

**MINISTRY OF HEALTHCARE OF UKRAINE  
HSEEU "Ukrainian Medical Stomatological Academy"**

**"Approved"**  
at the meeting of internal  
medicine №1 department  
Head of Department  
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Protocol № 4 from 13.10.2016

**GUIDELINES  
FOR STUDENTS  
INDEPENDENT WORK  
IN THE PRACTICAL CLASSES PREPARING**

<i>Academic discipline</i>	Internal medicine
<i>Module</i>	Current practice of internal medicine
<i>Content module</i>	Management of the patients with main symptoms and syndromes in pulmonology clinic
<i>Study subject</i>	<b>Management of the patients with broncho-obstructive syndrome</b>
<i>Course</i>	VI
<i>Faculty</i>	of foreign students training

## **1. The aims of the training course:**

### **To Know:**

Differential diagnosis of conditions that accompanied COPD syndrome: bronchial asthma and COPD.

Test plan, the role of instrumental and laboratory methods of examination (spirometry, radiography, CT, bronchoscopy).

Tactic of patients depending.

Indications for patient transfer to intensive care.

Drug and non-medicamentous treatment.

Existing standards of treatment.

Primary and secondary prevention.

Weather and performance

### **To be able to:**

Conduct surveys and examination of patients with major Pulmonological syndromes

- draft examination of patients with major Pulmonological syndromes
- justify the use of basic diagnostic methods in pulmonology, identify indications and contraindications for their conduct, possible complications
- prescribe treatment, determine prognosis and to conduct primary and secondary prevention in the major respiratory diseases
- diagnose and assist in respiratory distress
- justify the need of pleural puncture
- Perform spirometry

Demonstrate knowledge of moral principles

### **The contents of topic:**

#### **Text**

*Merck Manual Professional Version <http://www.merckmanuals.com/professional>*

*Last full review/revision July 2014 by Noah Lechtzin, MD, MHS*

Cough is an explosive expiratory maneuver that is reflexively or deliberately intended to clear the airways. It is one of the most common symptoms prompting physician visits.

Likely causes of cough differ depending on whether the symptom is acute (present < 3 wk) or chronic.

In acute cough, the most common causes are

- URI (including acute bronchitis)
- Postnasal drip
- COPD exacerbation
- Pneumonia

In chronic cough, the most common causes are

- Chronic bronchitis
- Postnasal drip
- Airway hyperresponsiveness after resolution of a viral or bacterial respiratory infection (ie, postinfection cough)
- Gastroesophageal reflux

The causes in children are similar to those in adults, but asthma and foreign body aspiration may be more common.

Very rarely, impacted cerumen or a foreign body in the external auditory canal triggers reflex cough through stimulation of the auricular branch of the vagus nerve. Psychogenic cough is even rarer and is a diagnosis of exclusion.

Patients with chronic cough may develop a secondary reflex or psychogenic component to their cough. Also, protracted coughing may injure the bronchial mucosa, which may trigger more coughing.

### ***Evaluation***

#### **History**

**History of present illness** should cover the duration and characteristics of the cough (eg, whether dry or productive of sputum or blood, and whether it is accompanied by dyspnea, chest pain, or both). Asking about precipitating factors (eg, cold air, strong odors) and the timing of the cough (eg, primarily at night) can be revealing.

**Review of systems** should seek symptoms of possible cause, including runny nose and sore throat (URI, postnasal drip); fever, chills, and pleuritic chest pain (pneumonia); night sweats and weight loss (tumor, TB); heartburn (gastroesophageal reflux); and difficulty swallowing or choking episodes while eating or drinking (aspiration).

**Past medical history** should note recent respiratory infections (ie, within previous 1 to 2 mo); history of allergies, asthma, COPD, and gastroesophageal reflux disease; risk factors for (or known) TB or HIV infection; and smoking history. Drug history should specifically include use of ACE inhibitors. Patients with chronic cough should be asked about exposure to potential respiratory irritants or allergens and travel to or residence in regions with endemic fungal illness.

#### **Physical examination**

Vital signs should be reviewed for the presence of tachypnea and fever.

General examination should look for signs of respiratory distress and chronic illness (eg, wasting, lethargy).

Examination of the nose and throat should focus on appearance of the nasal mucosa (eg, color, congestion) and presence of discharge (external or in posterior pharynx). Ears should be examined for triggers of reflex cough.

The cervical and supraclavicular areas should be inspected and palpated for lymphadenopathy.

A full lung examination is done, particularly including adequacy of air entry and exit; symmetry of breath sounds; and presence of crackles, wheezes, or both. Signs of consolidation (eg, egophony, dullness to percussion) should be sought.

#### **Red flags**

The following findings are of particular concern:

- Dyspnea
- Hemoptysis
- Weight loss
- Risk factors for TB or HIV infection

#### **Interpretation of findings**

Some findings point to particular diagnoses.

Other important findings are less specific. For example, the color (eg, yellow, green) and thickness of sputum do not help differentiate bacterial from other causes. Wheezing may occur with several causes. Hemoptysis in small amounts may occur with severe cough of many etiologies, although larger amounts of hemoptysis suggest bronchitis, bronchiectasis, TB, or primary lung cancer. Fever, night sweats, and weight loss may occur with many chronic infections as well as with cancer.

### **Testing**

Patients with red flag findings of dyspnea or hemoptysis and patients in whom suspicion of pneumonia is high should have pulse oximetry and chest x-ray. Patients with weight loss or risk factors should have a chest x-ray and testing for TB and HIV infection.

For many patients without red flag findings, clinicians can base the diagnosis on history and physical examination findings and begin treatment without testing. For patients without a clear cause but no red flag findings, many clinicians empirically begin treatment for postnasal drip (eg, antihistamine and decongestant combinations, nasal corticosteroid sprays) or gastroesophageal reflux disease (eg, proton pump inhibitors, H<sub>2</sub> blockers). An adequate response to these interventions usually precludes the need for further evaluation.

Patients with chronic cough in whom presumptive treatment is ineffective should have a chest x-ray. If the x-ray findings are unremarkable, many clinicians sequentially test for asthma (pulmonary function tests with methacholine challenge), sinus disease (sinus CT), and gastroesophageal reflux disease (esophageal pH monitoring). Sputum culture is helpful for patients with a possible indolent infection, such as pertussis, TB, or nontuberculous mycobacterial infection. Sputum cytology is noninvasive and should be done if cancer is suspected and the patient is producing sputum or having hemoptysis. Chest CT and possibly bronchoscopy should be done in patients in whom lung cancer or another bronchial tumor is suspected (eg, patients with a long smoking history, nonspecific constitutional signs) and in patients in whom empiric therapy has failed and who have inconclusive findings on preliminary testing.

### **Treatment**

Treatment is management of the cause.

There is little evidence to support the use of cough suppressants or mucolytic agents. Coughing is an important mechanism for clearing secretions from the airways and can assist in recovery from respiratory infections. Therefore, although patients often expect or request cough suppressants, such treatment should be given with caution and reserved for patients with a URI and for patients receiving therapy for the underlying disorder for whom cough is still troubling. Cough suppressants may help some patients with chronic cough who have a reflex or psychogenic component to their cough or who develop bronchial mucosal injury.

**Antitussives** depress the medullary cough center ([dextromethorphan](#) and [codeine](#)) or anesthetize stretch receptors of vagal afferent fibers in bronchi and alveoli ([benzonatate](#)). [Dextromethorphan](#), a congener of the opioid levorphanol, is effective as a tablet or syrup at a dose of 15 to 30 mg po 1 to 4 times/day for adults or 0.25 mg/kg po qid for

children. Codeine has antitussive, analgesic, and sedative effects, but dependence is a potential problem, and nausea, vomiting, constipation, and tolerance are common adverse effects. Usual doses are 10 to 20 mg po q 4 to 6 h as needed for adults and 0.25 to 0.5 mg/kg po qid for children. Other opioids (hydrocodone, hydromorphone, methadone, morphine) have antitussive properties but are avoided because of high potential for dependence and abuse. Benzonatate, a congener of tetracaine that is available in liquid-filled capsules, is effective at a dose of 100 to 200 mg po tid.

**Expectorants** are thought to decrease viscosity and facilitate expectoration (coughing up) of secretions but are of limited, if any, benefit in most circumstances. Guaifenesin (200 to 400 mg po q 4 h in syrup or tablet form) is most commonly used because it has no serious adverse effects, but multiple expectorants exist, including bromhexine, ipecac, and saturated solution of K iodide (SSKI). Aerosolized expectorants such as *N* -acetylcysteine and DNase are generally reserved for hospital-based treatment of cough in patients with bronchiectasis or cystic fibrosis. Ensuring adequate hydration may facilitate expectoration, as may inhalation of steam, although neither technique has been rigorously tested.

**Topical treatments**, such as acacia, licorice, glycerin, honey, and wild cherry cough drops or syrups (demulcents), are locally and perhaps emotionally soothing, but their use is not supported by scientific evidence.

**Protussives**, which stimulate cough, are indicated for such disorders as cystic fibrosis and bronchiectasis, in which a productive cough is thought to be important for airway clearance and preservation of pulmonary function. DNase or hypertonic saline is given in conjunction with chest physical therapy and postural drainage to promote cough and expectoration. This approach is beneficial in cystic fibrosis but not in most other causes of chronic cough.

**Bronchodilators**, such as albuterol and ipratropium or inhaled corticosteroids, can be effective for cough after URI and in cough-variant asthma.

### **Key Points**

- Danger signs include respiratory distress, chronic fever, weight loss, and hemoptysis.
- Clinical diagnosis is usually adequate.
- Occult gastroesophageal reflux disease should be remembered as a possible cause.
- Antitussives and expectorants should be used selectively.

*Last full review/revision July 2014 by Noah Lechtzin, MD, MHS*

Chronic obstructive pulmonary disease (COPD) is partially reversible airflow limitation caused by an inflammatory response to inhaled toxins, often cigarette smoke.  $\alpha_1$ -Antitrypsin deficiency and various occupational exposures are less common causes in nonsmokers. Symptoms are productive cough and dyspnea that develop over years; common signs include decreased breath sounds, prolonged expiratory phase of respiration, and wheezing. Severe cases may be complicated by weight loss, pneumothorax, frequent acute decompensation episodes, right heart failure, and acute or chronic respiratory failure. Diagnosis is based on history, physical examination, chest x-ray, and pulmonary function tests. Treatment is with bronchodilators, corticosteroids, and, when necessary,  $O_2$  and antibiotics. About 50% of patients with severe COPD die within 10 yr of diagnosis.

COPD comprises

- Chronic obstructive bronchitis (clinically defined)
- Emphysema (pathologically or radiologically defined)

Many patients have features of both.

**Chronic obstructive bronchitis** is chronic bronchitis with airflow obstruction. Chronic bronchitis is defined as productive cough on most days of the week for at least 3 mo total duration in 2 successive years. Chronic bronchitis becomes chronic obstructive bronchitis if spirometric evidence of airflow obstruction develops. Chronic asthmatic bronchitis is a similar, overlapping condition characterized by chronic productive cough, wheezing, and partially reversible airflow obstruction; it occurs predominantly in smokers with a history of asthma. In some cases, the distinction between chronic obstructive bronchitis and chronic asthmatic bronchitis is unclear.

**Emphysema** is destruction of lung parenchyma leading to loss of elastic recoil and loss of alveolar septa and radial airway traction, which increases the tendency for airway collapse. Lung hyperinflation, airflow limitation, and air trapping follow. Airspaces enlarge and may eventually develop bullae.

### ***Epidemiology***

In the US, about 24 million people have airflow limitation, of whom about half have a diagnosis of COPD. COPD is the 3rd leading cause of death, resulting in 135,000 deaths in 2010—compared with 52,193 deaths in 1980. From 1980 to 2000, the COPD mortality rate increased 64% (from 40.7 to 66.9/100,000) and has remained steady since then. Prevalence, incidence, and mortality rates increase with age. Prevalence is now higher in women, but total mortality is similar in both sexes. Incidence and mortality are generally higher in whites and lower income groups, probably because these groups have a higher prevalence of smoking. COPD seems to aggregate in families independent of  $\alpha_1$ -antitrypsin ( $\alpha_1$ -antiprotease inhibitor) deficiency. COPD is increasing worldwide because of the increase in smoking in developing countries, the reduction in mortality due to infectious diseases, and the widespread use of biomass fuels such as wood, grasses, or other organic materials. COPD mortality may also affect developing nations

more than developed nations. COPD affects 64 million people and caused > 3 million deaths worldwide in 2005 and is projected to become the 3rd leading cause of death globally by the year 2030.

### ***Etiology***

There are several causes of COPD:

- Smoking (and less often other inhalational exposures)
- Genetic factors

### **Inhalational exposure**

Of all inhalational exposures, cigarette smoking is the primary risk factor in most countries, although only about 15% of smokers develop clinically apparent COPD; an exposure history of 40 or more pack-years is especially predictive. Smoke from indoor cooking and heating is an important causative factor in developing countries. Smokers with preexisting airway reactivity (defined by increased sensitivity to inhaled methacholine), even in the absence of clinical asthma, are at greater risk of developing COPD than are those without.

Low body weight, childhood respiratory disorders, and exposure to passive cigarette smoke, air pollution, and occupational dust (eg, mineral dust, cotton dust) or inhaled chemicals (eg, cadmium) contribute to the risk of COPD but are of minor importance compared with cigarette smoking.

### **Genetic factors**

The best-defined causative genetic disorder is  $\alpha_1$ -antitrypsin deficiency, which is an important cause of emphysema in nonsmokers and influences susceptibility to disease in smokers.

In recent years, > 30 genetic variants have been found to be associated with COPD or decline in lung function in selected populations, but none has been shown to be as consequential as  $\alpha_1$ -antitrypsin.

### ***Pathophysiology***

Various factors cause the airflow limitation and other complications of COPD.

### **Inflammation**

Inhalational exposures can trigger an inflammatory response in airways and alveoli that leads to disease in genetically susceptible people. The process is thought to be mediated by an increase in protease activity and a decrease in antiprotease activity. Lung proteases, such as neutrophil elastase, matrix metalloproteinases, and cathepsins, break down elastin and connective tissue in the normal process of tissue repair. Their activity is normally balanced by antiproteases, such as  $\alpha_1$ -antitrypsin, airway epithelium-derived secretory leukoprotease inhibitor, elafin, and matrix metalloproteinase tissue inhibitor. In patients with COPD, activated neutrophils and other inflammatory cells release proteases as part of the inflammatory process; protease activity exceeds antiprotease activity, and tissue destruction and mucus hypersecretion result. Neutrophil and macrophage activation also leads to accumulation of free radicals, superoxide anions, and hydrogen peroxide, which inhibit antiproteases and cause bronchoconstriction, mucosal edema, and mucous hypersecretion. Neutrophil-induced oxidative damage, release of profibrotic neuropeptides (eg, bombesin), and reduced levels of vascular endothelial growth factor may contribute to apoptotic destruction of lung parenchyma.



The inflammation in COPD increases as disease severity increases, and, in severe (advanced) disease, inflammation does not resolve completely despite smoking cessation. This chronic inflammation does not seem to respond to corticosteroids.

### **Infection**

Respiratory infection (which COPD patients are prone to) may amplify progression of lung destruction.

Bacteria, especially *Haemophilus influenzae*, colonize the lower airways of about 30% of patients with COPD. In more severely affected patients (eg, those with previous hospitalizations), colonization with *Pseudomonas aeruginosa* or other gram-negative bacteria is common. Smoking and airflow obstruction may lead to impaired mucus clearance in lower airways, which predisposes to infection. Repeated bouts of infection increase the inflammatory burden that hastens disease progression. There is no evidence, however, that long-term use of antibiotics slows the progression of COPD.

### **Airflow limitation**

The cardinal pathophysiologic feature of COPD is airflow limitation caused by airway obstruction, loss of elastic recoil, or both.

Airway obstruction is caused by inflammation-mediated mucus hypersecretion, mucus plugging, mucosal edema, bronchospasm, peribronchial fibrosis, and destruction of small airways or a combination of these mechanisms. Alveolar septa are destroyed, reducing parenchymal attachments to the airways and thereby facilitating airway closure during expiration.

Enlarged alveolar spaces sometimes consolidate into bullae, defined as airspaces  $\geq 1$  cm in diameter. Bullae may be entirely empty or have strands of lung tissue traversing them in areas of locally severe emphysema; they occasionally occupy the entire hemithorax.

These changes lead to loss of elastic recoil and lung hyperinflation.

Increased airway resistance increases the work of breathing, as does lung hyperinflation.

Increased work of breathing may lead to alveolar hypoventilation with hypoxia and hypercapnia, although hypoxia is also caused by ventilation/perfusion (V/Q) mismatch.

### **Complications**

In addition to airflow limitation and sometimes respiratory insufficiency, complications include

- Pulmonary hypertension
- Respiratory infection
- Weight loss and other comorbidities

Chronic hypoxemia increases pulmonary vascular tone, which, if diffuse, causes pulmonary hypertension and cor pulmonale. The increase in pulmonary vascular pressure may be augmented by the destruction of the pulmonary capillary bed due to destruction of alveolar septa. Viral or bacterial respiratory infections are common among patients with COPD and cause a large percentage of acute exacerbations. It is currently thought that acute bacterial infections are due to acquisition of new strains of bacteria rather than overgrowth of chronic colonizing bacteria.

Weight loss may occur, perhaps in response to decreased caloric intake and increased levels of circulating tumor necrosis factor (TNF)- $\alpha$ .



Other coexisting or complicating disorders that adversely affect quality of life and survival include osteoporosis, depression, coronary artery disease, lung cancer, muscle atrophy, and gastroesophageal reflux. The extent to which these disorders are consequences of COPD, smoking, and the accompanying systemic inflammation is unclear.

### ***Symptoms and Signs***

COPD takes years to develop and progress. Most patients have smoked  $\geq 20$  cigarettes/day for  $> 20$  yr. Productive cough usually is the initial symptom, developing among smokers in their 40s and 50s. Dyspnea that is progressive, persistent, exertional, or worse during respiratory infection appears when patients are in their late 50s or 60s. Symptoms usually progress quickly in patients who continue to smoke and in those who have a higher lifetime tobacco exposure. Morning headache develops in more advanced disease and signals nocturnal hypercapnia or hypoxemia.

**Acute exacerbations** occur sporadically during the course of COPD and are heralded by increased symptom severity. The specific cause of any exacerbation is almost always impossible to determine, but exacerbations are often attributed to viral URIs, acute bacterial bronchitis, or exposure to respiratory irritants. As COPD progresses, acute exacerbations tend to become more frequent, averaging about 1 to 3 episodes/yr.

Signs of COPD include wheezing, increased expiratory phase of breathing, lung hyperinflation manifested as decreased heart and lung sounds, and increased anteroposterior diameter of the thorax (barrel chest). Patients with advanced emphysema lose weight and experience muscle wasting that has been attributed to immobility, hypoxia, or release of systemic inflammatory mediators, such as TNF- $\alpha$ . Signs of advanced disease include pursed-lip breathing, accessory muscle use, paradoxical inward movement of the lower intercostal interspaces during inspiration (Hoover sign), and cyanosis. Signs of cor pulmonale include neck vein distention, splitting of the 2nd heart sound with an accentuated pulmonic component, tricuspid insufficiency murmur, and peripheral edema. Right ventricular heaves are uncommon in COPD because the lungs are hyperinflated.

Spontaneous pneumothorax may occur (possibly related to rupture of bullae) and should be suspected in any patient with COPD whose pulmonary status abruptly worsens.

### ***Diagnosis***

- Chest x-ray
- Pulmonary function testing

Diagnosis is suggested by history, physical examination, and chest imaging and is confirmed by pulmonary function tests. Similar symptoms can be caused by asthma, heart failure, and bronchiectasis (see Table: [Differential Diagnosis of COPD](#)). COPD and asthma are sometimes easily confused.

Systemic disorders that may have a component of airflow limitation may suggest COPD; they include HIV infection, abuse of IV drugs (particularly cocaine and amphetamines), sarcoidosis, Sjögren syndrome, bronchiolitis obliterans, lymphangioleiomyomatosis, and eosinophilic granuloma. COPD can be differentiated from interstitial lung diseases (ILD) by chest imaging,

which shows increased interstitial markings in ILD, and pulmonary function testing, which shows a restrictive ventilatory defect rather than an obstructive ventilatory defect. In some patients, COPD and ILD coexist (combined pulmonary fibrosis and emphysema [CPFE]) in which lung volumes are relatively preserved, but gas exchange is severely impaired.

### **Pulmonary function tests**

Patients suspected of having COPD should undergo pulmonary function testing to confirm airflow limitation, to quantify its severity and reversibility, and to distinguish COPD from other disorders. Pulmonary function testing is also useful for following disease progression and monitoring response to treatment. The primary diagnostic tests are

- FEV<sub>1</sub>, which is the volume of air forcefully expired during the first second after taking a full breath
- Forced vital capacity (FVC), which is the total volume of air expired with maximal force
- Flow-volume loops, which are simultaneous spirometric recordings of airflow and volume during forced maximal expiration and inspiration

Reductions of FEV<sub>1</sub>, FVC, and the ratio of FEV<sub>1</sub>/FVC are the hallmark of airflow limitation. Flow-volume loops show a concave pattern in the expiratory tracing. FEV<sub>1</sub> declines up to 60 mL/yr in smokers, compared with a less steep decline of 25 to 30 mL/yr in nonsmokers, beginning at about age 30. In young adult smokers who already have a low FEV<sub>1</sub>, the decline occurs more rapidly. When the FEV<sub>1</sub> falls below about 1 L, patients develop dyspnea with activities of daily living (although dyspnea is more closely related to the degree of dynamic hyperinflation [progressive hyperinflation due to incomplete exhalation] than to the degree of airflow limitation); when the FEV<sub>1</sub> falls below about 0.8 L, patients are at risk of hypoxemia, hypercapnia, and cor pulmonale. FEV<sub>1</sub> and FVC are easily measured with office spirometry and define severity of disease because they correlate with symptoms and mortality. Normal reference values are determined by patient age, sex, and height.

Additional pulmonary function testing is necessary only in specific circumstances, such as before lung volume reduction surgery. Other test abnormalities may include increased total lung capacity, functional residual capacity, and residual volume, which can help distinguish COPD from restrictive pulmonary disease, in which these measures are diminished; decreased vital capacity; and decreased single-breath diffusing capacity for carbon monoxide (DL<sub>CO</sub>).

Decreased DL<sub>CO</sub> is nonspecific and is reduced in other disorders that affect the pulmonary vascular bed, such as interstitial lung disease, but can help distinguish emphysema from asthma, in which DL<sub>CO</sub> is normal or elevated.

### **Imaging tests**

**Chest x-ray** may have characteristic findings. In patients with emphysema, changes can include lung hyperinflation manifested as a flat diaphragm (ie, increase in the angle formed by the sternum and anterior diaphragm on a lateral film from the normal value of 45° to > 90°), rapid tapering of hilar vessels, and bullae (ie, radiolucencies > 1 cm surrounded by arcuate, hairline shadows). Other typical findings include widening of the retrosternal airspace and a narrow cardiac shadow. Emphysematous changes occurring predominantly in the lung bases

suggest  $\alpha_1$ -antitrypsin deficiency. The lungs may look normal or have increased lucency secondary to loss of parenchyma. Among patients with chronic obstructive bronchitis, chest x-rays may be normal or may show a bibasilar increase in bronchovascular markings as a result of bronchial wall thickening.

### **Chronic Obstructive Pulmonary Disease (Chest X-ray)**

Prominent hila suggest large central pulmonary arteries that may signify pulmonary hypertension. Right ventricular enlargement that occurs in cor pulmonale may be masked by lung hyperinflation or may manifest as encroachment of the heart shadow on the retrosternal space or by widening of the transverse cardiac shadow in comparison with previous chest x-rays.

**Chest CT** may reveal abnormalities that are not apparent on the chest x-ray and may also suggest coexisting or complicating disorders, such as pneumonia, pneumoconiosis, or lung cancer. CT helps assess the extent and distribution of emphysema, estimated either by visual scoring or with analysis of the distribution of lung density. Indications for obtaining CT in patients with COPD include evaluation for lung volume reduction surgery, suspicion of coexisting or complicating disorders that are not clearly evident or excluded by chest x-ray, and suspicion of cancer.

### **Adjunctive tests**

$\alpha_1$ -Antitrypsin levels should be measured in patients < 50 yr with symptomatic COPD and in nonsmokers of any age with COPD to detect  $\alpha_1$ -antitrypsin deficiency. Other indications of possible  $\alpha_1$ -antitrypsin deficiency include a family history of premature COPD or unexplained liver disease, lower-lobe distribution of emphysema, and COPD associated with antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis. If levels of  $\alpha_1$ -antitrypsin are low, the diagnosis should be confirmed by genetic testing to establish the  $\alpha_1$ -antitrypsin phenotype. ECG, often done to exclude cardiac causes of dyspnea, typically shows diffusely low QRS voltage with a vertical heart axis caused by lung hyperinflation and increased P-wave voltage or rightward shifts of the P-wave vector caused by right atrial enlargement in patients with advanced emphysema. Findings of right ventricular hypertrophy include an R or R' wave as tall as or taller than the S wave in lead V<sub>1</sub>; an R wave smaller than the S wave in lead V<sub>6</sub>; right-axis deviation >110° without right bundle branch block; or some combination of these. Multifocal atrial tachycardia, an arrhythmia that can accompany COPD, manifests as a tachyarrhythmia with polymorphic P waves and variable PR intervals.

Echocardiography is occasionally useful for assessing right ventricular function and pulmonary hypertension, although air trapping makes it technically difficult in patients with COPD.

Echocardiography is most often indicated when coexistent left ventricular or valvular heart disease is suspected.

CBC is of little diagnostic value in the evaluation of COPD but may show erythrocythemia (Hct > 48%) if the patient has chronic hypoxemia. Patients with anemia (for reasons other than COPD) have disproportionately severe dyspnea. Serum electrolytes are of little value but may show an elevated HCO<sub>3</sub> level if patients have chronic hypercapnia.

### **Evaluation of exacerbations**

Patients with acute exacerbations usually have combinations of increased cough, sputum, dyspnea, and work of breathing, as well as low  $O_2$  saturation on pulse oximetry, diaphoresis, tachycardia, anxiety, and cyanosis. However, patients with exacerbations accompanied by retention of  $CO_2$  may be lethargic or somnolent, a very different appearance. All patients requiring hospitalization for an acute exacerbation should undergo testing (eg, ABG sampling) to quantify hypoxemia and hypercapnia. Hypercapnia may exist without hypoxemia.

Findings of  $PaO_2 < 50$  mm Hg or  $PaCO_2 > 50$  mm Hg in the setting of respiratory acidemia define acute respiratory failure. However, some patients chronically manifest such levels of  $PaO_2$  and  $PaCO_2$  in the absence of acute respiratory failure.

A chest x-ray is often done to check for pneumonia or pneumothorax. Very rarely, among patients receiving chronic systemic corticosteroids, infiltrates may represent *Aspergillus* pneumonia.

Yellow or green sputum is a reliable indicator of neutrophils in the sputum and suggests bacterial colonization or infection. Culture is usually done in hospitalized patients but is not usually necessary in outpatients. In samples from outpatients, Gram stain usually shows neutrophils with a mixture of organisms, often gram-positive diplococci ( *Streptococcus pneumoniae* ), gram-negative bacilli ( *H. influenzae* ), or both. Other oropharyngeal commensal organisms, such as *Moraxella* ( *Branhamella* ) *catarrhalis*, occasionally cause exacerbations. In hospitalized patients, cultures may show resistant gram-negative organisms (eg, *Pseudomonas*) or, rarely, *Staphylococcus*.

### **Prognosis**

Severity of airway obstruction predicts survival in patients with COPD. The mortality rate in patients with an  $FEV_1 \geq 50\%$  of predicted is slightly greater than that of the general population. If the  $FEV_1$  is 0.75 to 1.25 L, 5-yr survival is about 40 to 60%; if  $< 0.75$  L, about 30 to 40%. More accurate prediction of death risk is possible by simultaneously measuring body mass index ( *B* ), the degree of airflow obstruction ( *O* , which is the  $FEV_1$  ), dyspnea ( *D* , which is measured with a Modified Medical Research Council [MMRC] dyspnea scale, and exercise capacity ( *E* , which is measured with a 6-min walking test); this is the BODE index. Also, older age, heart disease, anemia, resting tachycardia, hypercapnia, and hypoxemia decrease survival, whereas a significant response to bronchodilators predicts improved survival. Risk factors for death in patients with acute exacerbation requiring hospitalization include older age, higher  $PaCO_2$ , and use of maintenance oral corticosteroids.

Patients at high risk of imminent death are those with progressive unexplained weight loss or severe functional decline (eg, those who experience dyspnea with self-care, such as dressing, bathing, or eating). Mortality in COPD may result from intercurrent illnesses rather than from progression of the underlying disorder in patients who have stopped smoking. Death is generally caused by acute respiratory failure, pneumonia, lung cancer, heart disease, or pulmonary embolism.

### **Treatment of Stable COPD**

- Inhaled bronchodilators, corticosteroids, or both

- Supportive care (eg, smoking cessation, O<sub>2</sub> therapy, pulmonary rehabilitation)

COPD management involves treatment of chronic stable disease and of exacerbations. Treatment of cor pulmonale, a common complication of long-standing, severe COPD, is discussed elsewhere.

Treatment of chronic stable COPD aims to prevent exacerbations and improve lung and physical function through drug and O<sub>2</sub> therapy, smoking cessation, exercise, enhancement of nutrition, and pulmonary rehabilitation. Surgical treatment of COPD is indicated for selected patients.

### **Drug therapy**

**Inhaled bronchodilators** are the mainstay of COPD management; drugs include

- $\beta$ -agonists
- Anticholinergics (antimuscarinics)

These two classes are equally effective. Patients with mild (group A) disease are treated only when symptomatic. Patients with group B, C, or D COPD should be taking drugs from one or both of these classes regularly to improve pulmonary function and increase exercise capacity. The frequency of exacerbations can be reduced with the use of anticholinergics, inhaled corticosteroids, or long-acting  $\beta$ -agonists. However, there is no evidence that regular bronchodilator use slows deterioration of lung function. The initial choice among short-acting  $\beta$ -agonists, long-acting  $\beta$ -agonists, anticholinergics (which have a greater bronchodilating effect), and combination  $\beta$ -agonist and anticholinergic therapy is often a matter of tailoring cost and convenience to the patient's preferences and symptoms.

For home treatment of chronic stable disease, drug administration by metered-dose inhaler or dry-powder inhaler is preferred over administration by nebulizer; home nebulizers are prone to contamination due to incomplete cleaning and drying. Therefore, nebulizers should be reserved for people who cannot coordinate activation of the metered-dose inhaler with inhalation or cannot develop enough inspiratory flow for dry powder inhalers. For metered-dose inhalers, patients should be taught to exhale to functional residual capacity, inhale the aerosol slowly to total lung capacity, and hold the inhalation for 3 to 4 sec before exhaling. Spacers help ensure optimal delivery of drug to the distal airways and reduce the importance of coordinating activation of the inhaler with inhalation. Some spacers alert patients if they are inhaling too rapidly. Newer metered-dose inhalers that use hydrofluoroalkane (HFA) propellants require slightly different techniques than inhalers containing older environmentally damaging chlorinated fluorocarbon propellants; inhalers containing HFA require 2 to 3 priming doses if they are new or not recently used.

**$\beta$ -Agonists** relax bronchial smooth muscle and increase mucociliary clearance. **Albuterol** aerosol, 2 puffs (90 to 100 mcg/puff) inhaled from a metered-dose inhaler 4 to 6 times/day prn, is usually the drug of choice because of low cost. Long-acting  $\beta$ -agonists are preferable for patients with nocturnal symptoms or for those who find frequent dosing inconvenient. Options include **salmeterol** powder, 1 puff (50 mcg) inhaled bid, **indacaterol** 1 puff (75 mcg) inhaled once/day (150 mcg once/day in Europe), and **formoterol** powder, 1 puff (12 mcg) inhaled bid. The dry-powder formulations may be more effective for patients who have

trouble coordinating use of a metered-dose inhaler. Patients should be taught the difference between short-acting and long-acting drugs, because long-acting drugs that are used as needed or more than twice/day increase the risk of cardiac arrhythmias. Adverse effects commonly result from use of any  $\beta$ -agonist and include tremor, anxiety, tachycardia, and mild, temporary hypokalemia.

**Anticholinergics** (antimuscarinics) relax bronchial smooth muscle through competitive inhibition of muscarinic receptors ( $M_1$ ,  $M_2$ , and  $M_3$ ). **Ipratropium** is a short-acting anticholinergic; dose is 2 to 4 puffs (18 mcg/puff) from a metered-dose inhaler q 4 to 6 h. **Ipratropium** has a slower onset of action (within 30 min; peak effect in 1 to 2 h), so a  $\beta_2$ -agonist is often prescribed with it in a single combination inhaler or as a separate as-needed rescue drug. **Tiotropium** is a long-acting quaternary anticholinergic inhaled as a powder formulation. Dose is 1 puff (18 mcg) once/day. **Aclidinium** bromide is available as a multidose dry-powder inhaler. Dose is 1 puff (400 mcg/puff) bid. Umeclidinium can be used as a once/day combination with vilanterol (a long-acting beta-agonist) in a dry-powder inhaler. Adverse effects of all anticholinergics are pupillary dilation (and risk of triggering or worsening acute angle closure glaucoma), urinary retention, and dry mouth.

**Corticosteroids** are often part of treatment. Inhaled corticosteroids seem to reduce airway inflammation, reverse  $\beta$ -receptor down-regulation, and inhibit leukotriene and cytokine production. They do not alter the course of pulmonary function decline in patients with COPD who continue to smoke, but they do relieve symptoms and improve short-term pulmonary function in some patients, are additive to the effect of bronchodilators, and may diminish the frequency of COPD exacerbations. They are indicated for patients who have repeated exacerbations or symptoms despite optimal bronchodilator therapy. Dose depends on the drug; examples include **fluticasone** 500 to 1000 mcg/day and **beclomethasone** 400 to 2000 mcg/day. The long-term risks of inhaled corticosteroids in elderly people are not proved but probably include osteoporosis, cataract formation, and an increased risk of nonfatal pneumonia. Long-term users therefore should undergo periodic ophthalmologic and bone densitometry screening and should possibly receive supplemental calcium, vitamin D, and a bisphosphonate as indicated. Combinations of a long-acting  $\beta$ -agonist (eg, **salmeterol**) and an inhaled corticosteroid (eg, **fluticasone**) are more effective than either drug alone in the treatment of chronic stable disease.

Oral or systemic corticosteroids should usually not be used to treat chronic stable COPD.

**Theophylline** plays only a small role in the treatment of chronic stable COPD now that safer, more effective drugs are available. **Theophylline** decreases smooth muscle spasm, enhances mucociliary clearance, improves right ventricular function, and decreases pulmonary vascular resistance and arterial pressure. Its mode of action is poorly understood but appears to differ from that of  $\beta_2$ -agonists and anticholinergics. Its role in improving diaphragmatic function and dyspnea during exercise is controversial. Low-dose oral **theophylline** (300 to 400 mg/day) has anti-inflammatory properties and may enhance the effects of inhaled corticosteroids.



**Theophylline** can be used for patients who have not adequately responded to inhaled drugs and who have shown symptomatic benefit from a trial of the drug. Serum levels need not be monitored unless the patient does not respond to the drug, develops symptoms of toxicity, or is questionably adherent; slowly absorbed oral **theophylline** preparations, which require less frequent dosing, enhance adherence. Toxicity is common and includes sleeplessness and GI upset, even at low blood levels. More serious adverse effects, such as supraventricular and ventricular arrhythmias and seizures, tend to occur at blood levels > 20 mg/L. Hepatic metabolism of **theophylline** varies greatly and is influenced by genetic factors, age, cigarette smoking, hepatic dysfunction, and some drugs, such as macrolide and fluoroquinolone antibiotics and non-sedating histamine <sub>2</sub> blockers.

**Phosphodiesterase-4 inhibitors** are more specific than **theophylline** for pulmonary phosphodiesterase and have fewer adverse effects. They have anti-inflammatory properties and are mild bronchodilators. Phosphodiesterase-4 inhibitors include **roflumilast** and **cilomilast**, but **roflumilast** is the only one in routine clinical use. It can be used in addition to other bronchodilators for reduction of exacerbations in patients with COPD. The dose is 500 mcg po once/day. Common adverse effects include nausea, headache, and weight loss, but these effects may subside with continued use.

### **O<sub>2</sub> therapy**

Long-term O<sub>2</sub> therapy prolongs life in patients with COPD whose Pa O<sub>2</sub> is chronically < 55 mm Hg. Continual 24-h use is more effective than a 12-h nocturnal regimen. O<sub>2</sub> therapy brings Hct toward normal levels; improves neuropsychologic factors, possibly by facilitating sleep; and ameliorates pulmonary hemodynamic abnormalities. O<sub>2</sub> therapy also increases exercise tolerance in many patients.

O<sub>2</sub> saturation should be measured during exercise and while at rest. Similarly, a sleep study should be considered for patients with advanced COPD who do not meet the criteria for long-term O<sub>2</sub> therapy while they are awake, but whose clinical assessment suggests pulmonary hypertension in the absence of daytime hypoxemia. Nocturnal O<sub>2</sub> may be prescribed if a sleep study shows episodic desaturation to ≤ 88%. Such treatment prevents progression of pulmonary hypertension, but its effects on survival are unknown.

O<sub>2</sub> is administered by nasal cannula at a flow rate sufficient to achieve a Pa O<sub>2</sub> > 60 mm Hg (Sa O<sub>2</sub> > 90%), usually ≤ 3 L/min at rest. O<sub>2</sub> is supplied by electrically driven O<sub>2</sub> concentrators, liquid O<sub>2</sub> systems, or cylinders of compressed gas. Concentrators, which limit mobility but are the least expensive, are preferable for patients who spend most of their time at home. Such patients require small O<sub>2</sub> tanks for backup in case of an electrical failure and for portable use. A liquid system is preferable for patients who spend much time out of their home. Portable canisters of liquid O<sub>2</sub> are easier to carry and have more capacity than portable cylinders of compressed gas. Large compressed-air cylinders are the most expensive way of providing O<sub>2</sub> and should be used only if no other source is available. All patients must be taught the dangers of smoking during O<sub>2</sub> use.



Various O<sub>2</sub>-conserving devices can reduce the amount of O<sub>2</sub> used by the patient, either by using a reservoir system or by permitting O<sub>2</sub> flow only during inspiration. Systems with these devices correct hypoxemia as effectively as do continuous flow systems.

Some patients need supplemental O<sub>2</sub> during air travel, because flight cabin pressure in commercial airliners is below sea level air pressure (often equivalent to 1830 to 2400 m [6000 to 8000 ft]). Eucapnic COPD patients who have a Pa O<sub>2</sub> > 68 mm Hg at sea level generally have an in-flight Pa O<sub>2</sub> > 50 mm Hg and do not require supplemental O<sub>2</sub>. All patients with COPD with a Pa O<sub>2</sub> ≤ 68 mm Hg at sea level, hypercapnia, significant anemia (Hct < 30), or a coexisting heart or cerebrovascular disorder should use supplemental O<sub>2</sub> during long flights and should notify the airline when making their reservation. Airlines can provide supplemental O<sub>2</sub>, and most require a minimum notice of 24 h, a physician's statement of necessity, and an O<sub>2</sub> prescription before the flight. Patients should bring their own nasal cannulas, because some airlines provide only face masks. Patients are not permitted to transport or use their own liquid O<sub>2</sub>, but many airlines now permit use of portable battery-operated O<sub>2</sub> concentrators, which also provide a suitable O<sub>2</sub> source on arrival.

### **Smoking cessation**

Smoking cessation is both extremely difficult and extremely important; it slows but does not halt the rate of FEV<sub>1</sub> decline. Simultaneous use of multiple strategies is most effective: establishment of a quit date, behavior modification techniques, group sessions, [nicotine](#) replacement therapy (by gum, transdermal patch, inhaler, lozenge, or nasal spray), [varenicline](#) or [bupropion](#), and physician encouragement. Quit rates > 50% at 1 yr have not been demonstrated even with the most effective interventions, such as use of [bupropion](#) combined with [nicotine](#) replacement or use of [varenicline](#) alone.

### **Vaccinations**

All patients with COPD should be given annual influenza vaccinations. If a patient is unable to receive a vaccination or if the prevailing influenza strain is not included in the annual vaccine formulation, prophylactic treatment with a neuraminidase inhibitor ([oseltamivir](#) or [zanamivir](#)) is sometimes used if there is close exposure to influenza-infected people. Treatment with a neuraminidase inhibitor should be started at the first sign of an influenza-like illness.

Pneumococcal polysaccharide vaccine, although of unproven efficacy in COPD, has minimal adverse effects and should probably also be given.

### **Nutrition**

COPD patients are at risk of weight loss and nutritional deficiencies because of a higher energy cost of daily activities; reduced caloric intake relative to need because of dyspnea; and the catabolic effect of inflammatory cytokines such as TNF-α. Generalized muscle strength and efficiency of O<sub>2</sub> use are impaired. Patients with poorer nutritional status have a worse prognosis, so it is prudent to recommend a balanced diet with adequate caloric intake in conjunction with exercise to prevent or reverse undernutrition and muscle atrophy. However, excessive weight gain should be avoided, and obese patients should strive to gradually reduce body fat. Studies of nutritional supplementation alone have not shown improvement in pulmonary function or exercise capacity. Trials of appetite stimulants, anabolic steroids, growth hormone

supplementation, and TNF antagonists in reversing undernutrition and improving functional status and prognosis in COPD have been disappointing.

### **Pulmonary rehabilitation**

Pulmonary rehabilitation programs serve as adjuncts to drug treatment to improve physical function; many hospitals and health care organizations offer formal multidisciplinary rehabilitation programs. Pulmonary rehabilitation includes exercise, education, and behavioral interventions. Treatment should be individualized; patients and family members are taught about COPD and medical treatments, and patients are encouraged to take as much responsibility for personal care as possible. The benefits of rehabilitation are greater independence and improved quality of life and exercise capacity. Pulmonary rehabilitation typically does not improve pulmonary function. A carefully integrated rehabilitation program helps patients with severe COPD accommodate to physiologic limitations while providing realistic expectations for improvement. Patients with severe disease require a minimum of 3 mo of rehabilitation to benefit and should continue with maintenance programs.

An exercise program can be helpful in the home, in the hospital, or in institutional settings. Graded exercise can ameliorate skeletal muscle deconditioning resulting from inactivity or prolonged hospitalization for respiratory failure. Specific training of respiratory muscles is less helpful than general aerobic conditioning.

A typical training program begins with slow walking on a treadmill or unloaded cycling on an ergometer for a few minutes. Duration and exercise load are progressively increased over 4 to 6 wk until the patient can exercise for 20 to 30 min nonstop with manageable dyspnea. Patients with very severe COPD can usually achieve an exercise regimen of walking for 30 min at 1 to 2 mph. Maintenance exercise should be done 3 to 4 times/wk to maintain fitness levels.

O<sub>2</sub> saturation is monitored, and supplemental O<sub>2</sub> is provided as needed.

Upper extremity resistance training helps the patient in doing daily tasks (eg, bathing, dressing, house cleaning). The usual benefits of exercise are modest increases in lower extremity strength, endurance, and maximum O<sub>2</sub> consumption.

Patients should be taught ways to conserve energy during activities of daily living and to pace their activities. Difficulties in sexual function should be discussed and advice should be given on using energy-conserving techniques for sexual gratification.

### **Surgery**

Surgical options for treatment of severe COPD include lung volume reduction and transplantation.

**Lung volume reduction surgery** consists of resecting nonfunctioning emphysematous areas. The procedure improves lung function, exercise tolerance, and quality of life in patients with severe, predominantly upper-lung emphysema who have low baseline exercise capacity after pulmonary rehabilitation. Mortality is increased in the first 90 days after lung volume reduction surgery, but survival is higher at 5 yr. The effect on ABGs is variable and not predictable, but most patients who require O<sub>2</sub> before surgery continue to need it. Improvement is less than that with lung transplantation. The mechanism of improvement is believed to be enhanced lung recoil

and improved diaphragmatic function. Operative mortality is about 5%. The best candidates for lung volume reduction surgery are patients with an FEV<sub>1</sub> 20 to 40% of predicted, a DL<sub>CO</sub> > 20% of predicted, significantly impaired exercise capacity, heterogeneous pulmonary disease on CT with an upper-lobe predominance, Pa CO<sub>2</sub> < 50 mm Hg, and absence of severe pulmonary hypertension and coronary artery disease.

Rarely, patients have extremely large bullae that compress the functional lung. These patients can be helped by surgical resection of these bullae, with resulting relief of symptoms and improved pulmonary function. Generally, resection is most beneficial for patients with bullae affecting more than one third of a hemithorax and an FEV<sub>1</sub> about half of the predicted normal value. Improved pulmonary function is related to the amount of normal or minimally diseased lung tissue that was compressed by the resected bullae. Serial chest x-rays and CT scans are the most useful procedures for determining whether a patient's functional status is due to compression of viable lung by bullae or to generalized emphysema. A markedly reduced DL<sub>CO</sub> (< 40% predicted) indicates widespread emphysema and suggests a poorer outcome from surgical resection.

**Lung transplantation** can be single or double. Perioperative complications tend to be lower with single-lung transplantation, but some evidence shows that survival time is increased with double-lung transplantation. Candidates for transplantation are patients < 65 yr with an FEV<sub>1</sub> < 25% predicted after bronchodilator therapy or with severe pulmonary hypertension. The goal of lung transplantation is to improve quality of life, because survival time is not necessarily increased. The 5-yr survival after transplantation for emphysema is 45 to 60%. Lifelong immunosuppression is required, with the attendant risk of opportunistic infections.

#### ***Treatment of Acute COPD Exacerbation***

- O<sub>2</sub> supplementation
- Bronchodilators
- Corticosteroids
- Antibiotics
- Sometimes ventilatory assistance

The immediate objectives are to ensure adequate oxygenation and near-normal blood pH, reverse airway obstruction, and treat any cause.

The cause of an acute exacerbation is usually unknown, although some acute exacerbations result from bacterial or viral infections. Smoking, irritative inhalational exposure, and high levels of air pollution also contribute. Mild exacerbations often can be treated on an outpatient basis in patients with adequate home support. Elderly, frail patients and patients with comorbidities, a history of respiratory failure, or acute changes in ABG measurements are admitted to the hospital for observation and treatment. Patients with life-threatening exacerbations manifested by uncorrected moderate to severe acute hypoxemia, acute respiratory acidosis, new arrhythmias, or deteriorating respiratory function despite hospital treatment should be admitted to the ICU and their respiratory status monitored frequently.

O<sub>2</sub>

Most patients require O<sub>2</sub> supplementation, even those who do not need it chronically.

Hypercapnia may worsen in patients given O<sub>2</sub>. This worsening has traditionally been thought to result from an attenuation of hypoxic respiratory drive. However, increased V/Q mismatch probably is a more important factor. Before O<sub>2</sub> administration, pulmonary vasoconstriction minimizes V/Q mismatch by decreasing perfusion of the most poorly ventilated areas of the lungs. Increased V/Q mismatch occurs because O<sub>2</sub> administration attenuates this hypoxic pulmonary vasoconstriction. The Haldane effect may also contribute to worsening hypercapnia, although this theory is controversial. The Haldane effect is a decrease in Hb's affinity for CO<sub>2</sub>, which results in increased amounts of CO<sub>2</sub> dissolved in plasma. O<sub>2</sub> administration, even though it may worsen hypercapnia, is recommended; many patients with COPD have chronic as well as acute hypercapnia and thus severe CNS depression is unlikely unless Pa CO<sub>2</sub> is >85 mm Hg. The target level for Pa O<sub>2</sub> is about 60 mm Hg; higher levels offer little advantage and increase the risk of hypercapnia. O<sub>2</sub> is given via Venturi mask so it can be closely regulated, and the patient is closely monitored. Patients whose condition deteriorates with O<sub>2</sub> therapy (eg, those with severe acidemia or CNS depression) require ventilatory assistance.

Many patients who require home O<sub>2</sub> for the first time when they are discharged from the hospital after an exacerbation improve within 30 days and no longer require O<sub>2</sub>. Thus, the need for home O<sub>2</sub> should be reassessed 60 to 90 days after discharge.

### **Ventilatory assistance**

Noninvasive positive-pressure ventilation (eg, pressure support or bilevel positive airway pressure ventilation by face mask) is an alternative to full mechanical ventilation. Noninvasive ventilation appears to decrease the need for intubation, reduce hospital stay, and reduce mortality in patients with severe exacerbations (defined as a pH < 7.30 in hemodynamically stable patients not at immediate risk of respiratory arrest). Noninvasive ventilation appears to have no effect in patients with less severe exacerbation. However, it may be indicated for patients with less severe exacerbations whose ABGs worsen despite initial drug or O<sub>2</sub> therapy or who appear to be imminent candidates for full mechanical ventilation but who do not require intubation for control of the airway or sedation for agitation. Patients who have severe dyspnea, hyperinflation, and use of accessory muscles of respiration may also gain relief from positive airway pressure.

Deterioration while receiving noninvasive ventilation necessitates invasive mechanical ventilation.

Deteriorating ABG values and mental status and progressive respiratory fatigue are indications for endotracheal intubation and mechanical ventilation. Ventilator settings, management strategies, and complications are discussed elsewhere. Risk factors for ventilatory dependence include an FEV<sub>1</sub> < 0.5 L, stable ABGs with a Pa O<sub>2</sub> < 50 mm Hg, or a Pa CO<sub>2</sub> > 60 mm Hg, severe exercise limitation, and poor nutritional status. Therefore, if patients are at high risk, discussion of their wishes regarding intubation and mechanical ventilation should be initiated and documented while they are stable outpatients. However, overconcern about possible ventilator dependence should not delay management of acute respiratory failure; many patients who require mechanical ventilation can return to their pre-exacerbation level of health.

In patients who require prolonged intubation (eg, > 2 wk), a tracheostomy is indicated to facilitate comfort, communication, and eating. With a good multidisciplinary rehabilitation program, including nutritional and psychologic support, many patients who require prolonged mechanical ventilation can be successfully liberated and can return to their former level of function. Specialized programs are available for patients who remain ventilator-dependent after acute respiratory failure. Some patients can remain off the ventilator during the day. For patients with adequate home support, training of family members can permit some patients to be sent home with ventilators.

### **Drug therapy**

$\beta$ -Agonists and anticholinergics, with or without corticosteroids, should be started concurrently with O<sub>2</sub> therapy (regardless of how O<sub>2</sub> is administered) with the aim of reversing airway obstruction. Methylxanthines, once considered essential to treatment of acute COPD exacerbations, are no longer used; toxicities exceed benefits.

**Short-acting  $\beta$ -agonists** are the cornerstone of drug therapy for acute exacerbations. The most widely used drug is [albuterol](#) 2.5 mg by nebulizer or 2 to 4 puffs (100 mcg/puff) by metered-dose inhaler q 2 to 6 h. Inhalation using a metered-dose inhaler causes rapid bronchodilation; there are no data indicating that doses taken with nebulizers are more effective than the same doses correctly taken with metered-dose inhalers. In life-threatening exacerbations, risks of the exacerbation usually exceed those of high-dose  $\beta$ -agonists; thus,  $\beta$ -agonists may be given continuously via nebulizer until improvement occurs.

**[Ipratropium](#)**, an anticholinergic, is effective in acute COPD exacerbations and should be given concurrently or alternating with  $\beta$ -agonists. Dosage is 0.25 to 0.5 mg by nebulizer or 2 to 4 inhalations (17 to 18 mcg of drug delivered per puff) by metered-dose inhaler q 4 to 6 h. **[Ipratropium](#)** generally provides bronchodilating effect similar to that of usual recommended doses of  $\beta$ -agonists. The role of the longer-acting anticholinergic **[tiotropium](#)** in treating acute exacerbations has not been defined.

**Corticosteroids** should be begun immediately for all but mild exacerbations. Options include **[prednisone](#)** 30 to 60 mg po once/day for 5 days or tapered over 7 to 14 days and **[methylprednisolone](#)** 60 to 500 mg IV once/day for 3 days and then tapered over 7 to 14 days. Alternatively, a 5-day course of 40 mg of **[prednisone](#)** appears to be equally effective. These drugs are equivalent in their acute effects; inhaled corticosteroids have no role in the treatment of acute exacerbations.

**Antibiotics** are recommended for exacerbations in patients with purulent sputum. Some physicians give antibiotics empirically for change in sputum color or for nonspecific chest x-ray abnormalities. Routine cultures and Gram stains are not necessary before treatment unless an unusual or resistant organism is suspected (eg, in hospitalized, institutionalized, or immunosuppressed patients). Drugs directed against oral flora are indicated. **[Trimethoprim](#)**/sulfamethoxazole 160 mg/800 mg po bid, **[amoxicillin](#)** 250 to 500 mg po tid, **[tetracycline](#)** 250 mg po qid, and **[doxycycline](#)** 50 to 100 mg po bid given for 7 to 14 days are all effective and inexpensive. Choice of drug is dictated by local patterns of bacterial

sensitivity and patient history. If the patient is seriously ill or if clinical evidence suggests that the infectious organisms are resistant, broader spectrum 2nd-line drugs can be used. These drugs include [amoxicillin](#)/clavulanate 250 to 500 mg po tid, fluoroquinolones (eg, [ciprofloxacin](#), [levofloxacin](#)), 2nd-generation cephalosporins (eg, [cefuroxime](#), [cefaclor](#)), and extended-spectrum macrolides (eg, [azithromycin](#), [clarithromycin](#)). These drugs are effective against  $\beta$ -lactamase-producing strains of *H. influenzae* and *M. catarrhalis* but have not been shown to be more effective than first-line drugs for most patients. Patients can be taught to recognize a change in sputum from normal to purulent as a sign of impending exacerbation and to start a 10- to 14-day course of antibiotic therapy. Long-term antibiotic prophylaxis is recommended only for patients with underlying structural changes in the lung, such as bronchiectasis or infected bullae. In patients with frequent exacerbations, long-term macrolide use reduces exacerbation frequency but may have adverse effects.

**Antitussives**, such as [dextromethorphan](#) and [benzonatate](#), have little role.

**Opioids** (eg, [codeine](#), hydrocodone, [oxycodone](#)) should be used judiciously for relief of symptoms (eg, severe coughing paroxysms, pain) insofar as these drugs may suppress a productive cough, impair mental status, and cause constipation.

#### **End-of-life care**

With very severe disease, particularly when death is imminent, exercise is unwarranted and activities of daily living are arranged to minimize energy expenditure. For example, patients may arrange to live on one floor of the house, have several small meals rather than fewer large meals, and avoid wearing shoes that must be tied. End-of-life care should be discussed, including whether to pursue mechanical ventilation, the use of palliative sedation, and appointment of a surrogate medical decision-maker in the event of the patient's incapacitation.

#### **Key Points**

- Cigarette smoking in genetically predisposed people is the major cause of COPD in the developed world.
- Diagnose COPD and differentiate it from disorders that have similar characteristics (eg, asthma, heart failure) primarily by routine clinical information, such as symptoms (particularly time course), age at onset, risk factors, and results of routine tests (eg, chest x-ray, pulmonary function tests).
- Reductions of FEV<sub>1</sub>, FVC, and the ratio of FEV<sub>1</sub>/FVC are characteristic findings.
- Categorize patients based on FEV<sub>1</sub> and symptoms into one of 4 groups and use that category to guide drug treatment.
- Relieve symptoms rapidly with primarily short-acting beta-adrenergic drugs and decrease exacerbations with inhaled corticosteroids, long-acting beta-adrenergic drugs, long-acting anticholinergic drugs, or a combination.
- Encourage smoking cessation using multiple interventions.(eg, behavior modification, support groups, [nicotine](#) replacement, drug therapy).
- Optimize use of supportive treatments (eg, nutrition, pulmonary rehabilitation, self-directed exercise).

- Use antibiotics if patients have acute exacerbations and purulent sputum.
- For patients with end stage COPD, address end-of-life care proactively, including preferences regarding mechanical ventilation and palliative sedation.

*Last full review/revision June 2014 by Robert A. Wise, MD*



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Asthma is a disease of diffuse airway inflammation caused by a variety of triggering stimuli resulting in partially or completely reversible bronchoconstriction. Symptoms and signs include dyspnea, chest tightness, cough, and wheezing. The diagnosis is based on history, physical examination, and pulmonary function tests. Treatment involves controlling triggering factors and drug therapy, most commonly with inhaled  $\beta_2$ -agonists and inhaled corticosteroids. Prognosis is good with treatment.

### ***Epidemiology***

The prevalence of asthma has increased continuously since the 1970s, and it now affects an estimated 235 million people worldwide. More than 25 million people in the US are affected. Asthma is one of the most common chronic diseases of childhood, affecting more than 6 million children in the US; it occurs more frequently in boys before puberty and in girls after puberty. It also occurs more frequently in non-Hispanic blacks and Puerto Ricans. Despite its increasing prevalence, however, there has been a recent decline in mortality. In the US, About 3400 deaths occur annually as a result of asthma. However, the death rate is 2 to 3 times higher for blacks than for whites. Asthma is the leading cause of hospitalization for children and is the number one chronic condition causing elementary school absenteeism. Asthma is estimated to cost the US \$56 billion/yr in medical care and lost productivity.

### ***Etiology***

Development of asthma is multifactorial and depends on the interactions among multiple susceptibility genes and environmental factors.

**Susceptibility genes** are thought to include those for T-helper cells types 1 and 2 ( $T_H 1$  and  $T_H 2$ ), IgE, interleukins (IL-3, -4, -5, -9, -13), granulocyte-monocyte colony-stimulating factor (GM-CSF), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and the *ADAM33* gene, which may stimulate airway smooth muscle and fibroblast proliferation or regulate cytokine production.

**Environmental factors** may include the following:

- Allergen exposure
- Diet
- Perinatal factors

Evidence clearly implicates household allergens (eg, dust mite, cockroach, pet) and other environmental allergens in disease development in older children and adults. Diets low in vitamins C and E and in  $\omega$ -3 fatty acids have been linked to asthma, as has obesity. Asthma has also been linked to perinatal factors, such as young maternal age, poor maternal nutrition, prematurity, low birthweight, and lack of breastfeeding.

On the other hand, endotoxin exposure early in life can induce tolerance and may be protective. Air pollution is not definitively linked to disease development, although it may trigger exacerbations. The role of childhood exposure to cigarette smoke is controversial, with some studies finding a contributory and some a protective effect.

Genetic and environmental components may interact by determining the balance between  $T_H 1$  and  $T_H 2$  cell lineages. Infants may be born with a predisposition toward proallergic and

proinflammatory T<sub>H</sub> 2 immune responses, characterized by growth and activation of eosinophils and IgE production. Early childhood exposure to bacterial and viral infections and endotoxins may shift the body to T<sub>H</sub> 1 responses, which suppresses T<sub>H</sub> 2 cells and induces tolerance. Trends in developed countries toward smaller families with fewer children, cleaner indoor environments, and early use of vaccinations and antibiotics may deprive children of these T<sub>H</sub> 2-suppressing, tolerance-inducing exposures and may partly explain the continuous increase in asthma prevalence in developed countries (the hygiene hypothesis).

### **Reactive airways dysfunction syndrome (RADS)**

Indoor exposures to nitrogen oxide and volatile organic compounds (eg, from paints, solvents, adhesives) are implicated in the development of RADS, a persistent asthma-like syndrome in people with no history of asthma. RADS appears to be distinct from asthma and may be, on occasion, a form of environmental lung disease. However, RADS and asthma have many clinical similarities (eg, wheezing, dyspnea, cough), and both may respond to corticosteroids.

### ***Pathophysiology***

Asthma involves

- Bronchoconstriction
- Airway edema and inflammation
- Airway hyperreactivity
- Airway remodeling

In patients with asthma, T<sub>H</sub> 2 cells and other cell types—notably, eosinophils and mast cells, but also other CD4+ subtypes and neutrophils—form an extensive inflammatory infiltrate in the airway epithelium and smooth muscle, leading to airway remodeling (ie, desquamation, subepithelial fibrosis, angiogenesis, smooth muscle hypertrophy). Hypertrophy of smooth muscle narrows the airways and increases reactivity to allergens, infections, irritants, parasympathetic stimulation (which causes release of pro-inflammatory neuropeptides, such as substance P, neurokinin A, and calcitonin gene-related peptide), and other triggers of bronchoconstriction. Additional contributors to airway hyperreactivity include loss of inhibitors of bronchoconstriction (epithelium-derived relaxing factor, prostaglandin E<sub>2</sub>) and loss of other substances called endopeptidases that metabolize endogenous bronchoconstrictors. Mucus plugging and peripheral blood eosinophilia are additional classic findings in asthma and may be epiphenomena of airway inflammation. However, not all patients with asthma have eosinophilia.

### **Triggers**

Common triggers of an asthma exacerbation include

- Environmental and occupational allergens (numerous)
- Infections
- Exercise
- Inhaled irritants
- Emotion
- Aspirin
- Gastroesophageal reflux disease (GERD)

Infectious triggers in young children include respiratory syncytial virus, rhinovirus, and parainfluenza virus infection. In older children and adults, URIs (particularly with rhinovirus) and pneumonia are common infectious triggers. Exercise can be a trigger, especially in cold or dry environments. Inhaled irritants, such as air pollution, cigarette smoke, perfumes, and cleaning products, are often involved. Emotions such as anxiety, anger, and excitement sometimes trigger exacerbations.

Aspirin is a trigger in up to 30% of patients with severe asthma and in < 10% of all patients with asthma. Aspirin-sensitive asthma is typically accompanied by nasal polyps with nasal and sinus congestion.

GERD is a common trigger among some patients with asthma, possibly via esophageal acid-induced reflex bronchoconstriction or by microaspiration of acid. However, treatment of asymptomatic GERD (eg, with proton pump inhibitors) does not seem to improve asthma control.

Allergic rhinitis often coexists with asthma; it is unclear whether the two are different manifestations of the same allergic process or whether rhinitis is a discrete asthma trigger.

### **Response**

In the presence of triggers, there is reversible airway narrowing and uneven lung ventilation. Relative perfusion exceeds relative ventilation in lung regions distal to narrowed airways; thus, alveolar O<sub>2</sub> tensions fall and alveolar CO<sub>2</sub> tensions rise. Most patients can compensate by hyperventilating, but in severe exacerbations, diffuse bronchoconstriction causes severe gas trapping, and the respiratory muscles are put at a marked mechanical disadvantage so that the work of breathing increases. Under these conditions, hypoxemia worsens and Pa CO<sub>2</sub> rises. Respiratory and metabolic acidosis may result and, if left untreated, cause respiratory and cardiac arrest.

### **Classification**

Unlike hypertension (eg, in which one parameter (BP) defines the severity of the disorder and the efficacy of treatment), asthma causes a number of clinical and testing abnormalities. Also, unlike most types of hypertension, asthma manifestations typically wax and wane. Thus, monitoring (and studying) asthma requires a consistent terminology and defined benchmarks.

**Severity** is the intrinsic intensity of the disease process (ie, how bad it is). Severity can usually be assessed directly only before treatment is started, because patients who have responded well to treatment by definition have few symptoms. Asthma severity is categorized as

- Intermittent
- Mild persistent
- Moderate persistent
- Severe persistent

The term status asthmaticus describes severe, intense, prolonged bronchospasm that is resistant to treatment.

**Control** is the degree to which symptoms, impairments, and risks are minimized by treatment. Control is the parameter assessed in patients receiving treatment. The goal is for all patients to have well controlled asthma regardless of disease severity. Control is classified as

- Well controlled
- Not well controlled
- Very poorly controlled

**Impairment** refers to the frequency and intensity of patients' symptoms and functional limitations. Impairment is assessed by spirometry, mainly forced expiratory volume in 1 sec (FEV<sub>1</sub>), and the ratio of FEV<sub>1</sub> to forced vital capacity (FVC), as well as clinical features such as

- How often symptoms are experienced
- How often the patient awakens at night
- How often the patient uses a short-acting  $\beta_2$ -agonist for symptom relief
- How often asthma interferes with normal activity

**Risk** refers to the likelihood of future exacerbations or decline in lung function and the risk of adverse drug effects. Risk is assessed by long-term trends in spirometry and clinical features such as

- Frequency of need for oral corticosteroids
- Need for hospitalization
- Need for ICU admission
- Need for intubation

It is important to remember that the severity category does not predict how serious an exacerbation a patient may have. For example, a patient who has mild asthma with long periods of no or mild symptoms and normal pulmonary function may have a severe, life-threatening exacerbation.

### *Symptoms and Signs*

Patients with mild asthma are typically asymptomatic between exacerbations. Patients with more severe disease and those with exacerbations experience dyspnea, chest tightness, audible wheezing, and coughing. Coughing may be the only symptom in some patients (cough-variant asthma). Symptoms can follow a circadian rhythm and worsen during sleep, often around 4 AM. Many patients with more severe disease waken during the night (nocturnal asthma).

Signs include wheezing, pulsus paradoxus (ie, a fall of systolic BP > 10 mm Hg during inspiration, tachypnea, tachycardia, and visible efforts to breathe (use of neck and suprasternal [accessory] muscles, upright posture, pursed lips, inability to speak). The expiratory phase of respiration is prolonged, with an inspiratory:expiratory ratio of at least 1:3. Wheezes can be present through both phases or just on expiration, but patients with severe bronchoconstriction may have no audible wheezing because of markedly limited airflow.

Patients with a severe exacerbation and impending respiratory failure typically have some combination of altered consciousness, cyanosis, pulsus paradoxus > 15 mm Hg, SaO<sub>2</sub> < 90%, PaCO<sub>2</sub> > 45 mm Hg, or hyperinflation. Rarely, pneumothorax or pneumomediastinum is seen on chest x-ray.

Symptoms and signs disappear between exacerbations, although soft wheezes may be audible during forced expiration at rest, or after exercise in some asymptomatic patients. Hyperinflation of the lungs may alter the chest wall in patients with long-standing uncontrolled asthma, causing a barrel-shaped thorax.

All symptoms and signs are nonspecific, are reversible with timely treatment, and typically are brought on by exposure to one or more triggers.

### **Diagnosis**

- Clinical evaluation
- Pulmonary function testing

Diagnosis is based on history and physical examination and is confirmed with pulmonary function tests. Diagnosis of causes and the exclusion of other disorders that cause wheezing are also important. Asthma and COPD are sometimes easily confused; they cause similar symptoms and produce similar results on pulmonary function tests but differ in important biologic ways that are not always clinically apparent.

### **Pulmonary function tests**

Patients suspected of having asthma should undergo pulmonary function testing to confirm and quantify the severity and reversibility of airway obstruction. Pulmonary function data quality is effort-dependent and requires patient education before the test. If it is safe to do so, bronchodilators should be stopped before the test: 6 h for short-acting  $\beta_2$ -agonists, such as [albuterol](#); 8 h for [ipratropium](#); 12 to 36 h for [theophylline](#); 24 h for long-acting  $\beta_2$ -agonists, such as [salmeterol](#) and [formoterol](#); and 48 h for [tiotropium](#).

Spirometry should be done before and after inhalation of a short-acting bronchodilator. Signs of airflow limitation before bronchodilator inhalation include reduced FEV<sub>1</sub> and a reduced FEV<sub>1</sub>/FVC ratio. The FVC may also be decreased because of gas trapping, such that lung volume measurements may show an increase in the residual volume, the functional residual capacity, or both. An improvement in FEV<sub>1</sub> of > 12% or an increase  $\geq$  10% of predicted FEV<sub>1</sub> in response to bronchodilator treatment confirms reversible airway obstruction, although absence of this finding should not preclude a therapeutic trial of bronchodilators. Spirometry should be repeated at least every 1 to 2 yr in patients with asthma to monitor disease progression. Flow-volume loops should also be reviewed to diagnose vocal cord dysfunction, a common cause of upper airway obstruction that mimics asthma.

Provocative testing, in which inhaled methacholine (or alternatives, such as inhaled histamine, [adenosine](#), or bradykinin, or exercise testing) is used to provoke bronchoconstriction, is indicated for patients suspected of having asthma who have normal findings on spirometry and flow-volume testing and for patients suspected of having cough-variant asthma, provided there are no contraindications. Contraindications include FEV<sub>1</sub> < 1 L or < 50% predicted, recent MI or stroke, and severe hypertension (systolic BP > 200 mm Hg; diastolic BP > 100 mm Hg). A decline in FEV<sub>1</sub> of > 20% on a provocative testing protocol is relatively specific for the diagnosis of asthma. However, FEV<sub>1</sub> may decline in response to these drugs in other disorders,

such as COPD. If FEV<sub>1</sub> decreases by < 20% by the end of the testing protocol, asthma is less likely to be present.

### **Other tests**

Other tests may be helpful in some circumstances:

- Diffusing capacity for carbon monoxide (DL CO )
- Chest x-ray
- Allergy testing

DL CO testing can help distinguish asthma from COPD. Values are normal or elevated in asthma and usually reduced in COPD, particularly in patients with emphysema.

A chest x-ray may help exclude some causes of asthma or alternative diagnoses, such as heart failure or pneumonia. The chest x-ray in asthma is usually normal but may show hyperinflation or segmental atelectasis, a sign of mucous plugging. Infiltrates, especially those that come and go and that are associated with findings of central bronchiectasis, suggest allergic bronchopulmonary aspergillosis.

Allergy testing may be indicated for children whose history suggests allergic triggers (particularly for allergic rhinitis) because these children may benefit from immunotherapy. It should be considered for adults whose history indicates relief of symptoms with allergen avoidance and for those in whom a trial of therapeutic anti-IgE antibody therapy (see [Asthma and Related Disorders:Drug therapy](#)) is being considered. Skin testing and measurement of allergen-specific IgE via radioallergosorbent testing (RAST) can identify specific allergic triggers (see [Specific tests](#)).

Elevated blood eosinophils (> 400 cells/ $\mu$ L) and nonspecific IgE (>150 IU) are suggestive but not diagnostic of allergic asthma because they can be elevated in other conditions. However, eosinophilia is not sensitive.

Sputum evaluation for eosinophils is not commonly done; finding large numbers of eosinophils is suggestive of asthma but is neither sensitive nor specific.

Peak expiratory flow (PEF) measurements with inexpensive handheld flow meters are recommended for home monitoring of disease severity and for guiding therapy.

### **Evaluation of exacerbations**

Patients with asthma with an acute exacerbation should have certain tests:

- Pulse oximetry
- PEF or FEV<sub>1</sub> measurement

All 3 measures help establish the severity of an exacerbation and document treatment response. PEF values are interpreted in light of the patient's personal best, which may vary widely among patients who are equally well controlled. A 15 to 20% reduction from this baseline indicates a significant exacerbation. When baseline values are not known, the percent predicted FEV<sub>1</sub> value gives a general idea of airflow limitation but not the individual patient's degree of worsening. When measuring FEV<sub>1</sub> is impractical (eg, in an emergency department) and baseline PEF is unknown, percent of predicted PEF based on age, height and sex may be used. Although percent

predicted PEF is less accurate than comparison to a personal best, it may be helpful as a baseline to evaluate treatment response.

Chest x-ray is not necessary for most exacerbations but should be done in patients with symptoms or signs suggestive of pneumonia, pneumothorax, or pneumomediastinum.

ABG measurements should be done in patients with marked respiratory distress or symptoms and signs of impending respiratory failure.

### ***Prognosis***

Asthma resolves in many children, but for as many as 1 in 4, wheezing persists into adulthood or relapse occurs in later years. Female sex, smoking, earlier age of onset, sensitization to household dust mites, and airway hyperresponsiveness are risk factors for persistence and relapse.

Although a significant number of deaths each year are attributable to asthma, most of these are preventable with treatment. Thus, the prognosis is good with adequate access and adherence to treatment. Risk factors for death include increasing requirements for oral corticosteroids before hospitalization, previous hospitalization for acute exacerbations, and lower PEF values at presentation. Several studies show that use of inhaled corticosteroids decreases hospital admission and mortality rates.

Over time, the airways in some patients with asthma undergo permanent structural changes (remodeling) that prevent return to normal lung functioning. Early aggressive use of anti-inflammatory drugs may help prevent this remodeling.

### ***Treatment***

- Control of triggers
- Drug therapy
- Monitoring
- Patient education
- Treatment of acute exacerbations

Treatment objectives are to minimize impairment and risk, including preventing exacerbations and minimizing chronic symptoms, including nocturnal awakenings; to minimize the need for emergency department visits or hospitalizations; to maintain baseline (normal) pulmonary function and activity levels; and to avoid adverse treatment effects.

### **Control of triggering factors**

Triggering factors in some patients may be controlled with use of synthetic fiber pillows and impermeable mattress covers and frequent washing of bed sheets, pillowcases, and blankets in hot water. Upholstered furniture, soft toys, carpets, and pets should be removed to reduce dust mites and animal dander. Dehumidifiers should be used in basements and in other poorly aerated, damp rooms to reduce mold. Steam treatment of homes diminishes dust mite allergens. House cleaning and extermination to eliminate cockroach exposure is especially important. Although control of triggering factors is more difficult in urban environments, the importance of these measures is not diminished. High-efficiency particulate air (HEPA) vacuums and filters may relieve symptoms, but no beneficial effects on pulmonary function and on the need for drugs have been observed. Sulfite-sensitive patients should avoid red wine. Nonallergenic



triggers, such as cigarette smoke, strong odors, irritant fumes, cold temperatures, high humidity, and exercise, should also be avoided or controlled when possible. Limiting exposure to people with viral URIs is also important.

Patients with aspirin -sensitive asthma can use [acetaminophen](#), choline magnesium salicylate, or [celecoxib](#) in place of NSAIDs.

Asthma is a relative contraindication to the use of nonselective  $\beta$ -blockers, including topical formulations, but cardioselective drugs (eg, [metoprolol](#), [atenolol](#)) probably have no adverse effects.

### **Drug therapy**

Major drug classes commonly used in the treatment of chronic asthma and asthma exacerbations include

- Bronchodilators ( $\beta_2$ -agonists, anticholinergics)
- Corticosteroids
- Leukotriene modifiers
- Mast cell stabilizers
- Methylxanthines

Drugs in these classes are inhaled or taken orally; inhaled drugs come in aerosolized and powdered forms. Use of aerosolized forms with a spacer or holding chamber facilitates deposition of the drug in the airways rather than the pharynx; patients are advised to wash and dry their spacers after each use to prevent bacterial contamination. In addition, use of aerosolized forms requires coordination between actuation of the inhaler (drug delivery) and inhalation; powdered forms reduce the need for coordination, because drug is delivered only when the patient inhales.

**$\beta_2$ -Agonists** relax bronchial smooth muscle, decrease mast cell degranulation and histamine release, inhibit microvascular leakage into the airways, and increase mucociliary clearance.  $\beta_2$ -Agonists come in short- and long-acting preparations. Short-acting  $\beta_2$ -agonists (eg, [albuterol](#)) 2 puffs q 4 h inhaled prn are the drug of choice for relieving acute bronchoconstriction and preventing exercise-induced asthma. They should not be used alone for long-term maintenance of persistent asthma. They take effect within minutes and are active for up to 6 to 8 h, depending on the drug. Tachycardia and tremor are the most common acute adverse effects of inhaled  $\beta_2$ -agonists and are dose-related. Mild hypokalemia occurs uncommonly. Use of [levalbuterol](#) (a solution containing the *R*-isomer of [albuterol](#)) theoretically minimizes adverse effects, but its long-term efficacy and safety are unproved. Oral  $\beta_2$ -agonists have more systemic effects and generally should be avoided.

Long-acting  $\beta_2$ -agonists (eg, [salmeterol](#)) are active for up to 12 h and are used for moderate and severe asthma but should never be used as monotherapy. They interact synergistically with inhaled corticosteroids and permit lower dosing of corticosteroids. The safety of regular long-term use of  $\beta_2$ -agonists is controversial. Long-acting  $\beta_2$ -agonists may increase the risk of asthma-related death when used as monotherapy. Therefore, when treating patients with asthma, these drugs ([salmeterol](#) and [formoterol](#)) should be used only in combination with an inhaled

corticosteroid for patients whose condition is not adequately controlled with other asthma controllers (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants additional maintenance therapies. Daily use or diminishing effects of short-acting  $\beta_2$ -agonists or use of  $\geq 1$  canister per month suggests inadequate control and the need to begin or intensify other therapies.

**Anticholinergics** relax bronchial smooth muscle through competitive inhibition of muscarinic ( $M_3$ ) cholinergic receptors. **Ipratropium** may have an additive effect when combined with short-acting  $\beta_2$ -agonists. Adverse effects include pupillary dilation, blurred vision, and dry mouth. **Tiotropium** is a 24-h inhaled anticholinergic that can be used for patients with COPD. In patients with asthma, recent clinical trials of **tiotropium** added to either inhaled corticosteroids or to a combination of an inhaled long-acting  $\beta_2$ -agonist plus a corticosteroid have shown improved pulmonary function and decreased asthma exacerbations. Data concerning the long-term safety of **tiotropium** in patients with asthma are incomplete.

**Corticosteroids** inhibit airway inflammation, reverse  $\beta$ -receptor down-regulation, and inhibit cytokine production and adhesion protein activation. They block the late response (but not the early response) to inhaled allergens. Routes of administration include oral, IV, and inhaled. In acute asthma exacerbations, early use of systemic corticosteroids often aborts the exacerbation, decreases the need for hospitalization, prevents relapse, and speeds recovery. Oral and IV routes are equally effective. Inhaled corticosteroids have no role in acute exacerbations but are indicated for long-term suppression, control, and reversal of inflammation and symptoms. They substantially reduce the need for maintenance oral corticosteroid therapy. Adverse local effects of inhaled corticosteroids include dysphonia and oral candidiasis, which can be prevented or minimized by having the patient use a spacer, gargle with water after corticosteroid inhalation, or both. Systemic effects are all dose related, can occur with oral or inhaled forms, and occur mainly with inhaled doses  $> 800$  mcg/day. They include suppression of the adrenal-pituitary axis, osteoporosis, cataracts, skin atrophy, hyperphagia, and easy bruisability. Whether inhaled corticosteroids suppress growth in children is controversial. Most children treated with inhaled corticosteroids eventually reach their predicted adult height. Latent TB may be reactivated by systemic corticosteroid use.

**Mast cell stabilizers** inhibit histamine release from mast cells, reduce airway hyperresponsiveness, and block the early and late responses to allergens. They are given by inhalation prophylactically to patients with exercise-induced or allergen-induced asthma. They are ineffective once symptoms have occurred. They are the safest of all antiasthmatic drugs but the least effective.

**Leukotriene modifiers** are taken orally and can be used for long-term control and prevention of symptoms in patients with mild persistent to severe persistent asthma. The main adverse effect is liver enzyme elevation (which occurs with **zileuton**). Although rare, patients have developed a clinical syndrome resembling eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

**Methylxanthines** relax bronchial smooth muscle (probably by inhibiting phosphodiesterase) and may improve myocardial and diaphragmatic contractility through unknown mechanisms.

Methylxanthines appear to inhibit intracellular release of Ca, decrease microvascular leakage into the airway mucosa, and inhibit the late response to allergens. They decrease the infiltration of eosinophils into bronchial mucosa and of T cells into epithelium. The

methylxanthine **theophylline** is used for long-term control as an adjunct to  $\beta_2$ -agonists.

Extended-release **theophylline** helps manage nocturnal asthma. **Theophylline** has fallen into disuse because of its many adverse effects and interactions compared with other drugs. Adverse effects include headache, vomiting, cardiac arrhythmias, and seizures. Methylxanthines have a narrow therapeutic index; multiple drugs (any metabolized by the cytochrome P-450 pathway, eg, macrolide antibiotics) and conditions (eg, fever, liver disease, heart failure) alter methylxanthine metabolism and elimination. Serum **theophylline** levels should be monitored periodically and maintained between 5 and 15  $\mu\text{g/mL}$  (28 and 83  $\mu\text{mol/L}$ ).

**Immunomodulators** include **omalizumab**, an anti-IgE antibody developed for use in severely allergic patients with asthma who have elevated IgE levels. **Omalizumab** may decrease asthma exacerbations, decreases corticosteroid requirements, and relieves symptoms. Dosing is determined by a dosing chart based on the patient's weight and IgE levels. The drug is administered sc q 2 to 4 wk. Clinicians who administer **omalizumab** should be prepared to identify and treat anaphylaxis, which may occur after any dose of **omalizumab**, even if previous doses have been well tolerated.

**Other drugs** are used uncommonly in specific circumstances. Magnesium is often used in the emergency department, but it is not recommended in the management of chronic asthma.

Immunotherapy may be indicated when symptoms are triggered by allergy, as suggested by history and confirmed by allergy testing. Immunotherapy is generally more effective in children than adults. If symptoms are not significantly relieved after 24 mo, then therapy is stopped. If symptoms are relieved, therapy should continue for  $\geq 3$  yr, although the optimum duration is unknown. Other drugs that suppress the immune system are occasionally given to reduce dependence on high-dose oral corticosteroids, but these drugs have a significant risk of toxicity.

Low-dose **methotrexate** (5 to 15 mg po or IM once/wk) can lead to modest improvements in  $\text{FEV}_1$  and modest decreases in daily oral corticosteroid use. Gold and **cyclosporine** are also modestly effective, but toxicity and need for monitoring limit their use. Other therapies for management of chronic asthma include nebulized **lidocaine**, nebulized **heparin**, **colchicine**, and high-dose IV immune globulin. Limited evidence supports the use of any of these therapies, and their benefits are unproved, so none are currently recommended for routine clinical use.

#### **Monitoring response to treatment**

Guidelines recommend office use of spirometry ( $\text{FEV}_1$ ,  $\text{FEV}_1/\text{FVC}$ , FVC) to measure airflow limitation and assess impairment and risk. Outside the office, home PEF monitoring, in conjunction with patient symptom diaries and the use of an asthma action plan, is especially useful for charting disease progression and response to treatment in patients with moderate to severe persistent asthma. When asthma is quiescent, one PEF measurement in the morning

suffices. Should PEF measurements fall to <80% of the patient's personal best, then twice/day monitoring to assess circadian variation is useful. Circadian variation of > 20% indicates airway instability and the need to re-evaluate the therapeutic regimen.

### **Patient education**

The importance of patient education cannot be overemphasized. Patients do better when they know more about asthma—what triggers an exacerbation, what drug to use when, proper inhaler technique, how to use a spacer with a metered-dose inhaler (MDI), and the importance of early use of corticosteroids in exacerbations. Every patient should have a written action plan for day-to-day management, especially for management of acute exacerbations, that is based on the patient's best personal peak flow rather than on a predicted normal value. Such a plan leads to much better asthma control, largely attributable to improved adherence to therapies.

### **Treatment of acute exacerbation**

The goal of asthma exacerbation treatment is to relieve symptoms and return patients to their best lung function. Treatment includes

- Inhaled bronchodilators ( $\beta_2$ -agonists and anticholinergics)
- Usually systemic corticosteroids

Patients having an exacerbation are instructed to self-administer 2 to 4 puffs of inhaled [albuterol](#) or a similar short-acting  $\beta_2$ -agonist up to 3 times spaced 20 min apart for an acute exacerbation and to measure PEF if possible. When these short-acting rescue drugs are effective (symptoms are relieved and PEF returns to > 80% of baseline), the acute exacerbation may be managed in the outpatient setting. Patients who do not respond, have severe symptoms, or have a PEF persistently <80% should follow a treatment management program outlined by the physician or should go to the emergency department.

Inhaled bronchodilators ( $\beta_2$ -agonists and anticholinergics) are the mainstay of asthma treatment in the emergency department. In adults and older children, [albuterol](#) given by an MDI and spacer is as effective as that given by nebulizer. Nebulized treatment is preferred for younger children because of difficulties coordinating MDIs and spacers; evidence suggests that bronchodilator response improves when the nebulizer is powered with helium-O<sub>2</sub> (heliox) rather than with O<sub>2</sub>. Subcutaneous [epinephrine](#) 1:1000 solution or [terbutaline](#) is an alternative for children. [Terbutaline](#) may be preferable to [epinephrine](#) because of its lesser cardiovascular effects and longer duration of action, but it is no longer produced in large quantities and is expensive. Subcutaneous administration of  $\beta_2$ -agonists in adults raises concerns of adverse cardiostimulatory effects. However, clinically important adverse effects are few, and subcutaneous administration may benefit patients unresponsive to maximal inhaled therapy or patients unable to receive effective nebulized treatment (eg, those who cough excessively, have poor ventilation, or are uncooperative). Nebulized [ipratropium](#) can be co-administered with nebulized [albuterol](#) for patients who do not respond optimally to [albuterol](#) alone; some evidence favors simultaneous high-dose  $\beta_2$ -agonist and [ipratropium](#) as first-line treatment, but no data favor continuous  $\beta_2$ -agonist nebulization over intermittent administration. [Theophylline](#) has very little role in treatment.

Systemic corticosteroids ([prednisone](#), [prednisolone](#), [methylprednisolone](#)) should be given for all but the mildest acute exacerbation; they are unnecessary for patients whose PEF normalizes after 1 or 2 bronchodilator doses. IV and oral routes of administration are probably equally effective. IV [methylprednisolone](#) can be given if an IV line is already in place and can be switched to oral dosing whenever necessary or convenient. Tapering usually starts after 7 to 10 days and should last 2 to 3 wk.

Antibiotics are indicated only when history, examination, or chest x-ray suggests underlying bacterial infection; most infections underlying asthma exacerbations are probably viral in origin. Supplemental O<sub>2</sub> is indicated for hypoxemia and should be given by nasal cannula or face mask at a flow rate or concentration sufficient to maintain SaO<sub>2</sub> > 90%.

Reassurance is the best approach when anxiety is the cause of asthma exacerbation. Anxiolytics and [morphine](#) are relatively contraindicated because they are associated with increased mortality and the need for mechanical ventilation.

Hospitalization generally is required if patients have not returned to their baseline within 4 h of aggressive emergency department treatment. Criteria for hospitalization vary, but definite indications are failure to improve, worsening fatigue, relapse after repeated β<sub>2</sub>-agonist therapy, and significant decrease in Pa O<sub>2</sub> (< 50 mm Hg) or increase in Pa CO<sub>2</sub> (> 40 mm Hg), indicating progression to respiratory failure.

Patients who continue to deteriorate despite aggressive treatment are candidates for noninvasive positive pressure ventilation or endotracheal intubation and invasive mechanical ventilation (see [Respiratory Failure and Mechanical Ventilation](#)). Patients requiring intubation may benefit from sedation, but routine use of neuromuscular blocking agents should be avoided because of possible interactions with corticosteroids that can cause prolonged neuromuscular weakness. Generally, volume-cycled ventilation in assist-control mode is used because it provides constant alveolar ventilation when airway resistance is high and changing. The ventilator should be set to a relatively low frequency with a relatively high inspiratory flow rate (>80 L/min) to prolong exhalation time, minimizing auto positive end-expiratory pressure (PEEP). Initial tidal volumes can be set to 6 to 8 mL/kg of ideal body weight. High peak airway pressures will generally be present because they result from high airway resistance and inspiratory flow rates. In these patients, peak airway pressure does not reflect the degree of lung distention caused by alveolar pressure. However, if plateau pressures exceed 30 to 35 cm H<sub>2</sub>O, then tidal volume should be reduced to limit the risk of pneumothorax. When reduced tidal volumes are necessary, a moderate degree of hypercapnia is acceptable, but if arterial pH falls below 7.10, a slow NaHCO<sub>3</sub> infusion is indicated to maintain pH between 7.20 and 7.25. Once airflow obstruction is relieved and Pa CO<sub>2</sub> and arterial pH normalize, patients can usually be quickly weaned from the ventilator.

Other therapies are reportedly effective for asthma exacerbation, but none have been thoroughly studied. Heliox is used to decrease the work of breathing and improve ventilation through a decrease in turbulent flow attributable to helium, a gas less dense than O<sub>2</sub>. Despite the theoretical benefits of heliox, studies have reported conflicting results concerning its efficacy;

lack of ready availability and inability to concurrently provide high concentrations of O<sub>2</sub> (due to the fact that 70 to 80% of the inhaled gas is helium) may also limit its use. Magnesium sulfate relaxes smooth muscle, but efficacy in management of asthma exacerbation in the emergency department is debated. General anesthesia in patients with status asthmaticus causes bronchodilation by an unclear mechanism, perhaps by a direct relaxant effect on airway smooth muscle or attenuation of cholinergic tone.

### **Treatment of chronic asthma**

Current asthma guidelines initiate treatment based on the severity classification. Continuing therapy is based on assessment of control. Therapy is increased in a stepwise fashion until the best control of impairment and risk is achieved (step-up). Before therapy is stepped up, adherence, exposure to environmental factors (eg, trigger exposure), and presence of comorbid conditions (eg, obesity, allergic rhinitis, GERD, COPD, obstructive sleep apnea, vocal cord dysfunction) are reviewed. These factors should be addressed before increasing drug therapy. Once asthma has been well controlled for at least 3 mo, drug therapy is reduced if possible to the minimum that maintains good control (step-down). For specific drugs and doses

### **Exercise-induced asthma**

Exercise-induced asthma can generally be prevented by inhalation of a short-acting  $\beta_2$ -agonist or mast cell stabilizer before starting the exercise. If  $\beta_2$ -agonists are not effective or if exercise-induced asthma is associated with severe symptoms, the patient likely has more severe asthma than was initially recognized and requires controller therapy.

### **Aspirin-sensitive asthma**

The primary treatment for aspirin -sensitive asthma is avoidance of NSAIDs. [Celecoxib](#) does not appear to be a trigger. Leukotriene modifiers can blunt the response to NSAIDs. Alternatively, inpatient desensitization has been successful in a few patients.

### **Future therapies**

Multiple therapies are being developed to target specific components of the inflammatory cascade. Therapies directed at IL-4, IL-13, tumor necrosis factor- $\alpha$ , other chemokines, and cytokines or their receptors are all under investigation or consideration as therapeutic targets.

### ***Special Populations***

#### **Infants, children, and adolescents**

Asthma is difficult to diagnose in infants; thus, under-recognition and undertreatment are common. Empiric trials of inhaled bronchodilators and anti-inflammatory drugs may be helpful for both. Drugs may be given by nebulizer or MDI with a holding chamber with or without a face mask. Infants and children <5 yr requiring treatment > 2 times/wk should be given daily anti-inflammatory therapy with inhaled corticosteroids (preferred), leukotriene receptor antagonists, or [cromolyn](#).

Children > 5 yr and adolescents with asthma can be treated similarly to adults. They should be encouraged to maintain physical activities, exercise, and sports participation. Predicted norms for pulmonary function tests in adolescents are closer to childhood (not adult) standards.

Adolescents and mature younger children should participate in developing their own asthma management plans and establishing their own goals for therapy to improve adherence. The action



plan should be understood by teachers and school nurses to ensure reliable and prompt access to rescue drugs. [Cromolyn](#) and [nedocromil](#) are often tried in this group but are not as beneficial as inhaled corticosteroids. Long-acting drugs prevent the problems (eg, inconvenience, embarrassment) of having to take drugs at school.

### **Pregnant women**

About one third of women with asthma who become pregnant notice relief of symptoms, one third notice worsening (at times to a severe degree), and one third notice no change. GERD may be an important contributor to symptomatic disease in pregnancy. Asthma control during pregnancy is crucial, because poorly controlled maternal disease can result in increased prenatal mortality, premature delivery, and low birth weight. Asthma drugs have not been shown to have adverse fetal effects, but safety data are lacking. (See also guidelines from the National Asthma In general, uncontrolled asthma is more of a risk to mother and fetus than adverse effects due to asthma drugs. During pregnancy, normal blood  $P\text{ CO}_2$  level is about 32 mm Hg. Therefore,  $\text{CO}_2$  retention is probably occurring if  $\text{PCO}_2$  approaches 40 mm Hg.

### **Elderly patients**

The elderly have a high prevalence of other obstructive lung disease (eg, COPD, so it is important to determine the magnitude of the reversible component of airflow obstruction (eg, by a 2- to 3-wk trial of inhaled corticosteroids or pulmonary function testing with bronchodilator challenge). The elderly may be more sensitive to adverse effects of  $\beta_2$ -agonists and inhaled corticosteroids. Patients requiring inhaled corticosteroids, particularly those with risk factors for osteoporosis, may benefit from measures to preserve bone density (eg, Ca and vitamin D supplements, bisphosphonates).

### **Key Points**

- Asthma triggers range from environmental allergens and respiratory irritants to infections, [aspirin](#), exercise, emotion, and GERD.
- Consider asthma in patients who have unexplained persistent coughing, particularly at night.
- If asthma is suspected, arrange pulmonary function testing, with methacholine provocation if necessary.
- Educate patients on how to avoid triggers.
- Control chronic asthma with drugs that modulate the allergic and immune response—usually inhaled steroids—with other drugs (eg, long-acting bronchodilators, mast cell stabilizers, leukotriene inhibitors) added based on asthma severity.
- Treat acute exacerbations with inhaled  $\beta_2$ -agonists and anticholinergic drugs, systemic corticosteroids, and sometimes injected [epinephrine](#).
- If mechanical ventilation is necessary, consider using high inspiratory flow rates (to prolong expiration) with low tidal volumes, even at the cost of a slight increase in  $P\text{ CO}_2$  (permissive hypercapnia).
- Treat asthma aggressively during pregnancy.



## **More Information**

*Last full review/revision July 2014 by Matthew C. Miles, MD; Stephen P. Peters, MD, PhD*

### **Self preparation at class:**

Listen information;

Work with patients (with cardiac pathology);

Ask about the problems that have not been found in information given.

### **Self preparation at home:**

Compose the plan of your answer;

Answer the questions to the topic;

Do the test given above.

**1.** A 50-year-old patient with long-standing chronic obstructive lung disease develops the insidious onset of aching in the distal extremities, particularly the wrists bilaterally. There is a 10-lb weight loss. The skin over the wrists is warm and erythematous. There is bilateral clubbing. Plain film is read as periosteal thickening, possible osteomyelitis. Which of the following is the most appropriate management of this patient?

- a. Start ciprofloxacin
- b. Obtain chest x-ray
- c. Aspirate both wrists
- d. Begin gold therapy
- e. Obtain erythrocyte sedimentation rate

**2** A 70-year-old patient with chronic obstructive lung disease requires 2 L of nasal O<sub>2</sub> to treat his hypoxia, which is sometimes associated with angina. While receiving nasal O<sub>2</sub>, the patient develops pleuritic chest pain, fever, and purulent sputum. He becomes stuporous and develops a respiratory acidosis with CO<sub>2</sub> retention and worsening hypoxia. Which of the following is the treatment of choice?

- a. Stop oxygen
- b. Begin medroxyprogesterone
- c. Intubate and begin mechanical ventilation
- d. Observe patient 24 h before changing therapy
- e. Begin sodium bicarbonate

### **Recommended literature:**

#### **A. Main:**

- 1. "Harrison's principles of internal medicine", Editors: Anthony S. Fauci, Dennis L. Kasper, Stephen L Hauser, Dan L. Longo, Joseph Loscalzo, McGraw-Hill Education / Medical; 19 edition (April 8, 2015), 1-2 volumes, 3000 p.
- 2. CURRENT Medical Diagnosis and Treatment 2012, Fifty-First Edition (LANGE CURRENT Series) by Stephen McPhee, Maxine Papadakis and Michael W. Rabow (Paperback - Sep 12, 2011)
- 3. CURRENT Diagnosis and Treatment Emergency Medicine, Seventh Edition (LANGE CURRENT Series) by C. Keith Stone (May 23, 2011)
- 4. Goldman's Cecil medicine / [edited by] Lee Goldman, Andrew I. Schafer.—24th ed. Elsevier Sanders. Rev. ed. of: Cecil medicine. 23rd ed. — 2012. p.

**1** The answer is b. The clinical picture suggests hypertrophic osteoarthropathy. This process, the pathogenesis of which is unknown, is characterized by clubbing of digits, periosteal new bone formation, and arthritis. Hypertrophic osteoarthropathy is associated with intrathoracic

malignancy, suppurative lung disease, and congenital heart problems. Treatment is directed at the underlying disease process. While x-rays may suggest osteomyelitis, the process is usually bilateral and easily distinguishable from osteomyelitis. The first step in evaluation of this patient is to obtain a chest x-ray looking for lung infection and carcinoma.

**2** The answer is c. When stupor and coma supervene in CO<sub>2</sub> retention, fatal arrhythmias, seizures, and death are likely to follow. Stopping oxygen is the worst course of action, as it will exacerbate life-threatening hypoxia. Intubation is the treatment of choice. Bicarbonate plays no role in this acidosis, which is respiratory and caused by hypoventilation.

Methodical recommendations consisted by

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