not made or is missed is the elderly[45]. Although lung damage from smoking or extensive exposure to inhaled environmental insults results in such diseases as bronchitis, emphysema, or fibrosing lung disease in this age group, it is now becoming increasingly recognized that undiagnosed asthma is a frequent cause of treatable respiratory symptoms. A further complicating factor is the difficulty that some older people have in performing lung function tests, including PEF. This means that making a diagnosis of asthma or chronic bronchitis based purely on symptoms is fraught with difficulties.

Late-onset asthma occasionally occurs in association with vasculitis and marked eosinophilia (Churg-Strauss syndrome). In the older patient, longstanding asthma may enter a severe destructive phase associated with allergic bronchopulmonary aspergillosis. Characteristically, however, late-onset asthma is not associated with evidence for specific allergen sensitization.

Later in life, smoking and elevated serum IgE levels appear to be independent determinants of chronic airflow limitation, although they may interact[46]. This has led to a growing body of opinion that chronic obstructive pulmonary disease (COPD), associated with a long history of smoking, may have an important inflammatory component that is responsive to anti-inflammatory drug intervention, thus blurring the boundary between asthma and other forms of obstructive lung disease[47]. When doubt exists, a trial of oral glucocorticosteroids in which a greater than 12 percent improvement in FEV_1 or 15 percent improvement in PEF occurs, accompanied by improvement in symptoms and reduced bronchodilator requirement, usually confirms asthma as a cause of chronic respiratory symptoms.

The elderly are susceptible to episodes of wheezing, breathlessness, and cough caused by left ventricular failure (sometimes mistakenly labeled cardiac asthma)[45]. The presence of increased symptoms with exercise and at night may add to the diagnostic confusion. A careful history and physical examination looking for features of ischemic heart disease and cardiac dysfunction, together with an ECG and chest x ray usually clarify the picture, but if after this doubt still persists, a trial of diuretic treatment is helpful.

Not only is the diagnosis of asthma difficult in the elderly, but the assessment of severity also presents a particular problem because the perception of symptoms and their severity is reduced in this age group when compared to young adults and also as a consequence of lifestyle adaptation.

Occupational Asthma

Asthma acquired in the workplace is a diagnosis that is frequently missed unless the health care professional is made aware of the possibility. Many inhalant chemicals are now known to produce asthma in the occupational environment (**Figure 3-4**). They range from highly reactive small molecular weight chemicals such as isocyanates, to known immunogens such as platinum salts, as well as to complex plant and animal biological products. Because of its insidious onset, occupational asthma is often misdiagnosed as chronic bronchitis or some form of COPD and is therefore either not treated at all or treated inappropriately. The diagnosis requires a defined occupational history, especially in relation to exposure to

Figure 5-4. Overview of Lung Diseases

LUNG DISEASES

consist of

INFECTIONS

Simple colds, bronchiolitis, pneumonia, tuberculosis, and HIV/AIDS and related opportunistic infections

and

OBSTRUCTIVE DISEASES	**RESTRICTIVE DISORDERS**
Localized	Lung disease
Vocal cord paresis	Extrinsic allergic alveolitis
Laryngeal carcinoma	Sarcoidosis
Tracheal carcinoma	Fibrosing alveolitis
Bronchial carcinoma	Asbestosis
Foreign bodies	Eosinophilic pneumonia
Bronchopulmonary dysplasia	
	Pleural disease
Generalized	Pleural effusion
Chronic obstructive pulmonary disease	Pneumothorax
Asthma	Chest wall deformity
Obliterative bronchiolitis	Kyphoscoliosis
Cystic fibrosis	
Bronchiectasis	Respiratory muscle weakness
	Subdiaphragmatic problems
	Obesity
	Ascites

sensitizing agents; absence of asthma symptoms before beginning employment; and a documented relationship between development of symptoms at the workplace and reduction of these on withdrawal from the workplace. A confirmation of occupational asthma may be successfully achieved by lung function measurement, such as serial measurement of PEF at work and away from work (single measurements are less sensitive than serial measurements), and specific bronchial provocation testing[48]. The increasing recognition that occupational asthma can persist, or continue to deteriorate, even in the absence of continued exposure to the offending agent[49], emphasizes the need for an early diagnosis, appropriate strict avoidance of further exposure, and pharmacologic intervention.

Seasonal Asthma

In some sensitized individuals, asthma may be exacerbated by seasonal increases in specific aeroallergens. Examples include birch[50], grass[51], *Alternaria*[52], and ragweed pollens[53]. Seasonal asthma is usually associated with allergic rhinitis. This type of asthma may occur only intermittently, with the patient being entirely asymptomatic between seasons. Alternatively, it may occur as a seasonal worsening of asthma symptoms in a patient with persistent asthma.

Cough Variant Asthma

Another group of patients whose asthma can sometimes be missed are those with cough variant asthma[54]. These patients have chronic cough as their principal, if not only, symptom. Frequently this occurs at night; consequently evaluations during the day can be normal. For these patients, documentation of variability in lung function or of airway hyperresponsiveness, and possibly a search for sputum eosinophils, are particularly important. Within this group are patients who cough and have sputum eosinophils but who also have normal indices of lung function when assessed by spirometry and airway hyperresponsiveness[55].

Some patients with hypertension treated by angiotensin-converting-enzyme (ACE) inhibitors, or patients with gastroesophageal reflux, postnasal drip, or chronic sinusitis, may develop a cough that resembles cough variant asthma[56].

DIFFERENTIAL DIAGNOSIS

Asthma is one of the most common causes of respiratory symptoms, but it is only one cause of lung disease (**Figure 5-4**). An important step in ensuring diagnosis of asthma is the demonstration of reversible and variable airflow limitation, preferably by spirometry.

Although in children both asthma and acute respiratory infections produce wheezing as a consequence of widespread airway obstruction, respiratory symptoms may also arise from localized airway obstruction and inhaled foreign bodies[57], possibilities that must always be considered in the differential diagnosis (**Figure 5-5**). Another diagnosis to consider in both children and adults is pseudoasthma, most often caused by vocal cord dysfunction[58]. In adults, asthma superimposed on COPD is a common problem in past or present smokers.

CLASSIFICATION OF ASTHMA

Asthma may be classified on the basis of etiology, severity, and pattern of airflow limitation.

Figure 5-5. Differential Diagnosis of Obstructive Airway Disease

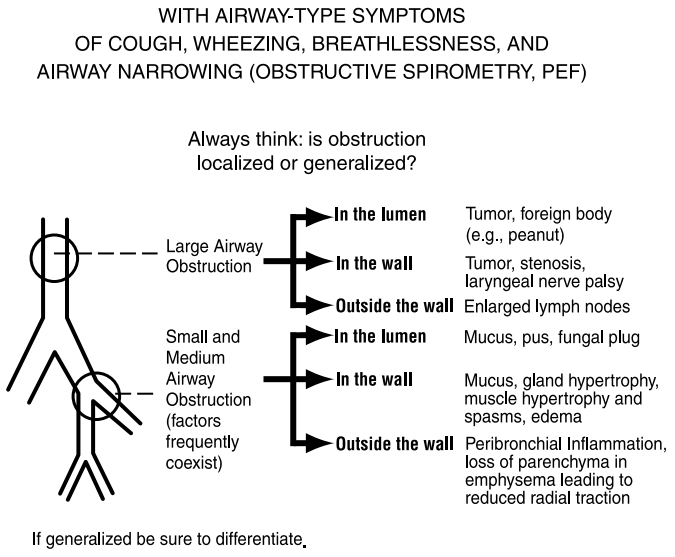


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Figure 5-6. Classification of Asthma Severity by Clinical Features Before Treatment

STEP 1: Intermittent
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month • FEV_1 or PEF ≥ 80% predicted • PEF or FEV_1 variability < 20%
STEP 2: Mild Persistent
Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month • FEV_1 or PEF ≥ 80% predicted • PEF or FEV_1 variability 20-30%
STEP 3: Moderate Persistent
Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting β_2-agonist • FEV_1 or PEF 60-80% predicted • PEF or FEV_1 variability > 30%
STEP 4: Severe Persistent
Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities • FEV_1 or PEF ≤ 60% predicted • PEF or FEV_1 variability > 30%

Etiology

Many attempts have been made to classify asthma according to etiology, particularly with regard to environmental sensitizing agents. Such a classification is, however, limited by the existence of patients in whom no environmental cause can be identified. Despite this, an effort to identify a specific environmental cause for asthma in an individual patient should be part of the initial clinical assessment, because it enables the use of avoidance strategies in asthma management.

Severity

Conventional assessments of asthma severity have combined assessments of symptoms, amounts of β_2-agonist used to treat symptoms, and lung function (**Figure 5-6**). An assessment of asthma based on clinical or symptom indices of disease severity over the preceding year has been shown to relate to pathological indices of airway inflammation[59]. Both the level of airflow limitation and its variability enable asthma to be subdivided by severity into four steps: Intermittent, Mild Persistent, Moderate Persistent, and Severe Persistent. This type of asthma classification, based on severity, is important when decisions must be made about management at the initial assessment of a patient. This is because asthma therapy involves a stepwise approach in which the level of therapy is increased as the severity of the asthma increases.

The severity of a patient's asthma may be classified into one of these four steps based on the clinical features present before treatment is begun (**Figure 5-6**). When the patient is already on treatment, the classification of severity should be based on the clinical features present and the step of the daily medication regimen that the patient is currently on[60] (**Figure 5-7**). Thus, a patient with ongoing symptoms of mild persistent asthma, despite being on the appropriate maintenance treatment for this step, should be regarded as having moderate persistent asthma. Similarly, a patient with ongoing symptoms of moderate persistent asthma, despite being on the appropriate maintenance treatment for this step, should be regarded as having severe persistent asthma. Thus, the combination of the current level of symptoms and the current maintenance treatment step should enable the establishment of the patient's asthma severity and the corresponding appropriate maintenance treatment. Once asthma control is achieved and maintained for a sufficient time, then a reduction in therapy should be tested. If control is maintained, then the patient should be reclassified according to the new maintenance treatment.

Figure 5-7. Classification of Asthma Severity by Daily Medication Regimen and Response to Treatment

	Current Treatment Step*		
	Step 1: Intermittent	Step 2: Mild Persistent	Step 3: Moderate Persistent
Patient Symptoms and Lung Function on Current Therapy	**Level of Severity**		
Step 1: Intermittent Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month Normal lung function between episodes	Intermittent	Mild Persistent	Moderate Persistent
Step 2: Mild Persistent Symptoms more than once a week but less than once a day Nocturnal symptoms more than twice a month but less than once a week Normal lung function between episodes	Mild Persistent	Moderate Persistent	Severe Persistent
Step 3: Moderate Persistent Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms at least once a week 60% < FEV_1 < 80% predicted OR 60% < PEF < 80% of personal best	Moderate Persistent	Severe Persistent	Severe Persistent
Step 4: Severe Persistent Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms $FEV_1 \leq$ 60% predicted OR PEF ≤ 60% of personal best	Severe Persistent	Severe Persistent	Severe Persistent

**Treatment as described in Chapter 7, Part 4A, Figure 7-5.*

The severity of acute asthma exacerbations is often underestimated by patients, their relatives, and their health care professional. The reasons for this are complex, but include a failure to use measurements of lung function for assessment. If severe asthma exacerbations are not recognized and treated appropriately, such exacerbations can be fatal[61]. It is important to recognize that any patient with asthma, however mild on a chronic basis, may have a severe acute asthma exacerbation. Specific factors have been identified that are associated with a higher risk of asthma mortality[62]. These include a previous history of life-threatening acute attacks, hospitalization within the previous year, psychosocial problems, a history of intubation for asthma, recent reductions or cessation of glucocorticosteroid therapy, and noncompliance with recommended medical therapy.

Time Trends of Airflow Limitation

Asthma may also be classified according to time trend patterns of airflow limitation monitored by PEF measurements. This form of classification is likely to reflect the different pathological causes of airflow limitation and has therapeutic implications. Intermittent asthma may be defined as the presence of occasional episodes of respiratory symptoms and PEF reductions (in the last year) with normal PEF and normal or near-normal airway responsiveness in between episodes. By contrast, persistent asthma is characterized by daytime and nocturnal PEF variability, frequent symptoms, and airway hyperresponsiveness. Some patients with longstanding persistent asthma with an irreversible component to their disease fail to achieve normal lung function despite intensive therapy with glucocorticosteroids. The term “brittle asthma” is sometimes used to describe patients with airway hyperresponsiveness and extreme day-to-day variability in airway obstruction. These patients are particularly at risk for sudden, severe, and life-threatening exacerbations.

REFERENCES

1. Sears MR. Natural history and epidemiology. In: Fitzgerald JM, Ernst P, Boulet LP, O’Byrne PM, eds. *Evidence-based asthma management.* Hamilton, BC: Decker; 2001. p. 1-12.

2. Helms PJ. Issues and unmet needs in pediatric asthma. *Pediatr Pulmonol* 2000;30:159-65.

3. Wilson NM. Wheezy bronchitis revisited. *Arch Dis Child* 1989;64:1194-9.

4. Abramson MJ, Hensley MJ, Saunders NA, Wlodarczyk JH. Evaluation of a new asthma questionnaire. *J Asthma* 1991;28:129-39.

5. Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, et al. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. *Eur Respir J* 1989;2:940-5.

6. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.

7. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14:32-8.

8. Jones PW. Quality of life measurement in asthma. *Eur Respir J* 1995;8:885-7.

9. Killian KJ, Summers E, Watson RM, O'Byrne PM, Jones NL, Campbell EJ. Factors contributing to dyspnoea during bronchoconstriction and exercise in asthmatic subjects. *Eur Respir J* 1993;6:1004-10.

10. Ryan G, Latimer KM, Dolovich J, Hargreave FE. Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre. *Thorax* 1982;37:423-9.

11. O'Byrne P, Cuddy L, Taylor DW, Birch S, Morris J, Syrotiuk J. The clinical efficacy and cost benefit of inhaled cortiocosteroids as therapy in patients with mild asthma in primary care practice. *Can Respir J* 1996:3;169-175.

12. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. *Am Rev Respir Dis* 1992;146:547-54.

13. Standardized lung function testing. Official statement of the European Respiratory Society. *Eur Respir J* 1993;16 Suppl:1-100.

14. Standardization of spirometry, 1994 update. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107-36.

15. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis* 1991;144:1202-18.

16. Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. *Eur Respir J* 1997;24 Suppl:2S-8S.

17. Killian KJ, Watson R, Otis J, St Amand TA, O'Byrne PM. Symptom perception during acute bronchoconstriction. *Am J Respir Crit Care Med* 2000;162:490-6.

18. Kendrick AH, Higgs CM, Whitfield MJ, Laszlo G. Accuracy of perception of severity of asthma: patients treated in general practice. *BMJ* 1993;307:422-4.

19. Nowak RM, Pensler MI, Sarkar DD, Anderson JA, Kvale PA, Ortiz AE, et al. Comparison of peak expiratory flow and FEV1 admission criteria for acute bronchial asthma. *Ann Emerg Med* 1982;11:64-9.

20. Gibson PG, Wong BJ, Hepperle MJ, Kline PA, Girgis-Gabardo A, Guyatt G, et al. A research method to induce and examine a mild exacerbation of asthma by withdrawal of inhaled corticosteroid. *Clin Exp Allergy* 1992;22:525-32.

21. Sawyer G, Miles J, Lewis S, Fitzharris P, Pearce N, Beasley R. Classification of asthma severity: should the international guidelines be changed? *Clin Exp Allergy* 1998;28:1565-70.

22. Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Can peak expiratory flow predict airflow obstruction in children with asthma? *Pediatrics* 2000;105:354-8.

23. Brand PL, Duiverman EJ, Waalkens HJ, van Essen-Zandvliet EE, Kerrebijn KF. Peak flow variation in childhood asthma: correlation with symptoms, airways obstruction, and hyperresponsiveness during long-term treatment with inhaled corticosteroids. Dutch CNSLD Study Group. *Thorax* 1999;54:103-7.

24. Quackenboss JJ, Lebowitz MD, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates. Relationship to symptoms and respiratory disease. *Am Rev Respir Dis* 1991;143:323-30.

25. Reddel HK, Salome CM, Peat JK, Woolcock AJ. Which index of peak expiratory flow is most useful in the management of stable asthma? *Am J Respir Crit Care Med* 1995;151:1320-5.

26. D'Souza WJ, Te Karu H, Fox C, Harper M, Gemmell T, Ngatuere M, et al. Long-term reduction in asthma morbidity following an asthma self-management programme. *Eur Respir J* 1998;11:611-6.

27. Venables KM, Chan-Yeung M. Occupational asthma. *Lancet* 1997;349:1465-9.

28. Cockcroft DW, Hargreave FE. Airway hyperresponsiveness. Relevance of random population data to clinical usefulness. *Am Rev Respir Dis* 1990;142:497-500.

29. O'Byrne P. Bronchial challenges by pharmacologic agents. In: Clark TJH, Godfrey S, Lee TH, Thomson NC, eds. *Asthma, 4th edition*. London: Arnold; 2000. p. 92-103.

30. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol* 1985;75:573-7.

31. van Haren EH, Lammers JW, Festen J, Heijerman HG, Groot CA, van Herwaarden CL. The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respir Med* 1995;89:209-14.

32 Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Bronchial responsiveness to methacholine in chronic bronchitis: relationship to airflow obstruction and cold air responsiveness. *Thorax* 1984;39:912-8.

33. Pizzichini MM, Popov TA, Efthimiadis A, Hussack P, Evans S, Pizzichini E, et al. Spontaneous and induced sputum to measure indices of airway inflammation in asthma. *Am J Respir Crit Care Med* 1996;154:866-9.

34. Kharitonov S, Alving K, Barnes PJ. Exhaled and nasal nitric oxide measurements: recommendations. The European Respiratory Society Task Force. *Eur Respir J* 1997;10:1683-93.

35. Horvath I, Barnes PJ. Exhaled monoxides in asymptomatic atopic subjects. *Clin Exp Allergy* 1999;29:1276-80.

36. Warner JO, Gotz M, Landau LI, Levison H, Milner AD, Pedersen S, et al. Management of asthma: a consensus statement. *Arch Dis Child* 1989;64:1065-79.

37. Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *BMJ (Clin Res Ed)* 1982;284:1665-9.

38. Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood–a birth cohort study. *Arch Dis Child* 1991;66:1050-3.

39. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133-8.

40. Holt PG, McMenamin C, Nelson D. Primary sensitization to inhalant allergens during infancy. *Pediatr Allergy Immunol* 1990;1:3-13.

41. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.

42. Stick SM, Arnott J, Turner DJ, Young S, Landau LI, Lesouef PN. Bronchial responsiveness and lung function in recurrently wheezy infants. *Am Rev Respir Dis* 1991;144:1012-5.

43. Sly PD, Cahill P, Willet K, Burton P. Accuracy of mini peak flow meters in indicating changes in lung function in children with asthma. *BMJ* 1994;308:572-4.

44. Eggleston PA. Exercise-induced asthma. In: Tinkleman DG, Naspitz CK, eds. *Childhood asthma: pathophysiology and treatment.* New York: Marcel Dekker; 1992. p. 429-46.

45. Dow L. Asthma in older people. *Clin Exp Allergy* 1998;28 Suppl 5:195-202, discussion 3-5.

46. Tracey M, Villar A, Dow L, Coggon D, Lampe FC, Holgate ST. The influence of increased bronchial responsiveness, atopy, and serum IgE on decline in FEV1. A longitudinal study in the elderly. *Am J Respir Crit Care Med* 1995;151:656-62.

47. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group [published erratum appears in *Lancet* 1998;351:1968]. *Lancet* 1998;351:773-80.

48. Tarlo SM, Boulet LP, Cartier A, Cockcroft D, Cote J, Hargreave FE, et al. Canadian Thoracic Society guidelines for occupational asthma. *Can Respir J* 1998;5:289-300.

49. Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma caused by western red cedar (*Thuja plicata*). *J Allergy Clin Immunol* 1987;79:792-6.

50. Harju T, Keistinen T, Tuuponen T, Kivela SL. Seasonal variation in childhood asthma hospitalisations in Finland, 1972-1992. *Eur J Pediatr* 1997;156:436-9.

51. Mitakakis TZ, Tovey ER, Xuan W, Marks GB. Personal exposure to allergenic pollen and mould spores in inland New South Wales, Australia. *Clin Exp Allergy* 2000;30:1733-9.

52. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991;324:359-63.

53. Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. *J Allergy Clin Immunol* 1983;71:399-406.

54. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979;300:633-7.

55. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. *Lancet* 1989;1:1346-8.

56. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis* 1990;141:640-7.

57. Mok Q, Piesowicz AT. Foreign body aspiration mimicking asthma. *Intensive Care Med* 1993;19:240-1.

58. Place R, Morrison A, Arce E. Vocal cord dysfunction. *J Adolesc Health* 2000;27:125-9.

59. Bousquet J, Chanez P, Lacoste JY, Barneon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. *N Engl J Med* 1990;323:1033-9.

60. Cockcroft DW, Swystun VA. Asthma control versus asthma severity. *J Allergy Clin Immunol* 1996;98:1016-8.

61. Strunk RC. Identification of the fatality-prone subject with asthma. *J Allergy Clin Immunol* 1989;83:477-85.

62. Jalaludin BB, Smith MA, Chey T, Orr NJ, Smith WT, Leeder SR. Risk factors for asthma deaths: a population-based, case-control study. *Aust N Z J Public Health* 1999;23:595-600.