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Managing Cough as a Defense Mechanism and as a Symptom*

A Consensus Panel Report of the American College of Chest Physicians

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SUMMARY AND RECOMMENDATIONS†

1. Cough can (a) be an important defense mechanism to help clear excessive secretions and foreign material from airways; (b) be an important factor in the spread of infection; (c) maintain consciousness during potentially lethal arrhythmias and/or convert arrhythmias to more normal cardiac rhythms; and (d) present as one of the most common symptoms for which patients seek medical attention and spend health-care dollars.

2. Cough involves a complex reflex arc that begins with the stimulation of an irritant receptor. Most receptors are probably located in the respiratory system; the existence of a discrete central cough center has not been demonstrated. Evidence to date suggests that the cough center is diffusely located in the medulla. An effective cough depends on the ability to achieve high gas flows and intrathoracic pressures, enhancing the removal of mucus adhering to the airway wall. Cough ineffectiveness may occur when respiratory muscles are weakened or when the surface adhesive properties of mucus are altered. While a variety of nonpharmacologic protussive treatment modalities may improve cough mechanics, clinical studies documenting improvement in patient morbidity and mortality are lacking.

3. It is the complications of cough that lead patients to seek medical attention. The most common complications are subjective perceptions of exhaustion and self-consciousness, and symptoms of insomnia, hoarseness, musculoskeletal pain, sweating, and urinary incontinence. The pressures produced during vigorous coughing can cause a variety of complications in nearly all organ systems.

4. The two categories of cough, are acute, lasting less than 3 weeks, and chronic, lasting 3 to 8 weeks or longer; they are not mutually exclusive (Grade II-2, III-3). Acute cough is most frequently due to the common cold (Grade III). Chronic cough is often simultaneously due to more than one condition (Grade II-2, II-3), but can be the sole clinical manifestation of asthma and gastroesophageal reflux disease (GERD) (Grade II-2). The most common causes of chronic cough in nonsmokers are postnasal drip syndrome (PNDS), asthma, and/or GERD (Grade II-2, II-3), whether or not the cough is described as dry or productive (Grade II-2). PNDS, asthma, and/or GERD are likely to be causes(s) of chronic cough approximately 100% of the time in nonsmokers who are not taking angiotensin-converting enzyme inhibitor (ACEI) drugs and who have normal or nearly normal chest radiographs showing no more than stable inconsequential scars (Grade II-2).

5. PNDS, either singly or in combination with other conditions, is the single most common cause of chronic cough for which patients seek medical attention (Grade II-2). The symptoms and signs of PNDS are nonspecific (Grade II-2), therefore, a definitive diagnosis of PNDS-induced cough cannot be made from history and physical examination alone. A favorable response to specific therapy for PNDS, with resolution of cough, is a crucial step in confirming that PNDS is present and is the etiology of cough. The combination of a first-generation antihistamine and a decongestant is considered to be the most consistently effective sole form of therapy in treating most patients with PNDS-in-
1. Cough is a principal feature of chronic bronchitis (CB). In most patients, some improvement in cough will be seen within 1 week of initiation of therapy. Newer-generation, relatively nonsedating antihistamines have been found ineffective in treating acute cough associated with the common cold (Grade I) and are not as effective as first-generation antihistamines in treating PNDS secondary to nonallergic conditions. The first-generation antihistamines should be used preferentially to treat PNDS-induced cough that is nonhistamine-mediated (Grade I, II-2).

2. Asthma is a common cause of chronic cough. A diagnosis of cough-variant asthma is suggested by the presence of airway hyperresponsiveness, and confirmed only when the cough resolves with asthma medications. The treatment of cough-variant asthma is the same as for asthma presenting with other symptoms. Inhaled medications prescribed for asthma may worsen the cough.

3. GERD can cause cough by aspiration, but it most likely causes chronic cough in patients with normal radiographs by a vagally mediated reflex mechanism (Grade II, II-2). When GERD is the cause of chronic cough, GI symptoms are often absent (Grade II-2). Twenty-four-hour esophageal pH monitoring is the most sensitive and specific test for GERD. In interpreting the test, it is important to assess the duration and frequency of reflux episodes, and the temporal relationship between reflux and cough episodes. Patients with normal standard reflux parameters may still have reflux as a cause of cough if a temporal relationship exists (Grade II-2). When 24-h esophageal pH monitoring cannot be done, an empiric trial of antireflux medication is appropriate when GERD is suspected as a cause of cough. However, if empiric treatment fails, GERD cannot be ruled out until objective studies are conducted (Grade III) because the empiric therapy may not have been intensive enough or medical therapy may have failed. Because minimum consistently effective therapy for GERD-induced chronic cough is not known, initial treatment should include diet and lifestyle changes in addition to drugs. Cough due to GERD has been reported to resolve with medical therapy in 70 to 100% of patients; mean time to recovery may take as long as 169 to 179 days (Grade II-2). Antireflux surgery may be considered after intensive medical therapy has been documented to have failed.

4. Cough is a principal feature of chronic bronchitis (CB) and its treatment should chiefly be directed to reduction of sputum production and airway inflammation (eg, by smoking cessation and removal of environmental irritants) (Grade II-2). While CB is among the most frequent causes of chronic cough in the community, it is the cause in only about 5% in series of patients who seek medical attention for cough. Ipratropium can decrease sputum production and cough (Grade I). Nonspecific cough suppressants should be avoided, and mucolytics are of uncertain benefit. Although the effectiveness of systemic corticosteroids and antibiotics on cough have not been specifically studied, they are likely to be helpful in decreasing cough during exacerbations of COPD (Grade III).

5. Bronchiectasis is a cause of chronic cough in a relatively small number of patients; the diagnosis is established by clinical history, chest radiograph, high-resolution CT scan of the thorax, and cough disappearance with specific therapy. Cough associated with flares of the disease can be treated with a combination of chest physiotherapy, drugs to stimulate mucociliary clearance, and systemic antibiotics (Grade II-2). Inhaled antibiotics are recommended only in cystic fibrosis (CF) patients with bronchiectasis (Grade I).

6. Postinfectious cough is a diagnosis of exclusion; it should be considered when a patient complains only of cough after a respiratory tract infection and has a normal chest radiograph. Postinfectious cough ultimately resolves over time; oral corticosteroids (Grade II-3), inhaled corticosteroids (Grade III), or ipratropium bromide (Grade I) may attenuate the cough.

7. Coughs that develop for the first time and last for months in susceptible groups are suggestive of bronchogenic carcinoma. Bronchogenic carcinoma is not a common cause of chronic cough (Grade II-2), and is very unlikely in never-smokers (Grade II-2). Present or prior cigarette smoking or occupational exposures increase the risk. Chest radiographs, sputum cytology, and flexible bronchoscopy are the most important initial tests for evaluating bronchogenic carcinoma as a cause of chronic cough.

8. Cough due to ACEIs is a class effect of these drugs and is not dose-related. The cough is typically nonproductive and is associated with an irritating, tickling, or scratchy sensation in the throat. ACEI-induced cough may appear hours to weeks or months after ACEI is started (Grade II). Because no laboratory test predicts who will have ACEI-induced cough, the diagnosis should be considered in any patient who has a cough while taking an ACEI (Grade III). Cough due to ACEIs will disappear or substantially improve within 4 weeks of discontinuing the drug (Grade I); definitive treatment of ACEI-induced cough is discontinuation of the drug.

9. Habit cough and psychogenic cough are diagnoses of exclusion (Grade III). The character of the cough (eg, honking or barking) is not diagnostically helpful in adults (Grade II-2). However, the pediatric literature suggests that honking and barking coughs are consistent with psychogenic cough (Grade III). After exclusion of other causes, psychological counseling and short-term antitussive therapy may be appropriate for psychogenic cough (Grade III).

10. Chronic interstitial pulmonary disease is an uncommon cause of cough; treatment of such cough is based on treatment of the underlying condition. If this treatment fails to resolve the cough, the cough...
may still be treatable with specific therapy for other comorbid conditions. The most common causes of chronic cough should be investigated before antitussives are prescribed (Grade III).

15. In children, asthma, upper and lower respiratory tract infections, and GERD are the most common causes of acute and chronic cough. Less common causes of cough in children are congenital anomalies, aspiration and environmental exposures. The approach to managing chronic cough in children is similar to the approach in adults (Grade III). Diagnostic testing may be limited because many children are unable to cooperate in testing, and positive tests do not necessarily establish diagnosis or predict a favorable response to specific therapy (Grade III). A chest radiograph should be obtained in nearly all children with chronic cough to rule out lower respiratory tract and cardiac pathology (Grade III). A sweat test for CF may be considered when no clear etiology for cough is established. The recommended diagnostic approach to cough in children is history, physical examination, and determination of a most likely etiology (Grade III).

16. The cause of chronic cough can be determined in most patients; specific therapy will be successful in the majority of patients when chronic cough is evaluated in a systematic manner. Guidelines and algorithms for evaluating acute and chronic cough in immunocompetent and immunocompromised adults, and children, with diagnostic caveats, are presented in the body of this report.

17. Pharmacologic treatment of cough is either (a) antitussive, to prevent, control, or eliminate cough, or (b) protussive, to make cough more effective. Antitussive therapy is indicated when cough serves no useful function such as clearing the airways. Specific antitussive therapy is directed at the etiology or mechanism causing cough (eg, cigarette smoking, postnasal drip). Nonspecific antitussive therapy is directed at the symptom rather than the etiology or mechanism. Because of the high probability of being able to determine the causes of cough and prescribe specific treatment that can be successful, there is a limited role for nonspecific antitussive treatment (Grade II-2, II-3). It is indicated (Grade III) when specific therapy has not had a chance to work or will not work (eg, inoperable lung cancer). Protussive therapy is indicated when cough performs a useful function and needs to be encouraged (eg, in bronchiectasis, CF). Although hypertonic saline, amiloride, and terbutaline by aerosol following chest physiotherapy have been shown to increase cough clearance (Grade I), or cough clearability in the case of amiloride, their clinical utility remains to be determined in future studies that assess short-term and long-term effects of these agents on the patient's condition. Hypertonic saline in CF appears promising.
Managing Cough as a Defense Mechanism and Symptom

**Chapter 1. Introduction**

The impact of cough on health is substantial. It can (1) be an important defense mechanism that helps clear excessive secretions and foreign material from the airways; (2) be an important factor in the spread of infection; (3) maintain patient consciousness during potentially lethal arrhythmias and/or convert these arrhythmias to more viable and normal cardiac rhythms as a form of cardiopulmonary resuscitation; and, (4) present as one of the most common symptoms for which patients seek medical attention and spend health-care dollars.

In the United States, cough is the most common complaint for which patients seek medical attention and the second most common reason for a general medical examination. The common cold, the most common affliction of man and woman, is almost always accompanied by cough. Referrals of patients with persistently troublesome chronic cough of unknown etiology have been shown to account for 10 to 35% of a pulmonologist’s outpatient practice.

The annual aggregate cost of treating cough in the United States exceeds $1 billion, including what Americans spend annually to buy a variety of nonprescription medications for their coughs and other associated symptoms. This estimate is primarily derived from data collected in the 1980s related to the common cold, in which cough is nearly always present. This figure clearly underestimates the total cost of treating cough since it does not include the cost of prescription drugs for the common cold or the treatment for chronic cough.

The Committee consisted of individuals with expertise and research experience related to cough from the fields of adult and pediatric pulmonology, pharmacology, and physiology. The Committee was international in scope, with individuals from the United States, Canada, Australia, and the United Kingdom. Representatives from the American College of Chest Physicians, the American Thoracic Society, the Canadian Thoracic Society, and the American College of Physicians were active participants in the panel.

When a disagreement occurred concerning the interpretation of the data, the committee reviewed the controversy in question and was able to agree by consensus. The final report was reviewed by the panel members, members of the Health and Science Policy Committee of the American College of Chest Physicians, the Board of Regents of the American College of Chest Physicians, the Board of Directors of the American Thoracic Society, and the Standards Committee of the Canadian Thoracic Society.

In developing a clinically useful document, the committee was compelled to do so within the context of the evidence that has been published. In this regard, since the committee was not aware of any studies that specifically addressed the role of empiric therapy as a diagnostic aid or any cost analyses (e.g., cost-identification, cost-benefit, or cost-effectiveness) that related to different ways of managing cough, no specific sections in this document deal with these issues. Nevertheless, while the recommendations that are made in this statement are first and foremost based upon graded evidence, they are considered by the committee to be reasonable and practical. Future studies will determine in which instances they are cost-effective.

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**Table 1—Grading of Evidence**

<table>
<thead>
<tr>
<th>Grading Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from at least one properly randomized controlled trial.</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from well-designed controlled trials without randomization.</td>
</tr>
<tr>
<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.</td>
</tr>
<tr>
<td>II-3</td>
<td>Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</td>
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In grading evidence from studies involving well-characterized groups of subjects with chronic cough, a grade of II-2 was given to prospective observational studies, and a grade of II-3 was given to retrospective observational studies.

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**Summary Statement:**

- The impact of cough on health and health-care expenditures is substantial.
- Cough is one of the most common complaints.
for which patients seek medical attention. In 1993, cough was the most common complaint for which patients sought medical care in the United States in the ambulatory setting.

CHAPTER 2. COUGH AS A DEFENSE MECHANISM

Anatomy of the Cough Reflex

The very thin lining of mucus that normally coats the tracheobronchial epithelium is cleared by the centripetal movement of the mucociliary escalator.6-8 Cough serves to clear the airways when there are (1) large amounts of inhaled material, (2) large amounts of mucus due to excessive secretions or impaired mucociliary clearance, and (3) large amounts of abnormal substances such as edema fluid or pus. Each cough involves a complex reflex arc. The reflex begins with stimulation of a receptor.

_airway Receptors:_ The receptors for cough belong to the general group of rapidly adapting irritant receptors.9-11 Histologic studies of the respiratory tract in both animals and humans have revealed nerve endings located within the epithelium throughout much of the respiratory system.12-15 They are most numerous on the posterior wall of the trachea, at the main carina, and at the branching points of large airways, and are less numerous in the more distal smaller airways. No nerve endings have been found beyond the respiratory bronchioles. The most distal sites may be more sensitive in eliciting cough.16

Outside of the lower respiratory tract, cough receptors have been demonstrated histologically only in the pharynx.17 It is inferred that they must exist in other sites since mechanical stimulation of the external auditory canals and eardrums, paranasal sinuses, pharynx, diaphragm, pleura, pericardium, and stomach have all been reported to cause cough.18-26 Whereas laryngeal and tracheobronchial receptors appear to be irritated by both chemical and mechanical stimuli,27 receptors in other sites most probably respond only to mechanical triggers.18,27

Mechanical receptors are sensitive to touch and displacement. They are concentrated in the larynx, trachea, and carina, and become progressively less numerous more distally in the tracheobronchial tree. Chemical receptors are sensitive primarily to noxious gases and fumes. They are concentrated more in the larynx and bronchi than in the trachea. Although both mechanical and chemical receptors become less sensitive when subjected to continuous stimulation, the mechanical receptors adapt more rapidly.18,20 Adaptation of mechanical receptors is seen frequently in patients who are able to tolerate prolonged endotracheal intubation without anesthesia, and in children with a retained foreign body.

_Afferents:_ A number of cough receptors are innervated through the branches of the vagus. The pulmonary branches of the vagus nerve carry impulses derived from irritation of tracheobronchial and pleural receptors.27 Other branches of the vagus involved with cough include the auricular branch (Arnold’s nerve) conducting impulses from the external acoustic canal and eardrum; the pharyngeal branches conducting impulses from the pharynx; the superior laryngeal branches innervating the larynx; the gastric branches innervating the stomach; and cardiac and esophageal branches from the diaphragm. While the experimental physiologist believes that cough is solely a vagal phenomenon, there are clinical data to suggest that other afferent nerves can also be involved. The glossopharyngeal, trigeminal, and phrenic nerves are also putatively thought to carry impulses from cough receptors located in the pharynx, the nose and paranasal sinuses, and the pericardium, respectively.19 Since cough may be voluntarily initiated, postponed, or suppressed, there may be afferent input from higher centers.

Vagal afferents appear to play the most crucial role in mediating cough induced in the tracheobronchial tree and larynx. This assertion is supported by the observations that (1) vagal denervation of the tracheobronchial tree following heart-lung transplant eliminates the cough that is usually provoked by the inhalation of distilled water,29 and (2) cough can be evoked in the pharynx even in the absence of superior laryngeal nerve stimulation.

Although vagal nonmyelinated C fibers may carry impulses from cough receptors,31 the fast-velocity myelinated vagal afferents appear to be more important in mediating cough.9,24 The role of myelinated vagal afferents from the lower airway was evaluated by cooling the vagus.19 In this setting, mechanical or chemical stimulation of receptors in the larynx or tracheobronchial tree generally failed to elicit cough.

In addition to traveling to the cough center, afferent impulses may stimulate secretion of mucus from airway submucosal glands.32,33 This would serve as a physiochemical protective barrier against irritant chemicals as well as enhance the clearance of substances from the airways.

_Central Pathway:_ The existence of a discrete central cough center is controversial; if one exists, its characterization will require better experimental approaches. Afferent fibers first relay impulses to an area near the nucleus of the tractus solitarius. These impulses are then integrated into a coordinated cough response in the medulla oblongata of the brain stem, probably separate from the medullary centers that control breathing.34 Electrical stimulation studies of different areas in the medulla suggest that the cough center is diffusely located.35-39

Opiates universally inhibit the cough reflex when given centrally. Their effects are blocked by naloxone, suggesting the presence of a μ receptor. It is probable that 5HT also is involved in mediating the antitussive effect of morphine. Opiates most likely act directly on the cough center. The local administration of opiates in the lung and the use of the peripherally acting analog 443C81 do not have the same antitussive effects as systemic opiates. The effects of opiates are not secondary to sedation, as equally sedative drugs such as clonidine are not antitussive and blocking 5HT reduced the antitussive but not the sedative effects of morphine. Other pharmacologic influences have been studied, including dopaminergic γ-aminobutyric acid
(GABA) and n-methyl-D-aspartate (NMDA). The relative importance of these other systems in mediating cough requires further assessment.

**Efferents:** The motor outputs from the cough center are in the ventral respiratory group, with nucleus retroambiguus sending motoneurons to the inspiratory and expiratory muscles, and nucleus ambiguus to the larynx and bronchial tree. The efferent impulses of the cough reflex are transmitted to the respiratory musculature through the phrenic and other spinal motor nerves and to the larynx through the recurrent laryngeal branches of the vagi. Vagal efferents also supply the tracheobronchial tree and mediate bronchial smooth muscle constriction that is believed to assist the cough effort by narrowing the central airways. During this expiratory phase of cough, there is a biphasic turbulent blast of air consisting of (1) a transient of the flow phase due to the high gas flows and velocities through the airways. These events depend on normally functioning afferent and efferent pathways and an effective interaction between the flowing gas and mucus lining the airways.

**Characteristics of Effective Cough:**

Cough Mechanics—The sequence of events during a typical cough have been well described. There is an initial inspiration of a volume of gas ranging from 50% of the tidal volume to 50% of vital capacity. An advantage of inhaling large volumes is to optimize the length-tension relationship of the expiratory muscles, thereby enabling them to achieve greater intrathoracic pressures. This initial phase is followed by the expiratory effort. At the onset of the expiratory effort, the glottis closes for about 0.2 s. This allows the expiratory muscles to generate greater expiratory pressures by (1) decreasing expiratory muscle-shortening velocity, and (2) maintaining the expiratory muscles at a more advantageous force-length relationship. However, glottic closure is not essential for an effective cough. Next, the glottis is opened. The high intrapleural pressures developed during glottic closure simultaneously promote high expiratory flow rates and narrow the central airways. During this expiratory phase of cough, there is a biphasic turbulent blast of air composed of (1) a flow transient (lasting 30 to 50 ms) with peak flow rates as great as 11 L/s, and (2) a prolonged lower flow rate. The transient of the flow phase is due to the additive effects of the gas expired from the distal parenchymal units and the gas displaced by the collapsing central airways. During the second phase (lasting 200 to 500 ms), the sustained flows from the parenchyma are in the range of 3 to 4 L/s and fall as lung volume decreases.

The dynamic compression of the airways during the expiratory phase of cough improves cough effectiveness by enhancing expiratory flow velocities. Dynamic compression decreases tracheal cross-sectional area, resulting in a five-fold increase in the linear velocity of the gas because velocity = flow/cross-sectional area. Since the kinetic energy of the airstream is proportional to the square of the velocity of the airstream, this degree of dynamic compression increases its kinetic energy 25-fold. The kinetic energy enhances the removal of mucus adhering to the airway wall. Normally, dynamic compression is initiated in the trachea and mainstem bronchi at high lung volumes and extends to the more peripheral airways as lung volume decreases, ensuring that the whole length of the tracheobronchial tree is “coughed.” For this to occur, high intrathoracic pressures must be sustained throughout the expiratory effort.

**Gas-Mucus Interaction**—For cough to effectively remove mucus, the secretions that line the airways must be dispersed into the expiratory gas. This interaction has been analyzed in the framework of two-phase gas-liquid flow. In this context, the major physical forces affecting the removal of secretions include the mean velocity of the airstream and the surface properties of the secretions. The mean velocity of the airstream is a major determinant of the type of airflow that occurs in liquid. At the high velocities that are commonly encountered during cough (greater than 2500 cm/s), mucus is torn off and droplets are suspended within the airway lumen. This flow pattern is termed misty flow. At lower velocities, the mucus-gas interaction is less effective. The physical properties of the mucus slug also affects cough efficiency. Cough effectiveness is directly proportional to the depth of the mucus, and is inversely proportional to mucus tenacity (the product of adhesiveness and cohesiveness).

Other factors may also be operant in removing mucus at the high gas velocities associated with misty flow. First, air flow, in the range seen during a cough, can create waves of mucus. These waves may further enhance particle clearance. Second, the airways behave more like collapsible tubes than rigid pipes. During cough they may vibrate and their walls approximate each other, further aiding in loosening mucus and promoting clearance.

Mucus properties that enhance transport by coughing may retard transport by cilia. Elasticity has a negative effect on mucus clearance by cough, but it has the opposite effect on the removal of secretions by ciliary beating. Native mucus may exhibit intermediate levels of viscosity because it must be capable of responding to both mucociliary and cough forms of clearance. Models of two-phase gas-liquid flow in tubes suggest that cough may be effective down to the 7th to 12th airway generations in healthy individuals. Under conditions of excess mucus production in which the serous layer has low viscosity, close to that of water, the effect of coughing can extend down to the level of the respiratory bronchioles. These experiments, however, deal with an in vitro mechanical model and not with the in vivo situation in which there is dynamic compression and flapping of the airway walls.

An alternate to the two-phase gas-liquid flow theory is the hypothesis that removal of airway secretions with cough has more to do with the stimulation of ciliary activity than dispersion of liquid into gas. The high-velocity expired air during cough may promote mucus clearance by stimulating the mucociliary apparatus, either by changing secretions of periciliary fluid or by increasing...
ciliary beat frequency. A similar mechanism has been proposed for the observed increase in mucus ciliary clearance induced by high-frequency oscillatory flows. However, this mechanism is highly improbable because mucociliary clearance seems to operate at a near optimum lever under normal circumstances and because clearance of pathologic secretions usually requires detachment of the adherent sputum from the epithelium. Stress has been known to open potassium channels in vascular endothelial cells, increasing potassium flux out of the cell and resulting in hyperpolarization. The goblet cells may respond similarly to shear stresses associated with the rapid flows of cough or rapid inhalations. Neural reflexes may be mediated by rapidly adapting receptors in the lung that respond to rapid deflation or inhalation by increasing mucus secretions.

Factors Contributing to Cough Inefficiency: Altered Cough Mechanics—Expiratory muscle weakness causes cough inefficiency by directly lowering expiratory pressures, whereas inspiratory muscle weakness will indirectly lower expiratory pressures by limiting the volume of inhaled gas prior to cough. At low lung volumes, the expiratory muscles are not near the optimal length and respiratory system elastic recoil is reduced; both factors decrease expiratory pressure during cough. Expiratory muscle weakness may, in fact, contribute to cough inefficiency more by limiting dynamic airway narrowing rather than by limiting cough expiratory flow.

In partially curarized healthy subjects, expiratory pressures were reduced but expiratory flows were only minimally reduced. However, the high flow transient normally seen on flow-volume curves during the first phase of cough and thought to be due to dynamic narrowing of the airways was absent. To the extent that the expiratory pressures are reduced and there is less dynamic airway narrowing, gas linear velocities will be reduced. In cervical spinal cord injury patients with weakness or paralysis of the expiratory muscles, cough is impaired, reducing the ability to clear airway secretions. Expiratory pressures in these individuals range between only 8 and 36 cm of water (expiratory pressures are usually greater than 100 cm of water in healthy subjects). Nonetheless, dynamic compression was still thought to occur, as evidenced by plateaus of flow on isovolume pressure-flow curves.

Disordered chest wall motion also contributes to cough ineffectiveness. When the muscles of the abdominal wall are weak or paralyzed, paradoxical expansion of the abdomen is seen during cough due to the unopposed contraction of the muscles acting on the rib cage. Since the passive abdomen is very compliant, thoracoabdominal pressure cannot rise substantially. Consequently, the muscles acting on the chest wall perform work shortening rather than generating pressure. Because the compliant abdomen is expanding during cough, some of the pressure generated by the expiratory muscles is dissipated across the abdomen and the rise in pleural pressure is less than that which would occur if the abdominal muscles were activated. Since dynamic narrowing of the airways depends on the magnitude of increase in pleural pressure, the cough is less effective. Diaphragmatic contraction during cough would adversely affect cough by further lowering intrathoracic pressure.

Altered Mucociliary Function—The normal function of the mucociliary apparatus is critical in maintaining an effective cough, as it is needed to transport secretions from the periphery to the more proximal airways where they can then be cleared by cough. Smoking inhibits ciliary beating. Its effect on mucociliary clearance, however, is controversial. Mucociliary clearance is reduced in young, asymptomatic cigarette smokers with normal pulmonary function. However, Agnew et al found that clearance from the peripheral airways of asymptomatic smokers was no different than that of healthy age-matched nonsmokers. The inability to find a difference in mucociliary clearance between these two groups may be due to the opposing effects of smoking; it can either decrease mucociliary clearance by inhibiting ciliary beating or increase it by increasing peripheral airway secretions. When smokers develop airways obstruction, mucociliary clearance becomes impaired as their system is overloaded with excessive secretions. Once smoking leads to the development of COPD, cough becomes a necessary adjunct to mucociliary clearance.

Enhancing Disordered Cough Mechanics By Nonpharmacologic Means (Protussive Therapy): In patients with abnormal cough mechanics, altered mucus adhesion, or altered mucociliary clearance, a variety of interventions may be employed to increase cough effectiveness. While a variety of treatment modalities may improve cough mechanics, clinical studies documenting improvement in patient morbidity and mortality are lacking. Protussive therapy by pharmacologic means is discussed in the Pharmacologic Treatment section.

Expiratory Muscle Training—Since weakness of the expiratory muscles impairs cough, strengthening them may improve cough effectiveness. In general, the respiratory muscles can be trained for strength or endurance. In quadriplegic subjects, the strength of the clavicular
portion of the pectoralis major can be increased by isometric training over a 6-week period resulting in a 46% increase in expiratory reserve volume88 (Grade II). Using such a protocol may improve cough effectiveness by enabling patients with neuromuscular weakness to generate higher intrathoracic pressures.

Mechanical Aids—Expiratory pressures and flows can be enhanced by manually compressing the lower thorax and abdomen. This maneuver consists of applying pressure with both hands to the upper abdomen following an inspiratory effort and glottic closure. The range of improvement in peak cough expiratory flow is between 14 and 100%86,87 (Grade II-3). Since paradoxical outward motion of the abdomen during cough contributes to cough inefficiency, reducing this paradox either by manually compressing the abdomen or by binding the abdomen will improve cough effectiveness. A disadvantage of the assisted cough maneuver is that it requires the presence of a caregiver and is not well tolerated in patients with stiff chest walls, osteoporotic ribs, or intra-abdominal catheters, or those who have just undergone abdominal surgery.

Electrical stimulation of the abdominal muscles can also increase expiratory pressures and has the advantage of not requiring the presence of a caregiver. Coughs produced by electrical stimulation are associated with expiratory flows equal to manually assisted coughs.88,89 These results suggest that the technique is worthy of more detailed study and may be a potentially effective modality for assisting spinal cord-injured patients. Rather than directly stimulating the abdominal muscles, DiMarco et al89 activated the expiratory muscles by stimulating the spinal cord at the level of T10 in dogs. The internal intercostal muscles shortened by 35 to 40%, and this was accompanied by an increase in expiratory pressure. This technique is in an investigational stage but may eventually be clinically useful in restoring a more normal and effective cough mechanism on demand without the need for trained health-care providers.

Modalities directed at increasing the volume inhaled during the inspiratory phase of cough also have the potential to increase cough effectiveness. Normally, the inspiratory phase of cough optimizes the length-tension properties of the expiratory muscles and increases lung recoil pressure. The inability of patients with respiratory muscle weakness to achieve high lung volumes is likely to contribute to cough ineffectiveness. Increasing the inhaled volume prior to cough by airstacking positive pressure breaths or by glossopharyngeal breathing increases cough expiratory flows by 80% in these patients.90 Cough efficiency may be further enhanced when the initial inspiration is followed by the application of negative pressure to the airway opening for a period of 1 to 3 s. Using this technique of mechanical insufflation-exsufflation, peak cough expiratory flows can be increased by more than four-fold.97

Submaximal Expiratory Maneuvers—The forced expiratory technique of huffing was introduced as an alternative to cough for the removal of excess secretions91,92 (Grade II). This maneuver is performed at reduced transpulmonary pressure and may have the advantage of producing less airway closure in patients with obstructive disease than cough performed with higher transpulmonary pressures.93 The huffing maneuver was as effective as cough in moving secretions proximally from all regions of the lung in patients with COPD76 (Grade II). These findings imply that patients can enhance clearance without having to try excessively hard to achieve their highest possible flow rate.

Chest Physiotherapy—In order to facilitate airways clearance and render cough more effective, various physical therapy maneuvers have been employed. Although no large, randomized, prospective trials evaluating the efficacy of these maneuvers exist, several review articles93-95 address this issue, and a number of studies provide some data regarding the benefits of postural drainage, vibration, percussion, and forced exhalation (huffing), a technique that requires a patient to forcibly exhale with the glottis open from a medium to a low lung volume.75,96-99 Published reports use various criteria to evaluate efficacy. These include assessment of mucociliary clearance using radioactive technetium, measurement of expectorated sputum weight or volume, and, on occasion, sputum rheology. Studies reporting clinical outcomes are rare. Patients with CF constitute the majority of subjects studied, although many studies also include patients with chronic bronchitis and bronchiectasis.

Evidence indicates that postural drainage is effective; however, it is also time-consuming. Studies evaluating the contribution of percussion and vibration to postural drainage have demonstrated little additional benefit. There is a belief, but little data, that long-term compliance with chest physical therapy is less than optimal. For this reason, techniques that either enhance the results of postural drainage and forced expiration techniques or produce comparable results with less rigorous demands on patient time and effort have been evaluated.

A number of studies examined the effectiveness of positive expiratory pressure (PEP) of 5 to 20 cm H2O, usually delivered by face mask. Studies of several small cohorts with CF or chronic bronchitis have been reported with contradictory results. Some studies demonstrate that PEP therapy is superior to conventional physical therapy maneuvers,100,101 while other studies demonstrate that conventional forced expiratory therapy and postural drainage techniques are more effective.102-104 Other reports on the use of PEP therapy in CF patients over a period of several months indicate that the treatment is comparable to conventional postural drainage techniques, and well accepted by patients.105 In the only outcome study to evaluate the clinical impact of PEP therapy, Christensen and colleagues106 compared PEP to conventional chest therapy over a period of 5 to 12 months in patients with chronic bronchitis. They reported that patients treated with PEP had significantly less cough and less mucus production (Grade I). The number of acute exacerbations calculated from patient diaries was lower in patients receiving PEP. Fifty-five percent of the patients in the PEP group were free from acute exacerbations of bronchitis, compared with 48% of the patients in the control group. The PEP group also used fewer antibiotics and mucolytics and experienced a small increase in FEV1, while the control group experienced a small decrease in
Thomas and colleagues selected 35 publications that indicate deleterious results. A single meta-analysis of chest physical therapy in CF has been completed. From a review of 456 citations, Thomas and colleagues selected 35 publications that used predetermined inclusion criteria and included these in an overview, which concluded that standard physical therapy (percussion, vibration, and postural drainage) resulted in greater sputum expectoration than no treatment (Grade I). The meta-analysis did not address the contribution of vibration and percussion to the effectiveness of standard chest physical therapy. The combination of exercise with standard physical therapy was associated with a statistically significant increase in FEV₁ over standard physical therapy alone. PEP mask and standard physical therapy were equivalent in efficacy. The forced exhalation technique resulted in a small, but not statistically significant, increase in sputum production when compared with standard physical therapy.

A device known as the Flutter (Vario Raw S.A.; Aubonne, Switzerland) has been employed to facilitate mucous clearance. This device consists of a plastic pipe with a mouth piece at one end and a perforated cover at the other. Within the device, a high-density stainless steel ball rests in a circular cone and creates a valve. Breathing through the device creates oscillations in the airway, the frequency of which can be modulated by changing the inclination of the pipe. Konstan et al evaluated the device in 18 patients with cystic fibrosis (Grade I). They found that the volume of sputum produced during a 15-min treatment session with the device was more than three times that expectorated with voluntary cough or postural drainage. However, there were several limitations to this study, including lack of blinding, no measurement of pulmonary function, and use of sputum weight as a primary outcome variable. Other investigators have not been able to reproduce these results.

In summary, the available data, although not abundant, indicate that in patients with copious secretions, clearance of secretions can be enhanced with selected physical therapy procedures. The forced expiratory technique appears slightly more effective in this regard. Postural drainage may augment forced exhalation, but percussion and vibration are of no additional benefit. PEP therapy provides benefits comparable to forced expiration and postural drainage in selected patients with mucous hypersecretion. Further studies are required to determine the role of the Flutter device. There is scant information relative to the influence of physical therapy maneuvers on health-care outcomes, including frequency of hospitalization, hospital length of stay, longevity, or quality of life; however, it is clear that these techniques are well entrenched in the management of patients with mucous hypersecretion, especially those with CF.

**Table 2—Complications of Cough**

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Arterial hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupture of subconjunctival, nasal, and anal veins</td>
<td></td>
</tr>
<tr>
<td>Dislodgement/malfunctioning of intravenous catheters</td>
<td></td>
</tr>
<tr>
<td>Bradyarrhythmias, tachyarrhythmias</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Cough syncope</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
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<tr>
<td>Cerebral air embolism</td>
<td></td>
</tr>
<tr>
<td>CSF fluid rhinorrhea</td>
<td></td>
</tr>
<tr>
<td>Acute cervical radiculopathy</td>
<td></td>
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<tr>
<td>Malfunctioning ventriculoatrial shunts</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Stroke due to vertebral artery dissection</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Gastroesophageal reflux events</td>
</tr>
<tr>
<td>Hydrothorax in peritoneal dialysis</td>
<td></td>
</tr>
<tr>
<td>Malfunction of gastrostomy button</td>
<td></td>
</tr>
<tr>
<td>Splenic rupture</td>
<td></td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Inversion of bladder through urethra</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>From asymptomatic elevations of serum creatine phosphokinase to rupture of rectus abdominis muscles</td>
</tr>
<tr>
<td>Rib fractures</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pulmonary interstitial emphysema, with potential risk of pneumatosis intestinals, pneumomediastinum, pneumoperitoneum, pneumomediastinum, pneumothorax, subcutaneous emphysema</td>
</tr>
<tr>
<td>Laryngeal trauma</td>
<td></td>
</tr>
<tr>
<td>Tracheobronchial trauma (eg, bronchitis, bronchial rupture)</td>
<td></td>
</tr>
<tr>
<td>Exacerbation of asthma</td>
<td></td>
</tr>
<tr>
<td>Intercostal lung herniation</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Petechiae and purpura</td>
</tr>
<tr>
<td>Disruption of surgical wounds</td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
</tr>
<tr>
<td>Lifestyle changes</td>
<td></td>
</tr>
<tr>
<td>Self-consciousness, hoarseness, dizziness</td>
<td></td>
</tr>
<tr>
<td>Fear of serious disease</td>
<td></td>
</tr>
<tr>
<td>Decrease in quality of life</td>
<td></td>
</tr>
</tbody>
</table>

*The evidence from which this compilation has been derived consists of case reports and descriptive (Grade III) studies.

FEV₁. The apparatus required to administer PEP therapy is relatively inexpensive. No reports of this therapy indicate deleterious results. A single meta-analysis of chest physical therapy in CF has been completed. From a review of 456 citations, Thomas and colleagues selected 35 publications that met predetermined inclusion criteria and included these in an overview, which concluded that standard physical therapy (percussion, vibration, and postural drainage) resulted in greater sputum expectoration than no treatment (Grade I). The meta-analysis did not address the contribution of vibration and percussion to the effectiveness of standard chest physical therapy. The combination of exercise with standard physical therapy was associated with a statistically significant increase in FEV₁ over standard physical therapy alone. PEP mask and standard physical therapy were equivalent in efficacy. The forced exhalation technique resulted in a small, but not statistically significant, increase in sputum production when compared with standard physical therapy.

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In summary, the available data, although not abundant, indicate that in patients with copious secretions, clearance of secretions can be enhanced with selected physical therapy procedures. The forced expiratory technique appears slightly more effective in this regard. Postural drainage may augment forced exhalation, but percussion and vibration are of no additional benefit. PEP therapy provides benefits comparable to forced expiration and postural drainage in selected patients with mucous hypersecretion. Further studies are required to determine the role of the Flutter device. There is scant information relative to the influence of physical therapy maneuvers on health-care outcomes, including frequency of hospitalization, hospital length of stay, longevity, or quality of life; however, it is clear that these techniques are well entrenched in the management of patients with mucous hypersecretion, especially those with CF.

**Summary Statement:**

- Each cough involves a complex reflex arc that begins with stimulation of an irritant receptor.
- An effective cough depends on the ability to achieve high gas flows and intrathoracic pressures. Dynamic compression due to the high intrathoracic pressures increases the velocity of the flowing gas, thereby enhancing the removal of mucus adhering to the airway wall.
- Cough ineffectiveness may occur when the expiratory or inspiratory muscles are weakened or when the rheologic properties of mucus are altered.
- While a variety of nonpharmacologic promotive treatment modalities may improve cough
mechanics, clinical studies documenting improvement in patient morbidity and mortality are lacking.

Complications of Cough

During vigorous coughing, intrathoracic pressures of up to 300 mm Hg\textsuperscript{110} and expiratory velocities of up to 28,000 cm/s or 500 miles per hour\textsuperscript{111} (85% of the speed of sound) may be generated. Coughing produces hemodynamic changes that compare favorably to chest compressions. During the expiratory phase of a vigorous cough, systolic pressures approach 140 mm Hg, compared with 75 mm Hg during chest compressions.\textsuperscript{112} It has been estimated that a vigorous cough can generate from 1 to 25 J of energy.\textsuperscript{113} While pressures, velocities, and energy of these magnitudes allow coughing to be an effective means of clearing the airways of excessive secretions or foreign material and providing cardiopulmonary resuscitation, they also can cause a variety of cardiovascular, CNS, GI, genitourinary, musculoskeletal, respiratory, and miscellaneous complications in both children and adults\textsuperscript{39} (Table 2). The most common complications of cough are perceiving that something is wrong (98%), exhaustion (57%), feeling self-conscious (55%), insomnia (45%), life-style change (45%), musculoskeletal pain (45%), hoarseness (43%), excessive perspiration (42%), and urinary incontinence (39%).\textsuperscript{114}

Summary Statement:

- The pressures, velocities, and energy produced during vigorous coughing can cause a variety of cardiovascular, CNS, GI, genitourinary, musculoskeletal, respiratory, and miscellaneous complications.
- It is the complications of cough that provoke patients to seek medical attention.
- The most common complications are perceiving that something is wrong, exhaustion, feeling self-conscious, insomnia, life-style change, musculoskeletal pain, hoarseness, excessive perspiration, and urinary incontinence.
Etiologies

Cough can be caused by a multiplicity of disorders located in a variety of locations. Literally hundreds of diseases can cause cough. Only the most common are discussed in this document.

Based on duration, there are two categories of cough that are not mutually exclusive: acute, lasting less than 3 weeks; or chronic, lasting 3 weeks or more. This definition of acute and chronic cough has been utilized in five prospective, descriptive studies (Grade II-2). Acute cough is most commonly transient, as in the common cold, but it can occasionally be associated with potentially life-threatening conditions such as pulmonary embolism, congestive heart failure, and pneumonia. Acute cough can persist and become a chronic problem. Because there are patients with acute respiratory infections (e.g., pertussis) more severe than the common cold who complain of cough for longer than 3 weeks and have it spontaneously disappear, some authors have chosen to define an acute cough as being of greater duration than 3 weeks and have withheld a diagnostic workup for 4 or 8 weeks. The 4- and 8-week definitions of acute and chronic cough have been primarily used in retrospective, descriptive studies (Grade II-2, III).

Chronic cough can be simultaneously due to more than one condition. In multiple prospective, descriptive studies, it has been shown that chronic cough may be due to a single cause from 38 to 82% of the time and to multiple causes from 18 to 62% of the time. Multiply caused cough has been due to three diseases as much as 42% of the time. Whether cough is dry or productive (Grade II-2), the most common causes of chronic cough in nonsmokers in all age groups are PNDS, asthma, and GERD (Grade II-2, II-3). This is true whether the cough is described as dry or productive (Grade II-2).

PNDS, asthma, and/or GERD are likely to be the cause(s) of chronic cough approximately 100% of the time in nonsmoking patients who are not taking an ACEI drug and who have normal chest radiographs (Grade II-2).

Postnasal Drip Syndrome

Definition: The diagnosis of PNDS largely rests on the patient reporting certain symptoms or sensations. Because we are defining a syndrome and because no pathognomonic finding proves the presence of PNDS, the diagnosis of postnasal drip (PND)-induced cough is best determined by considering a combination of criteria, including symptoms, physical examination, radiographic findings, and, ultimately, response to specific therapy.

Radiographic evidence of chronic sinusitis (e.g., greater than 6 mm of mucosal thickening, air-fluid levels, or opacification of any sinus) suggest possible PNDS secondary to chronic sinusitis.

A favorable response to specific therapy for PNDS with resolution of cough is a crucial step in confirming that PNDS was present and was the etiology of cough.

Clinical studies suggest that the pathogenesis of cough from PND is due to mechanical stimulation of the afferent limb of the cough reflex in the upper airway. This stimulation is secondary to secretions emanating from the nose and/or sinuses dripping down into the hypopharynx. A number of conditions can cause PNDS. The differential diagnosis includes seasonal allergic rhinitis, perennial allergic rhinitis, perennial nonallergic rhinitis, vasomotor rhinitis, postinfectious rhinitis, chronic (bacterial) sinusitis, allergic fungal sinusitis, nonallergic rhinitis due to medication abuse or environmental irritants, and nonallergic rhinitis associated with pregnancy.

Although cough from PNDS could conceivably be caused by aspirated secretions stimulating cough receptors in the lower respiratory tract, there are no data to support this mechanism.

Prevalence: Since the cause of cough associated with the common cold has been shown to be most likely stimulated by PND,2 the common cold can be considered a PNDS. It follows that since the common cold is the most common condition afflicting mankind, on a purely statistical basis, PNDS is the most common cause of acute cough.

Summary Statement:

- Cough can be divided into two categories that are not mutually exclusive (Grade II-2, II-3): acute, lasting less than 3 weeks; or chronic, lasting at least 3 to 8 weeks.
- Acute cough is most frequently due to the common cold (Grade III).
In multiple studies of adults, PNDS due to a variety of upper respiratory conditions also has been shown to be one of the most common causes of chronic cough, with prevalences ranging from 8 to 87%. In four prospective, descriptive studies (Grade II-2), PNDS either singly or in combination with other conditions, was the most common cause of chronic cough, followed by asthma, GERD, bronchitis, bronchiectasis, and left ventricular failure.

Clinical Presentation: The clinical presentation of patients with PNDS, in addition to cough, commonly involves complaints (or at least an affirmative response to questioning) of a sensation of something dripping into the throat, a need to clear the throat, a tickle in the throat, nasal congestion, or nasal discharge. Patients sometimes complain of hoarseness. Coughing also can occur with talking, but this is a nonspecific complaint associated with essentially all causes of cough. A preceding history of an upper respiratory illness (a cold) is often present. A history of wheeze is also common. Most patients with PNDS-induced cough will have symptoms or evidence of one or more of the following: drainage in posterior pharynx, throat clearing, nasal discharge, cobblestone appearance of the oropharyngeal mucosa, or mucus in the oropharynx. These clinical findings are relatively sensitive but are not specific. They are also found in many patients with cough due to other causes (Grade II-2).

A minority of patients with cough will have no upper respiratory signs or symptoms suggestive of PNDS, yet respond to antihistamine/decongestant therapy. The authors of one prospective study interpreted this response to treatment as implying that silent PNDS caused the cough (Grade III).

PNDS-induced cough can also be associated with chronic sputum production of greater than 30 cm³ per day. The etiology of PNDS with excessive sputum production is most often chronic sinusitis.

Diagnosis: A prospective study of chronic cough demonstrated that a careful history including the character and timing of cough and the complications associated with cough is of little diagnostic value. This certainly is true regarding PNDS-induced cough. The symptoms and signs of PNDS are nonspecific, and a definitive diagnosis of PNDS-induced cough cannot be made from the history and physical examination alone. Furthermore, the absence of any of the usual clinical findings does not rule out a response to treatment that is usually effective for PNDS-induced cough. Although this does not prove that silent PNDS is the cause of the cough, it at least suggests the possibility. Alternatively, it is possible that the first-generation antihistamines used empirically have a primary central antitussive effect, and therefore the apparent effectiveness of these agents in patients without findings for PNDS may be nonspecific. The fact that the resolution of cough in response to treatment with a first-generation antihistamine/decongestant is gradual and usually over a period of days to weeks argues against this interpretation.

Four-view sinus radiographs may detect the presence of chronic sinusitis, but this does not confirm that the chronic cough is PNDS-induced or, if it is a PNDS-induced cough, that the sinus disease is responsible for the PNDS. However, based upon a favorable response to sinusitis therapy, in patients with both chronic cough and excess sputum production, routine sinus radiographs have been shown to have a positive predictive value of 81% and a negative predictive value of 95% for predicting that chronic sinusitis was responsible for the PNDS-induced cough. In patients with chronic cough, the majority of whom did not have excess sputum production, positive and negative predictive values were 57% and 100%, respectively. Similar data do not exist for sinus CT scanning.

An allergy evaluation can detect the presence of skin reactivity to specific allergens, but this is not proof that allergy is of etiologic importance. Allergy testing is probably most useful when there is a seasonal component to the PNDS-induced cough (seasonal allergic rhinitis) and/or the history strongly suggests an association with specific allergen exposures such as pollen or animal dander. Testing for allergens such as house dust mite (Dermatophagoides farinae and Dermatophagoides pteronyssinus) and indoor mold may be of value when perennial allergic rhinitis is being considered. Skin testing for Aspergillus or other fungi may be indicated if allergic fungal sinusitis is suspected.

A history of a preceding upper respiratory tract infection is the key to making the diagnosis of postviral PNDS. A careful history of inappropriate use of either legal (eg, nasal oxymetazoline hydrochloride) or illegal (eg, snorting cocaine) nasal drug use is critical to diagnosing rhinitis medicamentosa. An environmental history (including occupational exposure) is critical to diagnosing PNDS due to irritants. Improvement with removal of the offending agent helps confirm the diagnosis. The onset of PNDS and cough during pregnancy (and its resolution postdelivery) in the absence of evidence of any other cause is key to the diagnosis of rhinitis associated with pregnancy.

Vasomotor rhinitis is characterized by excessive, thin, watery secretions sometimes precipitated by temperature changes. Patients with vasomotor rhinitis typically describe the sudden unexpected onset of profound rhinorrhea, or nasal congestion. These symptoms are frequently described by patients with concomitant rhinitis from some other cause and improve with successful treatment of the underlying rhinitis. When it occurs as an isolated symptom, it is thought to be related to autonomic imbalance. Nasal examination findings are nonspecific; watery rhinorrhea may be seen in patients with more secretory than congestive symptoms. Increased cholinergic tone or sensitivity is suggested by the effectiveness of ipratropium bromide in controlling vasomotor symptoms.

In summary, response to specific therapy for PNDS-induced cough and the absence of evidence for another cause of cough are the most useful diagnostic criteria available. No objective, definitive criteria exist for diagnosing PNDS-induced cough. The diagnosis is necessarily inferential and is based on a combination of clinical findings, the results of ancillary testing, and ultimately response to therapy.

Treatment: The treatment options for PNDS-induced cough are somewhat dependent on the subcategory of...
disease causing the PND. When a specific etiology of cough is not apparent, empiric therapy for PNDS should be applied before beginning an extensive diagnostic work-up.

**PNDS Due to Perennial Rhinitis or Postviral Upper Respiratory Infection**—An older generation of antihistamine/decongestant combinations has been shown to be consistently efficacious in one randomized, double-blind, placebo-controlled study of acute cough2 (Grade I), and in four prospective descriptive studies of chronic cough3,4,115,116 (Grade II-2). The combination of dexchlorpheniramine maleate (6 mg bid) or azatadine maleate (1 mg bid) plus sustained-release pseudoephedrine sulfate (120 mg bid) were the treatments used in these studies. In contradistinction, newer-generation, relatively nonsedating antihistamines, such as terfenadine in two studies123,124 and loratadine plus pseudoephedrine in one study,125 were found to be ineffective in treating acute cough associated with the common cold in randomized, controlled trials. Based upon this Grade I, II-2 evidence, the older generation of antihistamines should be used preferentially in PNDS that is nonhistamine-mediated. The older (first-generation) antihistamines probably work because of anticholinergic properties. In most patients, some improvement in cough will be seen within days to 2 weeks of initiation of therapy.116

Severe side effects have usually not been a major problem with the first-generation antihistamine/decongestant preparations in the context of treating cough; but in individual patients they may cause difficulties requiring discontinuation of the therapy. In a randomized, double-blind, placebo-controlled study assessing the effect of a first-generation antihistamine/decongestant combination medication on cough associated with the common cold, no patient dropped out of the study due to an adverse occurrence from the drug. Only dry mouth and transient dizziness were more common in the drug group2 (Grade I). Sedation is the primary side effect due to the antihistamine. It is our opinion that initiating therapy once a day at bedtime for a few days before going to bid therapy can sometimes obviate this problem (Grade III). Insomnia, difficulty with urination (primarily in older men), tachycardia or palpitations, worsening of hypertension, and increased intraocular pressures in patients with glaucoma are all potential concerns with the decongestant. Increased problems with urination or increased intraocular pressures in glaucoma can also occur with the use of an anticholinergic medication.

Other options include intranasal corticosteroids and ipratropium bromide. Data on the use of these medications for treatment of cough are limited.

**PNDS Due to Allergic Rhinitis**—Nasal steroids and/or cromolyn would be the initial drugs of choice for PNDS due to allergic rhinitis. Based upon numerous controlled studies of allergic rhinitis126a (Grade I), there is good reason to believe that nasal corticosteroids, nasal cromolyn, and all antihistamines will be efficacious for the treatment of cough due to PNDS from allergic rhinitis. Nonselecting antihistamines are likely to be more effective in this type of rhinitis than in nonallergic rhinitis. Sedating antihistamines plus decongestants are likely to be helpful if the other approaches prove unsatisfactory (Grade II-2).3,4,115,116

Environmental controls to avoid the offending allergens are highly desirable, when feasible. Allergen desensitization (allergen immunotherapy) may be of value over the long term, but not for immediate help. If the cough and other symptoms of allergic rhinitis are well controlled using environmental controls and intranasal therapy, allergen desensitization is not necessary.

**Vasomotor Rhinitis**—Although ipratropium bromide may be effective for this condition,126 studies suggesting that it is helpful in treating the cough due to this condition are limited to a few patients in a prospective study.4 In those few cases, ipratropium was found to be helpful when the older-generation antihistamine/decongestant preparations failed.

**Sinusitis**—Acute sinusitis usually involves bacterial infection and is generally defined as being of no more than 3 weeks’ duration. The most common organisms are Streptococcus pneumoniae and Haemophilus influenzae. Other organisms include anaerobes, streptococcal species, Moraxella catharralis (especially in children), and Staphylococcus aureus.

Therapy for acute bacterial sinusitis includes antibiotics, intranasal corticosteroids to decrease inflammation, and decongestants such as oxymetazoline hydrochloride. It should be noted, however, that no prospective, randomized, double-blind studies have proven either nasal or oral decongestants to be efficacious in patients with documented acute or chronic sinusitis. No one has investigated the efficacy of any of these medicines on acute cough related to acute sinusitis.

The treatment of chronic sinusitis is even less clear-cut. The role of bacterial infection and the importance of antibiotic therapy is controversial. However, in four prospective descriptive studies3,4,115,116 (Grade II-2), the following initial treatment regimen has been efficacious: a minimum of 3 weeks of an antibiotic effective against H influenzae, mouth anaerobes, and S pneumoniae; a minimum of 3 weeks of oral treatment with an older generation antihistamine/decongestant twice per day; and 5 days of nasal decongestant twice per day. When cough disappears with this therapy, intranasal corticosteroids have been given for 3 months. In certain refractory patients who do not respond to medical therapy or who have recurrent episodes of acute sinus infection, it is our opinion that sinus surgery may be an option (Grade III).

When environmental irritants may be involved, avoidance of exposure, improved ventilation and filters, and in rare circumstances, use of personal protective devices (eg, dust/mist/fume masks with HEPA filters for occupational exposures), are key.

Table 3 summarizes studies addressing PNDS and chronic cough.

**Summary Statement:**

- PNDS, either singly or in combination with other conditions, is the most common cause of...
**Table 3—Chronic Cough Due to Postnasal Drip Syndrome**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Reference</th>
<th>Age Range, yrs</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Follow-Up</th>
<th>Rx for PND</th>
<th>Result</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irwin, 1981</td>
<td>3</td>
<td>17-88</td>
<td>Prospective protocol, descriptive</td>
<td>49</td>
<td>18.9 mos postcough</td>
<td>A/D</td>
<td>100% Dx; 98% Rx+; 29% PND, 18% PND+asthma; 96% Dx; 94% Rx+; 8% PND, 25% PI</td>
<td>II-2</td>
</tr>
<tr>
<td>Poe, 1982</td>
<td>119</td>
<td>15-89</td>
<td>Retrospective, descriptive</td>
<td>109</td>
<td>12 mos</td>
<td>Not stated</td>
<td>88% Dx; 87% Rx+; in 54/102 pts PND was sole or partial Dx; PND=41% of all Dx; 100% of pts with Dx PND had symptoms or signs of PND</td>
<td>II-3</td>
</tr>
<tr>
<td>Poe, 1989</td>
<td>120</td>
<td>19-79</td>
<td>Retrospective, descriptive</td>
<td>139</td>
<td>12 mos</td>
<td>A/D</td>
<td>99% Dx; 98% Rx+; in 54/102 pts PND was sole or partial Dx; PND=41% of all Dx; 100% of pts with Dx PND had symptoms or signs of PND</td>
<td>II-2</td>
</tr>
<tr>
<td>Irwin, 1990</td>
<td>4</td>
<td>6-83</td>
<td>Prospective standardized protocol, descriptive</td>
<td>102</td>
<td>Until Rx+, avg 3-6 mos</td>
<td></td>
<td>99% Dx; 98% Rx+; in 54/102 pts PND was sole or partial Dx; PND=41% of all Dx; 100% of pts with Dx PND had symptoms or signs of PND</td>
<td>II-2</td>
</tr>
<tr>
<td>O’Connell, 1994</td>
<td>310</td>
<td>19-83</td>
<td>Prospective standardized protocol, descriptive</td>
<td>87</td>
<td>3 mos from start of Rx</td>
<td>Rx for rhinitis, nasal steroids &amp; ipratropium±terfenadine</td>
<td>Rhinitis sole or partial Dx in 63% of successfully treated pts</td>
<td>II-2</td>
</tr>
<tr>
<td>Gaffey, 1988</td>
<td>123</td>
<td>Mean 23, no range</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>250</td>
<td>4 d from start of therapy</td>
<td>Terfenadine 60 mg bid for PND &amp; cough of the common cold</td>
<td>No significant effect found</td>
<td>I</td>
</tr>
<tr>
<td>Curley, 1988</td>
<td>2</td>
<td>18 or older</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>73</td>
<td>.5 mo from onset of cold</td>
<td>A/D</td>
<td>Multiple linear regression: TC due to PND major factor in cough; cough less with A/D vs placebo (p=0.05)</td>
<td>I</td>
</tr>
<tr>
<td>Pratter, 1993</td>
<td>116</td>
<td>18-75</td>
<td>Prospective standardized protocol, descriptive</td>
<td>45</td>
<td>3 mos after resolution of cough</td>
<td>Principal Rx A/D; secondary Rx, nasal steroids</td>
<td>PND sole or partial Dx in 87%, based on response to Rx</td>
<td>II-2</td>
</tr>
<tr>
<td>Berkowitz, 1991</td>
<td>124</td>
<td>12-65</td>
<td>Prospective standardized protocol, descriptive</td>
<td>99</td>
<td>5 days from start of Rx</td>
<td>Terfenadine 120 mg bid for PND &amp; cough of the common cold</td>
<td>No significant effect found</td>
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</tr>
<tr>
<td>Smyrnios, 1995</td>
<td>115</td>
<td>18-86</td>
<td>Prospective standardized protocol, descriptive</td>
<td>71</td>
<td>Mean of 4.6 mos from onset of Dx and Rx</td>
<td>A/D, nasal steroids, intranasal ipratropium, oxymetazoline, antibiotic</td>
<td>PND most common cause of chronic cough in pts with normal chest radiograph, very high percentage of unexplained cough (45%) in pts with normal radiograph</td>
<td>II-2</td>
</tr>
<tr>
<td>Puolijoki, 1989</td>
<td>311</td>
<td>15-85</td>
<td>Prospective standardized protocol, descriptive</td>
<td>198</td>
<td>1 yr posttreatment</td>
<td>Rx for PND not described</td>
<td>PND second most common cause of chronic cough with excessive sputum production. Chronic sinusitis most common cause of PND-induced cough (31/52, or 63%)</td>
<td>II-3</td>
</tr>
</tbody>
</table>
chronic cough (Grade II-2).

- A favorable response to specific therapy for PNDS with resolution of cough is a crucial step in confirming that PNDS is present and is the etiology of cough.
- Because the symptoms and signs of PNDS are nonspecific (Grade II-2), a definitive diagnosis of PND-induced cough cannot be made from the history and physical examination alone. The diagnosis is necessarily inferential and is based upon a combination of clinical findings, the results of ancillary testing, and, ultimately, response to therapy. Furthermore, the absence of any of the usual clinical findings does not rule out a response to treatment usually effective for PND-induced cough.
- The combination of a first-generation antihistamine and a decongestant is considered to be the most consistently effective sole form of therapy in treating most patients with PND-induced cough not due to sinusitis (Grade II-2). In contradistinction, newer-generation, relatively nonsedating antihistamines have been found to be noneffective in treating acute cough associated with the common cold in randomized, controlled trials (Grade I). These data support the findings that the newer nonsedating antihistamines are also not as effective as the first-generation antihistamines in chronic cough due to PNDS secondary to nonallergic conditions. Based upon this Grade I and Grade II-2 evidence, the first-generation antihistamines should be used preferentially in PND-induced cough that is nonhistamine-mediated.

**Asthma**

*Definition and Prevalence:* Asthma has been a difficult disease to define because of the lack of precise information about its pathogenesis. It is best described as a chronic inflammatory disease of the airways presenting with characteristic symptoms and associated characteristic physiologic abnormalities of variable airflow obstruction and airway hyperresponsiveness. Asthma has been shown in multiple studies to be one of the most common causes of chronic cough in all age groups.

*Diagnosis: Symptoms—* The symptoms of asthma are usually chest tightness, wheezing, dyspnea, and cough. The symptoms can occur singly or in combination. Cough occurs in all asthmatics; sometimes, persisting cough can be the most troublesome symptom. In prospective descriptive studies of patients with chronic cough due to asthma, cough has been the only asthma symptom from 6.5 to 57% of the time. This is called cough-variant asthma.

The symptoms of asthma are not specific for asthma, and are described in several other chest diseases. Indeed,
the term cardiac asthma was used in the past to describe the symptoms of acute left ventricular failure. For this reason, symptoms cannot be relied upon alone to make a diagnosis of asthma.

**Variable Airflow Obstruction**—Variable airflow obstruction is the physiologic abnormality which is the sine qua non for a diagnosis of asthma. The airflow obstruction is often present at the time of the initial presentation of the patient; its reversibility, either spontaneously or after treatment with an inhaled β₂-agonist, is diagnostic for asthma, assuming the tests for airflow obstruction are performed correctly. Airflow obstruction is best evaluated by using spirometry and measuring the FEV₁, which is the most reliable measurement of airway caliber. A simpler, although less reliable, measurement can be made using a peak flow meter to measure peak expiratory flows. Patients can present initially with a history of symptoms, but no measurable airflow obstruction. In this instance, variable airflow can be measured by measuring peak expiratory flows morning and evening over time (usually 2 to 4 weeks) or, alternatively, by measuring airway responsiveness.

Defining reversibility can occasionally be difficult, as some patients with severe irreversible airflow obstruction can demonstrate small improvements after inhaled β₂-agonists. The American Thoracic Society has recommended that an increase of at least 12% over baseline is needed before reversibility can be established.¹²⁸

**Airway Hyperresponsiveness**—Airway hyperresponsiveness is an increased ability of the airways to narrow after exposure to constrictor agonists. It consists of both an increased sensitivity of the airways, as indicated by a small increase in the bronchoconstrictor response,¹²⁹ and a greater maximal response to the agonist.¹³⁰ Inhalation challenges with airway constrictor agonists, such as histamine or methacholine, are widely used to measure airway hyperresponsiveness. In populations of asthmatic patients, the severity of airway hyperresponsiveness correlates with the severity of asthma¹³¹ and with the amount of treatment needed to control symptoms.¹³² Airway hyperresponsiveness is not specific for asthma, and it has been described in patients with other airway diseases such as CF and irreversible airflow obstruction, as well as in up to 30% of nonasthmatic children.¹³³ Airway hyperresponsiveness is, however, very sensitive for a diagnosis of asthma.¹³⁴ Therefore, its absence makes a diagnosis of current asthma unlikely.

A diagnosis of asthma, therefore, should be made in a patient with characteristic symptoms who demonstrates variable airflow obstruction spontaneously, or who has airway hyperresponsiveness.

**Cough-Variant Asthma**: Cough is a symptom that all asthmatics experience as a consequence of their asthma. Cough-variant asthma is a term that describes the presence of cough as the only symptom of asthma in patients with demonstrable airway hyperresponsiveness.¹²⁷ Because chronic cough is a very common clinical presentation, it is important to recognize that the absence of other asthma symptoms, either in children or adults, does not exclude a diagnosis of asthma.

**Prevalence**—The prevalence of cough-variant asthma is very difficult to establish because no studies have examined the prevalence separate from that of more characteristic asthma. However, one study described persistent wheeze in 13% of more than 14,000 Canadian children, and persistent cough in 6%.¹³⁸ This supports the clinical observation that isolated cough is less common than the other clinical manifestations of asthma. In addition, the consequences of isolated cough appear to be less severe than persistent wheeze as measured by repeated episodes of airflow obstruction.¹³⁹

**Diagnosis**—A diagnosis of asthma should be considered in the differential diagnosis of all patients with a chronic cough. Patients with isolated cough usually do not have variable airflow obstruction at the time of presentation; however, if airflow obstruction can be shown to be present and is reversible with medications, this confirms the diagnosis of asthma. The definitive diagnosis of cough due to asthma is made when cough goes away with specific asthma medications.³,⁴,¹¹⁵,¹¹⁷ The diagnosis of cough-variant asthma is suggested by the presence of airway hyperresponsiveness in a patient with chronic cough. It is implausible that cough-variant asthma is the cause of chronic cough when airway hyperresponsiveness cannot be demonstrated.

This approach, however, may not work in young children, in whom tests of variable airflow obstruction are difficult to perform and not widely available. In this instance, a typical history of cough that is triggered by a viral respiratory illness or allergen exposure, is worse at night, and is exacerbated by exercise, cold air, or smoke, coupled with a favorable therapeutic trial with anti-inflammatory therapy, may be the only approach to diagnosis. A history of wheezing is present in up to 60% of these children and atelectasis or middle lobe collapse is commonly associated with cough even when the child is wheeze-free.¹³⁷

A therapeutic trial with corticosteroids by some is sometimes the only method used to attempt to establish a diagnosis of cough-variant asthma.¹³⁷ This method of diagnosis is not recommended, as other types of chronic cough (e.g., due to eosinophilic bronchitis) not associated with the physiologic abnormalities of asthma can also respond to anti-inflammatory medication. In this instance, labeling a patient as having asthma because of symptomatic improvement with corticosteroids would not be correct.

**Treatment**—Although there are relatively few drug studies that have specifically assessed cough as a primary outcome variable, the treatment of cough-variant asthma should be the same as for asthma presenting with other symptoms. Transient relief from the cough can be obtained by using inhaled β₂-agonists.¹³⁸ Nedocromil sodium also has been shown in a randomized, double-blind, placebo-controlled study to be effective in treating cough in asthmatics¹³⁹ (Grade I). However, based upon numerous prospective descriptive studies,³,⁴,¹¹⁵,¹¹⁷ the most benefit is likely to be obtained with corticosteroids, either oral corticosteroids initially followed by inhaled if the symptoms are very severe,¹⁴⁰ or with inhaled corticosteroids alone,¹⁴¹ together with inhaled β₂-agonists to relieve acute symptoms (Grade II-2). Uncommonly, cough-variant asthma appears to respond only to high doses of oral...
Eosinophilic Bronchitis: A population of chronic cough patients has been reported who have a predominance of eosinophils and an increase in metachromatic cells in sputum, indistinguishable from the findings in asthma. However, since they did not have airway hyperresponsiveness or variable airflow obstruction, they did not have asthma. These patients do, however, obtain marked clinical benefit from inhaled or oral corticosteroids as do patients with asthma and cough. This disease has not been reported in children.

Summary Statement:

- Cough is a symptom that occurs in all asthmatics; sometimes, however, persisting cough can be the most troublesome symptom. In prospective descriptive studies of patients with chronic cough due to asthma (Grade II-2), cough has been the only asthma symptom from 6.5 to 57% of the time. This is called cough-variant asthma.

- A diagnosis of asthma should be considered in the differential diagnosis of all patients with a chronic cough, since it is a common cause. Usually, patients with isolated cough do not have variable airflow obstruction at the time of presentation; if airflow obstruction can be shown to be present and is reversible with medications, this confirms the diagnosis of asthma. The diagnosis of cough-variant asthma is suggested by the presence of airway hyperresponsiveness in a patient with chronic cough and confirmed only when cough goes away with asthma medications. The treatment of cough-variant asthma should be the same as asthma presenting with other symptoms. The most benefit is likely to be obtained with corticosteroids, either oral initially followed by inhaled if the symptoms are very severe, or with inhaled alone, together with inhaled β₂-agonists to relieve acute symptoms (Grade II-2). The inhaled medications should be delivered from a dry powder device, or a pMDI together with a spacer. Inhalation from a pMDI alone can exacerbate cough acutely in patients with asthma, including cough-variant asthma. The maximal symptomatic benefit of the inhaled corticosteroids is often not seen for 6 to 8 weeks (Grade I). Once the cough is resolved, the corticosteroids should be discontinued. The cough is likely to recur, particularly if the cough-variant asthma has been caused by exposure to a precipitating stimulus to which the patient will be re-exposed. The time between stopping the inhaled corticosteroids and the recurrence of the cough is variable, and sometimes the cough does not return.

Gastroesophageal Reflux Disease

Definition: The primary event in gastroesophageal reflux (GER) is the movement of acid and other noxious substances from the stomach into the esophagus. In healthy individuals, reflux is a normal asymptomatic event. Gastroesophageal reflux disease (GERD) is defined as occurring when reflux leads to symptoms or physical complications. In the general population, excessive exposure of the distal esophageal mucosa to refluxed gastric contents most commonly results in heartburn, epigastric or retrosternal discomfort, and chest pain. Prolonged exposure can lead also to esophagitis, Barrett’s epithelium, and esophageal ulceration and its complications such as bleeding or stricture formation. However, esophageal reflux symptoms can also occur without esophagitis, and there can be pathologic reflux without classical GI symptoms (Grade I).

GER has long been associated with pulmonary symptoms and diseases, many of which present with cough. These range from bronchopulmonary dysplasia in infants, bronchial asthma, chronic bronchitis, and diffuse pulmonary fibrosis to the pulmonary aspiration syndromes, including lung abscess, bronchiectasis, pneumonitis, recurrent pneumonia, and respiratory failure.

As a cause of chronic cough, GERD has been shown in multiple studies to be one of the most common causes in all age groups (Grade II-2, II-3). The normal antireflux barrier. The crural diaphragm and the phrenoesophageal ligament are considered to be the anatomic structures that play a major role in the normal antireflux barrier. The intraluminal pressure at the gastroesophageal junction reflects the strength of the antireflux barrier, and reflux only occurs when this pressure is reduced.

The transdiaphragmatic pressure (Pdi) is +4 to 6 mm Hg during tidal volume expiration, and +10 to 18 mm Hg during tidal volume inspiration. During maximal inspiratory efforts to total lung capacity, Pdi can reach...
+60 to 80 mm Hg. However, GER does not result from raised Pdi alone. This is because as Pdi increases during inspiration, esophagogastric junction pressure also increases due to contraction of the crural diaphragm. Thus, during maximal inspiration when Pdi can reach 60 to 80 mm Hg, esophagogastric junction pressure reaches 100 to 150 mm Hg, effectively preventing reflux.

For GER to occur, there must be significant defects in the normal antireflux barrier since increases in Pdi are effectively counteracted by intact antireflux mechanisms. Reflux normally occurs because of transient relaxation of the lower esophageal sphincter (LES) tone, a phenomenon termed transient lower esophageal sphincter relaxation (TLESR).

Pathogenesis: It is currently thought that LES dysfunction is the major cause of defective gastroesophageal competence, and thus reflux, with nonsphincteric mechanisms playing a secondary role. The majority of patients with GERD have normal basal LES tone. Simultaneous measurements of esophageal pH and motility have shown that under resting conditions, LES pressure has to be absent for reflux to occur not only in normal subjects, but also in both adults and children with reflux disease. In the majority of reflux episodes, this is due to TLESR, with only a minor portion of episodes due to chronic absence of LES pressure, or reduced basal LES tone. TLESR is thought to be independent of normal esophageal body peristalsis, and thus not triggered by either spontaneous or voluntary swallowing.

The relationship between cough and esophageal reflux, with regards to mechanisms by which cough may aggravate or precipitate reflux episodes, is not known. There is no doubt that raised Pdi occurs as a result of chronic cough, but this alone is not sufficient to produce reflux on a background of normal basal LES tone. Possible mechanisms by which cough may precipitate reflux include cough stimulating either TLESR or swallow-induced LES relaxation.

Clearance of Esophageal Acid—Esophageal mucosal injury from reflux of gastric contents, or reflux esophagitis, is not only dependent on the frequency, potency, and amount of refluxate, but also on the duration of time the mucosa is exposed to the refluxed fluid. Studies have shown that patients with reflux esophagitis not only are there increased reflux events, but there is also a longer period of mucosal acidification, suggesting impaired esophageal acid clearance. Impaired clearance of acid in patients with cough and GERD has been demonstrated in some but not all patients.

Role of GER in the Pathogenesis of Chronic Cough—Chronic cough secondary to GERD has been associated with a wide range of syndromes. These can be categorized based on the pathogenesis of the cough (Table 4). Gross aspiration resulting in pulmonary aspiration syndromes is usually a result of free esophageal reflux with large-volume refluxate. Reduced basal LES tone and impaired esophageal motility and esophageal clearance are frequently seen. Often there are severe pathologic changes at endoscopy, such as Grade 3 or 4 esophagitis or Barrett’s epithelialization of the mucosa. Using pulmonary scintigraphy, up to 75% of patients with chronic bronchial disease and reflux symptoms may have some degree of lung contamination.

Microaspiration from proximal esophageal reflux results in less serious respiratory complications, but cough is still a prominent symptom. It results from a smaller volume of refluxate and produces laryngeal inflammation with or without bronchial inflammation; cough and hoarseness are the major complaints. Twenty-four-hour ambulatory esophageal pH monitoring with distal and proximal pH sensors have shown minor proximal reflux, including into the hypopharynx, in 9 of 15 patients (with cough, hoarseness, and laryngeal inflammation) in one study, but in only 10.7% in another study.

Tracheal pH monitoring via a pH probe inserted through the cricothyroid membrane has also been used in an attempt to quantify acid aspiration, but the results to date have been inconclusive. Vagally mediated distal esophageal-tracheobronchial reflex mechanisms have been described in patients with asthma as well as patients with chronic persistent cough without asthma. In patients with asthma, up to approximately 80% have documented pathologic GER on 24-h ambulatory esophageal pH monitoring (Grade II, II-2, II-3), and a number of authors have described reflex changes in airways caliber and resistance in response to acid in the distal esophagus.

Cough is often associated with GER in patients with chronic persistent cough that is unexplained after a standard diagnostic evaluation, including history and examination, chest radiographs, laryngoscopy, paranasal sinus radiographs, lung function testing, bronchial provocation testing, and home peak flow monitoring. In this setting, cough is likely a result of gastric contents stimulating a distal esophageal-tracheobronchial reflex mechanism with no evidence of microaspiration or proximal esophageal reflux. The afferent pathway has been inhibited by the esophageal instillation of local anesthetic (4% topical lignocaine), while the efferent pathway has been inhibited by nebulized ipratropium bromide (Grade II). This reflex arc is the likely mechanism by which reflux disease leads to cough in these patients, although intraesophageal acid may not be the sole mediator.
The Cough-Reflux Self-perpetuating Cycle—It has been proposed that a self-perpetuating positive feedback cycle between cough and esophageal reflux is operative, whereby cough from any cause may precipitate further reflux. The mechanisms by which GER is worsened or triggered by cough is unknown.

Prevalence of GERD in the Etiology of Chronic Cough: GERD from a GI standpoint has a prevalence in the community of up to 25%. Symptoms occur mostly in the postprandial period. Between 10 and 20% of patients suffering from GERD have associated respiratory manifestations, including cough, dyspnea, wheeze, and sputum production.

Using a systematic diagnostic protocol for evaluating adults with previously unexplained chronic cough, GER with prominent GI symptoms has been established as a cause of cough in 6 to 10% of patients (Grade II-2, II-3). The diagnosis of GERD was made on the basis of reflux symptoms plus the demonstration of abnormalities on endoscopy or esophageal pH monitoring and the disappearance of cough with antireflux therapy. However, cough may be the only manifestation of GERD, and when 24-h ambulatory esophageal pH monitoring is incorporated into the protocol, GERD has been found to be a cause of chronic cough in up to 21% of patients. The increased yield is accounted for by patients with GERD without reflux symptoms prior to the onset of cough.

In children, the prevalence of GERD as a cause of chronic persistent cough is 15-19 (Grade II-3). In infants and children under age 16 with normal chest radiographs, GERD was a common cause of cough, following only asthma and sinusitis in frequency.

Clinical Presentation: Apart from cough, the clinical presentation of GERD in adults is dependent on the underlying pathogenesis. The most common clinical syndrome appears due to vagally mediated distal esophageal-tracheobronchial reflex mechanisms. In these patients, GER symptoms such as heartburn, sour taste, and regurgitation are unusual. Between 50 and 75% of patients (Grade II) have no reflux symptoms, while the remainder have symptoms only after the development of cough. In one study, cough was the sole presenting manifestation of GERD in nine patients. The cough occurred predominantly during the day and in the upright posture, with minimal nocturnal symptoms. This likely results from preservation of the normal esophageal function, which suppresses TLESR when supine. The cough is usually unproductive and often long-standing, with a mean duration of 13 to 58 months. The majority of patients recall its onset after an upper respiratory tract infection. It can, however, be associated with a history of excessive sputum production. There is also evidence to suggest that chronic cough from any cause may precipitate GERD via the cough-reflux self-perpetuating cycle, and thus GERD should be suspected as a contributory cause of cough in any patient with persistent symptoms even when another specific diagnosis is made.

In patients with microaspiration, GI symptoms of GERD are more prominent and may predominate the onset of cough. Laryngeal symptoms such as dysphonia, hoarseness, and a sore throat are also prominent, and laryngoscopic findings may be abnormal. Patients with pulmonary macroaspiration syndromes may present with cough in association with a wide spectrum of other respiratory symptoms, including purulent sputum, wheeze and dyspnea, hemoptysis, and chest pain. Unexplained nocturnal fevers and night sweats may be due to aspiration. Dysphagia and choking while eating may be indications of esophageal motility disorders. GI symptoms are prominent, especially heartburn, water brash, and oral regurgitation, and are worse in the supine position.

Children present in similar fashion to adults, although GER symptoms may be more prominent. Cough as the sole manifestation of GERD is less common, perhaps due to the relative incompetence of the LES, which matures with increasing age. Associated symptoms found more frequently in children include irritability and chest pain. Apnea, bradycardia, and attacks of unusual posturing have also incidentally been related to reflux. There is also a higher incidence of microaspiration with associated hoarseness and wheeze. In children with gross aspiration, there may be failure to thrive, bronchopulmonary dysplasia, and retardation of development.

Diagnosis: The diagnosis of GERD as the cause of cough can only be made with certainty when cough goes away with specific antireflux therapy. In patients with typical GI symptoms, 24-h ambulatory esophageal pH monitoring is the most sensitive and specific test of GERD, with up to 96% sensitivity and specificity. Less effective investigations include esophagoscopy, acid perfusion or Bernstein test, radiologic imaging of the esophagus, esophageal radionuclide studies including reflux scintiscanning, and esophageal manometry. Genuine symptomatic reflux can occur in the absence of macroscopic damage seen at esophagoscopy.

In patients with unexplained chronic cough and no other symptoms, the initial investigation of choice to assess for GERD is 24-h ambulatory esophageal pH monitoring. In addition to being the most sensitive test for pathologic reflux indices, it also gives a temporal relationship between cough and reflux, as well as quantifying the degree of reflux. In two prospective studies, 24-h esophageal pH monitoring had positive predictive values of 89 to 100% and negative predictive values of 100% in diagnosing GERD as the cause of chronic cough. It may be the only method of diagnosing GERD in up to 32% of patients with chronic cough. In interpreting the results of esophageal pH monitoring, it is essential not only to record the severity and frequency of reflux episodes, but also to determine the temporal relationship between reflux and cough episodes. Patients with normal standard reflux parameters may still have acid reflux diagnosed as a cause of cough if a clear temporal relationship exists. In one prospective study, patients with chronic cough due to GERD more frequently had GER-induced coughs noted on 24-h pH monitoring than abnormal...
In patients with suspected GERD, empirical therapeutic trials are common to the diagnosis of chronic cough. Given the frequency of GERD as a potential cause of cough and the inability to perform prolonged esophageal pH monitoring in some settings, a trial antireflux regimen is reasonable in patients with chronic cough that remains unexplained after a systematic diagnostic protocol. If there are no GI symptoms. However, if treatment fails, full investigation of GERD is then recommended since medical treatment may not have been intense enough or may have failed.

Treatment: The objective of therapy is to decrease the frequency and duration of reflux events and decrease the irritative nature of gastric secretions.

Conservative measures should be tried in all patients: weight reduction, a high-protein, low-fat antireflux diet that eliminates foods and beverages with low pH that have the potential of decreasing LES tone, elevation of the head of the bed, and lifestyle measures such as avoiding coffee and smoking. These measures, in addition to prokinetic agents and/or H2 antagonists, resulted in the resolution of cough in 70 to 100% of adult patients, although mean time to recovery was relatively long at 161 to 179 days (Grade II-2, II-2). In patients who failed to respond to this therapy, antireflux surgery including fundoplication has been successful (Grade II-3).

H2 antagonists have been the most widely studied antireflux medications in patients with GERD and chronic cough (Table 5). Therapy with cimetidine and ranitidine have been most commonly reported, although most studies also use conservative measures. Treatment regimens using H2 antagonists produced response rates of 80 to 84%, with inconsistent correlation between 24-h ambulatory esophageal pH monitoring results and response. Also no important difference in pH monitoring results between partial and complete responders has been reported. The antitussive and antireflux effects of H2 antagonists were prolonged: both cough symptoms and reflux parameters as measured by repeat 24-h esophageal monitoring were significantly suppressed for more than 6 weeks after the drug was stopped. This implies that H2 antagonists break the cough-reflux self-perpetuating cycle in patients due to the distal esophageal-tracheobronchial reflex mechanism.

In patients with suspected GERD whose cough does not respond to conservative measures and H2 antagonists, repeat 24-h ambulatory esophageal pH monitoring or treatment is indicated to determine if therapy was successful in reducing GER events. Upper GI endoscopy may also be indicated to exclude mucosal complications. If pathologic GER events are still persistent, more profound acid suppression may be required. Proton-pump inhibitors including omeprazole and lanoprazole have been tried with anecdotal success. Theoretically, these agents may be more efficacious; however, no prospective or retrospective trials have been published utilizing these medications for chronic cough due to GERD.

Prokinetic agents including cisapride and domperidone have also been given investigatively for cough in patients with proven GERD, mostly children with nocturnal cough and possible microaspiration. Response rates for cough were between 64.5 and 100%, (Grade II-2, II-2). No difference was detected between cisapride and domperidone with regard to clinical response or resolution of GERD. Although not proven in adults, it would seem appropriate for prokinetic agents to be used in patients with cough and documented impaired esophageal clearance or motility, including patients suspected of having microaspiration.

Antireflux surgery, including open or laparoscopic fundoplication, is generally reserved for patients with proven GERD who have failed to respond to medical treatment, including high-dose proton-pump inhibitors. It may also be indicated in patients with continuing micro- or macroaspiration (including those with recurrent aspiration pneumonia) who fail to respond to appropriate dietary measures, prokinetic agents, and proton-pump inhibitors. One prospective study of fundoplication found that chronic respiratory symptoms (including cough) due to GERD improved after surgery only if normal esophageal motility had been documented beforehand (Grade II-2). Other studies found that surgery raises LES tone significantly, returns repeat 24-h ambulatory esophageal pH monitoring parameters to normal, and abolishes aspiration secondary to esophageal motor disorders. Clinical symptomatic improvement in patients with cough and aspiration following fundoplication has been reported in 45 to 84% of patients with follow-up periods of 3 to 18 months.

Summary Statement:

- GERD, along with asthma and PNDS, is one of the three most common causes of chronic cough in both adult (Grade II-2) and pediatric populations (Grade II-3).
- While GERD can cause cough by aspiration, it most likely causes chronic cough in patients with normal chest radiographs by a vagally mediated distal esophageal-tracheobronchial reflex mechanism (Grade II, II-2).
- When GERD is the cause of chronic cough, there may be no GI symptoms up to 75% of the time (Grade II-2).
- A cough-reflux self-perpetuating cycle is likely to exist whereby cough from any cause may precipitate further reflux (Grade III). Therefore, in managing patients with chronic cough, consideration should be given to breaking this cycle.
- The most sensitive and specific test for GERD is 24-h esophageal pH monitoring.
<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
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<th>Study Design</th>
<th>No. of Patients</th>
<th>Treatment</th>
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<td>147</td>
<td>52±11 yrs</td>
<td>Prospective, unblinded,</td>
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<td>Conservative, metoclopramide and/or (H_2) antagonists</td>
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<td>Time to response = 161±74 d (p=0.029 for cough reductions; p=0.001 for reflux reduction)</td>
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<td>Time to response = 179±205 d</td>
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<td>Prospective, unblinded,</td>
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<td>Relapse in 20%</td>
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<td>70% (after 3 mos)</td>
<td>4 pts (20%) required fundoplication</td>
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<td>Conservative, (H_2) antagonists, proton pump inhibitors</td>
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<td>Only pts without heartburn had full resolution of cough</td>
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<tr>
<td>Dordal, 1994</td>
<td>205</td>
<td>Infants</td>
<td>Prospective, unblinded,</td>
<td>55</td>
<td>Cisapride, domperidone</td>
<td>64.5%</td>
<td>No significant difference between cisapride and domperidone</td>
<td>II-2</td>
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<td></td>
<td></td>
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<td>uncontrolled</td>
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<tr>
<td>DuPont, 1989</td>
<td>206</td>
<td>1 mo to 12.7 yrs</td>
<td>Prospective, unblinded,</td>
<td>18</td>
<td>Domperidone</td>
<td>100%</td>
<td>No side effects recorded (p&lt;0.05 for reflux and cough scores)</td>
<td>II-2</td>
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<td></td>
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<td>uncontrolled</td>
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<tr>
<td>Smyrnios, 1995</td>
<td>115</td>
<td>Adult, 58±17 yrs</td>
<td>Prospective, unblinded,</td>
<td>20</td>
<td>Conservative, (H_2) antagonists±prokinetic agent</td>
<td>97% overall</td>
<td>Cough with excess sputum</td>
<td>II-2</td>
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<td>uncontrolled</td>
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<tr>
<td>De Meester, 1990</td>
<td>181</td>
<td>Adult</td>
<td>Prospective, unblinded,</td>
<td>17</td>
<td>Fundoplication</td>
<td>100% only if normal motility</td>
<td>No response in those whose respiratory symptoms induced GER</td>
<td>II-2</td>
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<td>uncontrolled</td>
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<tr>
<td>Pellegrini, 1979</td>
<td>155</td>
<td>Adult</td>
<td>Prospective, unblinded,</td>
<td>5</td>
<td>Fundoplication</td>
<td>100% selected patients</td>
<td>Only 5/100 pts with GER considered suitable</td>
<td>II-2</td>
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<td>uncontrolled</td>
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<tr>
<td>Giudicelli, 1990</td>
<td>207</td>
<td>Adult</td>
<td>Prospective, unblinded,</td>
<td>13</td>
<td>Fundoplication</td>
<td>84.6%</td>
<td>13/140 pts with GER considered suitable</td>
<td>II-2</td>
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<td>uncontrolled</td>
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*pts=patients
Chronic Bronchitis

Definition, Prevalence, and Clinical Presentation: CB, one of the two main entities (with emphysema) described as COPD, is among the most frequent causes of chronic cough,\textsuperscript{206,209} in the community. However, in series of patients who sought medical attention for cough, CB was the cause in approximately 5% of cases\textsuperscript{3,4} (Grade II-2). Recurrent productive cough is included in the description of CB, defined as the presence of cough and phlegm production on most days over a period of at least 3 months and for more than 2 consecutive years in a patient in whom other causes of chronic cough have been excluded.\textsuperscript{210} In CB, cough is primarily evident in the morning but may occur at night during exacerbations.

Diagnosis: In diagnosing CB as the cause of cough, the history is most important. CB is unlikely in nonsmokers without significant long-term exposure to dusts or fumes. On examination, the typical patient is a blue bloater, generally a man in his 60s with a history of productive cough lasting more than 10 years, with peripheral edema, obesity, and central cyanosis.\textsuperscript{211} This represents the severe end of the disease spectrum, while milder forms of CB are more prevalent, although less often detected.

Pathogenesis of Cough in CB: In patients with CB, cough is induced by inhalation of irritants, particularly tobacco smoke. Smoke can induce airway inflammation and mucus hypersecretion and impair mucociliary clearance, all conditions that may activate the afferent limb of the cough reflex and trigger cough.\textsuperscript{46,212} In CB, cough may therefore result from the underlying chronic airway inflammation but also from the need to eliminate large volumes of bronchial secretions. Because mucus clearance is slow in these patients compared with normal subjects, cough is a useful addition in helping to clear secretions, even when it seems nonproductive.\textsuperscript{75,213,214} Respiratory infections, which are associated with an increase in inflammation and phlegm production, will exacerbate cough.

Treatment: The specific therapy of cough due to CB is removal of environmental irritants such as cigarette smoke. For those patients who seek medical attention complaining of cough, smoking cessation has been nearly uniformly successful.\textsuperscript{3,4} Cough has been shown to disappear or markedly decrease in 94 to 100% of patients after smoking cessation; 54% of the time, cough resolution occurred within 4 weeks.\textsuperscript{215} Bronchodilators such as \(\beta_2\)-agonists and theophylline\textsuperscript{216} have not been evaluated for cough suppression in COPD. On the other hand, ipratropium can decrease sputum production and cough in this condition\textsuperscript{217} (Grade I), although it does not seem to have beneficial effects on cough clearance of mucus.\textsuperscript{217,218}

Corticosteroids may theoretically contribute to reduced cough by reducing sputum production and airway inflammation, but their specific effect on cough in chronic bronchitis has not been specifically assessed.\textsuperscript{219} This is also true for antibiotics, which can help reduce overall respiratory symptoms in the presence of bronchial infection.\textsuperscript{220}

Regarding mucokinetic agents, iodopropylidene glycerol has been reported to reduce cough frequency\textsuperscript{221} (Grade II), and a multicenter, double-blind, placebo-controlled, parallel-design study on organic iodide showed a reduction in cough frequency and severity in stable patients with COPD\textsuperscript{222} (Grade I), but these effects were considered to be insufficient and marketing of the drug was discontinued.
Complications and Other Considerations: The most frequent complication of CB is respiratory infection, which will lead to an increase in phlegm production and cough. If bacterial, it is frequently due to *H influenzae* or *S pneumoniae*. It should also be kept in mind that when the character of the cough changes for prolonged periods in patients with COPD, the possibility of underlying bronchogenic carcinoma or another complication should be considered.

**Summary Statement:**

- Cough is one of the main features of CB and is provoked by inhalation of irritants, airway inflammation, mucus hypersecretion, and impaired mucociliary clearance.
- While most smokers have a chronic cough, they are not the group of patients who most commonly seek medical attention complaining of cough (Grade II-2).
- Treatment of cough should mainly target a reduction of sputum production and airway inflammation by removing environmental irritants, particularly smoking cessation (Grade II). Ipratropium can decrease sputum production and cough (Grade I). Nonspecific cough suppressants should be avoided and mucolytics are of uncertain benefit. Although the effectiveness of corticosteroids and antibiotics on cough have not been specifically studied, they are likely to be helpful in decreasing cough during exacerbations of COPD (Grade III).

**Bronchiectasis**

Cough is a cardinal symptom of bronchiectasis. Because recent reviews update current understanding of this disease, this summary concentrates on cough as a symptom and its treatment.

**Definition:** Bronchiectasis is defined by abnormal pathology of the airways, mainly subsegmental bronchi. The abnormalities include simple dilatation of the bronchi without loss of bronchial contour (cylindrical bronchiectasis), patchy destruction of cartilage leading to irregular bronchial outline with abnormal dilatations and constrictions (varicose bronchiectasis), and ballooning of bronchial remnants forming cysts frequently filled with purulent material (cystic bronchiectasis).

**Pathogenesis:** The pathogenesis of bronchiectasis involves interaction between the insult (inhalational, severe childhood infections, or aspiration) and the disorder of host defenses. The resulting inflammatory response sets up a vicious circle of progressive airway damage, beginning with impairment of bronchial clearance that leads to chronic colonization of the airways by microorganisms. The resulting inflammatory response eventually becomes overwhelmed by the persistent bacterial flora. The mediators released during this process cause damage to the mucociliary transport mechanism, leading to further impairment of the clearance mechanism, further colonization of the respiratory tract, more inflammation, weakening of the elastic support, and progressive destruction of the airway wall. Whether the etiologic factors are inherited (eg, CF) or acquired (eg, poorly treated recurrent infections), and whether the abnormality is diffuse or localized to a particular segment or lobe, the final common pathway leading to fully developed bronchiectasis is chronic infection.

**Prevalence:** Although there are no reliable data regarding the prevalence of bronchiectasis, the general consensus is that it is low and decreasing. This is likely due to the reduction in the major etiologic factors of bronchiectasis—multiple recurrent childhood infections, and poorly treated chronic infections such as TB, which used to be one of the most common causes of bronchiectasis. As a cause of chronic cough, bronchiectasis has been diagnosed in prospective studies with a frequency of approximately 4%. CF is the most common cause of childhood bronchiectasis in North America. Bronchiectasis in children can also follow severe pneumonia, retained foreign body, hydrocarbon aspiration, and primary ciliary dyskinesia syndromes.

**Clinical Presentation:** The cardinal symptom is chronic cough with production of sputum; some patients may have dry cough (bronchiectasis sicca). Most patients will produce sputum on a chronic basis, sometimes in copious amounts. The sputum is usually mucoid or mucopurulent, becoming frankly purulent during an exacerbation. At all times it is thick, tenacious, and difficult to expectorate. While a history of excessive sputum production is typical of bronchiectasis, it is not specific. It is more commonly associated with PNDS, asthma, GERD, and bronchitis. The bronchial tree is chronically colonized and this is reflected in the bacterial cultures of the sputum, which grow a variety of microorganisms. The most commonly found pathogens include *H influenzae*, *S aureus*, various strains of *Pseudomonas aeruginosa* (commonly seen in patients with CF), anaerobic bacteria, Aspergillus, Nocardia, and mycobacteria. Some patients may present initially with hemoptysis, although more commonly hemoptysis occurs during an exacerbation of bronchiectasis. Wheezing is another common finding; few patients have fully developed airway hyperresponsiveness documented by positive methacholine challenge tests. Some patients, particularly those with CF, have chronic constitutional symptoms (tiredness, fatigue, poor appetite, weight loss). In addition to wheezing, infants with CF typically present with symptoms of recurrent respiratory infections, poor weight gain, and large, foul-smelling bowel movements containing oil and grease. In these infants the cough may be mild and associated with intermittent wheezing and hyperinflation on a chest radiograph, or it may be life-threatening when associated with cyanosis and severe bronchiolitis-like syndromes.

**Diagnosis:** Although the definition of bronchiectasis is a pathologic one, the diagnosis is usually made by clinical history, suggestive chest radiographic changes (eg, crowded markings, increase in size and loss of definition of segmental markings), and imaging of the lungs. The
optimal method for evaluating patients suspected of having bronchiectasis is high-resolution chest CT (Grade II), which has a sensitivity of 60 to 100% and a specificity of 92 to 100%. Bronchography, which for many years was considered to be the gold standard of diagnosis, is employed very seldom, usually for specific surgical indications. Flexible bronchoscopy is not necessary for the diagnosis of bronchiectasis, but is usually performed for therapeutic reasons, such as during an exacerbation to facilitate removal of secretions, or for investigation of hemoptysis (although there is evidence that even in this case CT may be superior), or to rule out an obstructive lesion. The sweat test remains the gold standard for diagnosing CF and should be performed in children of any age with ill-defined respiratory complaints without clear etiology, even in the absence of pancreatic insufficiency. Sweat testing should also be performed in children and adults in the presence of digital clubbing.

Treatment: The cough of bronchiectasis partially serves a useful function by facilitating clearance of excessive mucus. It becomes a symptom requiring treatment mainly during exacerbations. While cough associated with flares can be successfully treated, it is not realistic to expect that it can be totally eliminated as a recurrent problem. Treatment of bronchiectasis consists of chest physiotherapy (with or without antibiotics), other maneuvers designed to mobilize secretions, and surgery. Two prospective, descriptive studies specifically examined the effect of antibiotics, chest physiotherapy, and drugs to stimulate mucociliary clearance (e.g., β2-agonists, theophylline) on cough, concluding that the cough of bronchiectasis can be successfully treated in all patients; however, a total of only 10 patients with bronchiectasis was seen in both studies.

Chast physiotherapy, consisting of vibration, percussion, postural drainage, directed cough, and forced expiration technique, has been examined in five studies (Table 6). None were prospective, there was no patient randomization, only the immediate effect of physiotherapy was studied, sample sizes were small, patient populations were heterogeneous, and cough was not assessed as an independent outcome measure. All of the studies found that chest physiotherapy increased the amount of expectorated sputum, but had no effect on FEV1. Forced expiration technique combined with postural drainage appeared to mobilize sputum better than vibration and percussion alone. Chest physiotherapy was beneficial only for patients who produced large volumes of sputum (more

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Age, yrs</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Result</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane, 1977</td>
<td>231</td>
<td>18-62</td>
<td>CS</td>
<td>23 cases:</td>
<td>One 30-min session of V+P=PD</td>
<td>Lung volumes, airway resistance, specific conductance, spirometry, sputum volume</td>
<td>1. 18% increase in specific conductance (p&lt;0.05)</td>
<td>II-2</td>
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<td>10 B</td>
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<td></td>
<td>2. No difference in FEV1</td>
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<td></td>
<td></td>
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<td>11 CF</td>
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<td></td>
<td>3. Sputum volume measured but not reported</td>
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<tr>
<td>Sutton, 1983</td>
<td>92</td>
<td>19-60</td>
<td>CS, C</td>
<td>10 cases:</td>
<td>One 30-min session of a) control</td>
<td>Spirometry, sputum volume, radioaerosol clearance</td>
<td>1. No difference in FEV1</td>
<td>II-2</td>
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<td>5 B</td>
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<td>2. FET (with or without PD) eliminated radioaerosol best</td>
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<td>4 CF</td>
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<td>3. FET+PD results in highest volume of sputum</td>
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<tr>
<td>Marzocco, 1985</td>
<td>232</td>
<td>31-68</td>
<td>CS, C</td>
<td>13 cases:</td>
<td>One 10-min session of a) control</td>
<td>Spirometry, oxygen saturation, sputum volume</td>
<td>1. No difference in FEV1</td>
<td>II-2</td>
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<td></td>
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<td>all B</td>
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<td>2. Physiotherapy resulted in expectation of 19% (range; 2 to 50%) of daily sputum production</td>
<td></td>
</tr>
<tr>
<td>Sutton, 1985</td>
<td>233</td>
<td>48±11</td>
<td>CS, C</td>
<td>8 cases:</td>
<td>One 30-min session of a) control</td>
<td>FEV1, radioaerosol clearance, sputum volume</td>
<td>1. No difference in FEV1</td>
<td>II-2</td>
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<td></td>
<td></td>
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<td>5 B</td>
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<td>2. No difference in aerosol clearance</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2 CB</td>
<td></td>
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<td>3. PD+P+FET resulted in highest amount of sputum production</td>
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<td></td>
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<td>1 CF</td>
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<tr>
<td>Gallon, 1991</td>
<td>234</td>
<td>22-58</td>
<td>CS, C</td>
<td>9 cases:</td>
<td>Three wks of daily sessions of a) control+PD +DBE+FET</td>
<td>Spirometry, oxygen saturation, sputum volume</td>
<td>1. No difference in FEV1</td>
<td>II-2</td>
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<td>all B</td>
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<td>2. Fast P results in highest rate of sputum production</td>
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</table>

*A=*asthma; **B=*bronchiectasis; **C=*control session included; **CB=*chronic bronchitis; **CF=*cystic fibrosis; **CS=*case control; **DBE=*deep breathing exercises; **DC=*directed coughing; **FET=*forced expiration technique; **P=*percussion; **PD=*postural drainage; **PFT=*pulmonary function tests; **V=*vibration
than 20 to 30 mL in 24 h) during an acute exacerbation or chronically, rather than for all patients with a diagnosis of bronchiectasis.235-237

In two randomized, placebo-controlled, double-blind studies, cough (along with sputum volume and pulmonary function) was assessed when chest physiotherapy was supplemented by the use of bromhexine236 and beclomethasone.237 Neither of these drugs was shown to decrease cough frequency or severity.

The rationale for using antibiotics238,239 to treat patients with bronchiectasis probably dates back to the British MRC trial of long-term tetracycline238 in patients with severe bronchiectasis, which showed mild improvement in symptoms, including cough. There are three studies240-242 (Grade I, II-2, II-3) documenting the efficacy of antibiotics, only one which was placebo-controlled242 (Grade I); see Table 7. Based on the available information, the following recommendations can be made: (1) the antibiotic must be active against H influenzae, S aureus, or Pseudomonas; (2) initial therapy should be continued for at least 2 weeks; (3) if there is no improvement or rapid recurrence, a longer course of treatment lasting up to 4 months may be required. The role of inhaled antibiotics, particularly in non-CF bronchiectasis, has not been studied; however, in CF patients, aerosolized antibiotics have been shown to be effective244 (Grade I).

Surgical treatment of bronchiectasis is seldom used today, simply because most patients are managed well with medical treatment, have widespread disease, or are poor surgical candidates. However, if persistent localized pulmonary suppuration is present, requiring frequent hospitalizations and interfering with a patient’s quality of life, surgery should be considered. Given present surgical and anesthetic techniques, the risk of complications is low. The efficacy, judged by the earlier surgical series, is quite good, reaching up to 85%,242,243 Lung transplantation, currently performed in some patients with CF and in a few patients with non-CF bronchiectasis, is too recent a procedure to be evaluated at this time.

### Summary Statement:

- As a cause of chronic cough, bronchiectasis has been diagnosed in prospective studies with a frequency of approximately 4%,4,115 (Grade II-2). Its diagnosis is established by compatible clinical history, chest radiograph, high-resolution CT scan of the thorax, and cough disappearance with specific therapy. Cough associated with flares of the disease can be treated successfully with a combination of chest physiotherapy, drugs to stimulate mucociliary clearance, and systemic antibiotics (Grade II). Aerosolized antibiotics have been shown to be effective in CF patients with bronchiectasis (Grade I), but their use in non-CF patients is not recommended.

### Postinfectious Cough

**Definition and Prevalence:** When patients complain of chronic cough only after a respiratory tract infection and have normal chest radiographs, some authors have referred to these coughs as postinfectious in causation119-121 (Grade II-3, II). An important part of the definition of postinfectious cough is that it eventually resolves, seemingly on its own.

In adults, postinfectious cough has been reported with variable frequencies. In retrospective studies of unselected patients with a history of preceding upper respiratory tract infection, the frequency has ranged from 11 to 25%.119-121 During outbreaks of obvious infection with mycoplasma and Bordetella pertussis infections, the frequency of postinfectious cough increases to 25 to 50% in selected series.245 In four prospective studies of unselected patients,3,4,115,117 many of whom had a history of preceding upper respiratory tract infection, postinfectious cough was not diagnosed. The explanation for this variable frequency is not clear; it may relate to differences in study populations.

In children, while the specific infection causing chronic cough in most cases remains unidentified, respiratory viruses (particularly respiratory syncytial virus and parainfluenza), Mycoplasma pneumoniae, Chlamydia pneumoniae strain TWAR, and B pertussis have all been implicated246-248 (Grade II-3). Children have an average of six to eight respiratory infections per year, and children with siblings or in day-care have even more infections per year.246 Back-to-back infections, which are particularly common in winter months, can frequently result in a chronic cough.

Infants with a Chlamydia trachomatis infection are afebrile and typically present with tachypnea and a high-pitched, staccato, nonproductive cough that begins around 4 weeks of age; 50% of these infants have a history of conjunctivitis.249 Infants with chlamydia may cough for several weeks, even after therapy with erythromycin. B pertussis and pertussis-like viral infections can result in a cough that has been nicknamed the 100-day cough.250 Complete immunization is not protective for all children and many children are incompletely immunized. Other infections occurring in an afebrile infant with crackles on auscultation include Ureaplasma urealyticum, cytomegalovirus, and Pneumocystis carinii.251,252 M catarrhalis (formerly Branhamella) can also produce cough and lower respiratory tract disease, especially in young children with lung disease.251 Measles causes a cough with coryza, conjunctivitis, and fever.249 In the immunized patient, atypical measles is more likely to cause cough or pneumonia than the usual rash.

**Pathogenesis:** While the pathogenesis of the postinfectious cough is not known, it has been thought to be due to airway inflammation with or without transient airway hyperresponsiveness252-254 (Grade II, II-2).

**Diagnosis:** The diagnosis of postinfectious cough is clinical and one of exclusion. A careful history and sometimes the physical examination may provide clues to the diagnosis. The cough is usually self-limited and should resolve in time. When M pneumoniae infection is sus-
### Table 7—Effect of Antibiotics in Bronchiectasis

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Age, yrs</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Result</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Hill, 1988</td>
<td>240</td>
<td>29-76</td>
<td>CS, B/A</td>
<td>33 cases: 27 completed</td>
<td>Amoxicillin 750 mg/d for 14 d; if no response, amoxicillin 6 g/d for 14 d</td>
<td>Sputum appearance, sputum volume, symptoms</td>
<td>1. Sputum clearance achieved in 60% with low dose, and in 90% with high dose</td>
<td>II-3</td>
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<td>2. Significant reduction in cough</td>
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<td>Currie, 1990</td>
<td>241</td>
<td>21-70</td>
<td>CS, B/A</td>
<td>10 cases</td>
<td>Amoxicillin 6 g/d for 4 mos (in 3 pts); amoxicillin 750 mg/d for 4 mos (in 2 pts); amoxicillin 1 g/d (inhaled) for 4 mos (in 5 pts)</td>
<td>Sputum appearance; sputum volume, symptoms, sputum bacteriology, sputum &amp; serum biochemical markers</td>
<td>1. Sputum clearance achieved in all pts</td>
<td>II-2</td>
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<td>2. Significant improvement in cough and sputum volume</td>
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<td>3. No difference in sputum bacteriology</td>
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<td>4. Transient reduction in biochemical markers</td>
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<tr>
<td>Le Roux, 1986</td>
<td>242</td>
<td>20-81</td>
<td>R, PC, DB</td>
<td>38 cases: 19 completed</td>
<td>Amoxicillin 6 g/d for 32 wks; follow-up for 20 additional wks</td>
<td>Sputum appearance, sputum volume, symptoms, sputum bacteriology, sputum &amp; serum biochemical markers, FFT side-effects, chest radiographs</td>
<td>1. 65% clinical improvement vs 21% with placebo</td>
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<td>2. Significant reduction in sputum volume</td>
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<td>3. Reduction in the severity of exacerbations</td>
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<td>4. Improvement in biochemical markers</td>
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<td>In both groups:</td>
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<td>1. No difference in sputum bacteriology</td>
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<td>2. No difference in frequency of exacerbations</td>
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<td>3. No difference in FEV₁</td>
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<td></td>
<td>4. No change in chest radiographs</td>
<td></td>
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</tbody>
</table>

*B/A=before and after treatment; CS=cross-sectional; DB=double-blind; PC=placebo-controlled; PFT=pulmonary function testing; pts=patients; R=randomized
PECTED, AS IN SCHOOL-AGED CHILDREN OR YOUNG ADULTS, PARTICULARLY MILITARY RECRUITS, IN THE LATE SUMMER OR FALL, A HIGH COLD AGGLUTININ TITER OR ACUTE AND CONVALESCENT SPECIFIC SEROLOGIC STUDIES MAY HELP TO CONFIRM THE DIAGNOSIS.

PERTUSSIS CAN PRESENT IN A VARIETY OF WAYS. THE ADULT WITH PERTUSSIS MAY COMPLAIN OF SHORTNESS OF BREATH AND A TINGLING SENSATION IN THE THROAT. IN CHILDREN YOUNGER THAN 2 YEARS OF AGE, VOMITING OR APNEA IS MORE COMMON THAN THE TYPICAL WHOOP.240 A HISTORY OF CONTACT WITH A KNOWN CASE OF PERTUSSIS IS VERY IMPORTANT. THE COUGH TENDS TO BE SPASMODIC AND OCCUR MORE FREQUENTLY AT NIGHT; IT USUALLY LASTS 4 TO 6 WEEKS, BUT CAN PERSIST FOR LONGER. THE CHARACTERISTIC WHOOP IS USUALLY ABSENT AND LENKOCYTOSIS AND LYMPHOCYTOSIS, THOUGHT TO BE TYPICAL, ARE FREQUENTLY NOT SEEN.255,256 B. PERTUSSIS-SPECIFIC SERUM ACUTE IGA ANTIBODY BY ENZYMELINKED IMMUNOSORBENT ASSAY IS A SENSITIVE TEST FOR DIAGNOSIS, AND CAN DISTINGUISH BETWEEN A RESPONSE TO NATURAL INFECTION AND THAT FROM PRIOR IMMUNIZATION.255,256 IN MANY PLACES, HOWEVER, THIS IS AVAILABLE ONLY AS A RESEARCH TOOL. BOTH IMMUNOFLOUORESCENT VISUALIZATION AND/OR ISOLATION OF THE ORGANISM BY CULTURE OF THE NASOPHARYNGEAL SECRETIONS ARE USUALLY NEGATIVE IN THE ADULT. WHILE SEROLOGIC DIAGNOSIS FOR C. TRACHOMATIS STRAIN TWAR IS POSSIBLE, THE TEST IS EXPENSIVE AND NOT WIDELY AVAILABLE.

TREATMENT: POSTINFECTIOUS COUGH IS SELF-LIMITED AND WILL USUALLY RESOLVE IN TIME. BASED UPON THE SPECULATION THAT THE POSTINFECTIOUS COUGH IS DUE TO INFLAMMATION, SOME AUTHORS IN UNCONTROLLED STUDIES HAVE SUCCESSFULLY TREATED THE COUGH WITH A BRIEF COURSE OF CORTICOSTEROIDS STARTING WITH 30 TO 40 MG OF PREDNISONE (OR EQUIVALENT) IN THE MORNING, TAPERING TO ZERO OVER 2 TO 3 WEEKS FOR THOSE PATIENTS WHOSE COUGHS BECOME PROTRACTED AND PERSISTENTLY TROUBLESOME.159,257 (GRADE II-3). IT IS REASONABLE TO TRY AN INHALED CORTICOSTEROID IF TOLERATED AND THE COUGH IS NOT SEVERE (GRADE III), BUT DATA TO SUPPORT THIS APPROACH ARE LACKING. IPRATROPium HAS ALSO BEEN SHOWN TO ATTENUATE POSTINFECTIOUS COUGH.255 (GRADE I). ON OCCASION, ANTITussives HAVE BEEN ADDED (GRADE II-3). INHALED CORTICOSTEROIDS (GRADE III) OR IPRATROPium (GRADE I) MAY ALSO ATTENUATE THE COUGH.


**Summary Statement:**

- The diagnosis of postinfectious cough is clinical and one of exclusion. It should be considered when patients complain of cough only after a respiratory tract infection and have normal chest radiographs.
- Postinfectious cough ultimately resolves in time, but on occasion appears to respond to a brief course of an oral corticosteroid (Grade II-3). Inhaled corticosteroids (Grade III) or ipratropium (Grade I) may also attenuate the cough.
- The infection causing the cough in most cases remains unidentified but respiratory viruses, *M. pneumoniae*, *C. pneumoniae* strain TWAR, and *B. pertussis* have been implicated in the adult. In infants and children, respiratory viruses, *C. trachomatis*, *U. urealyticum*, cytomegalovirus and *P. carinii* may be the cause of a persistent cough.

**Bronchogenic Carcinoma**

**Definition:** Bronchogenic carcinoma is a term usually applied to primary malignant neoplasms of the airways of the lung: squamous cell carcinoma (also called epidermoid carcinoma), adenocarcinoma, small cell carcinoma (also called oat cell carcinoma), large cell carcinoma, and adenosquamous carcinoma.

**Etiology:** Tobacco smoking is the cause of approximately 85% of the cases of bronchogenic carcinoma. The risk of developing bronchogenic carcinoma increases with duration of smoking and the quantity of tobacco smoked per day. A subtype of adenocarcinoma known as bronchoalveolar carcinoma is considered to be unrelated to tobacco smoking. Important occupational exposures that are known to increase the risk for developing bronchogenic carcinoma include exposure to asbestos, uranium, radon gas, and other chemicals. Other factors suspected to increase the risk of lung cancer include exposure to second-hand smoke, familial tendencies, dietary influences, COPD, and chronic scarring of lung.

**Pathogenesis:** Cough is thought to occur when cough receptors are irritated by the endobronchial process. Those patients with bronchogenic carcinoma who never complain of cough likely have more peripheral tumors arising from smaller bronchi and bronchioles, where cough receptors are few in number or even absent.

**Prevalence:** While cough is generally regarded as a common symptom associated with bronchogenic carcinoma, bronchogenic carcinoma is not a common cause of chronic cough.3,4,115,116,119-121 Multiple studies have shown that bronchogenic carcinoma is the cause of chronic cough from 0 to 2% of the time.

**Clinical Presentation:** Squamous cell and small cell carcinomas tend to occur in the more central airways and thus are more likely to produce symptoms such as cough (with or without sputum), hemoptysis of varying degrees, and wheezing from bronchial obstruction. Although the frequency of cough in bronchogenic carcinoma varies on initial presentation from 21 to 87%, it occurs in 70 to 90% of cases.
Cough as a presenting symptom of lung cancer may be ignored by patients who are smokers and by physicians because cough is present in most smokers. Hemoptysis in bronchogenic carcinoma may signify bleeding from an endobronchial tumor or cavitated neoplasm in the pulmonary parenchyma. While expectoration of more than 100 mL of thin serous sputum in a 24-h period is suggestive of bronchogenic carcinoma, most patients with this condition will have an unproductive cough. Adenocarcinoma is more likely to occur in the periphery of the lung and thus may remain asymptomatic for longer periods.

**Diagnosis:** Bronchogenic carcinoma should be considered a potential cause of chronic cough in all patients, but especially in present and prior cigarette smokers and those patients who have had occupational exposures that place them at increased risk for the disease. In evaluating bronchogenic carcinoma as the cause of cough, chest radiographs, sputum cytology, and fiberoptic bronchoscopy are the most important initial tests to consider. The testing characteristics of chest radiographs and fiberoptic bronchoscopy in diagnosing the cause of chronic cough have been reported in two prospective, descriptive studies.\(^{115}\) (Grade II-2). There were very few subjects who ever smoked in both studies. Chest radiographs had a positive predictive value of 36% and 38% and a negative predictive value of 100%; bronchoscopy had a positive predictive value of 50% and 89% and a negative predictive value of 100%. Consequently, in nonsmokers, when chest radiographs are normal or show nothing more than a stable, inconsequential scar, bronchogenic carcinoma is so unlikely that other causes of cough preferentially should be actively pursued. However, when chest radiographs are abnormal and suggest bronchogenic carcinoma, sputum cytology and bronchoscopy should be performed. Because epidemiologic data reveal that coughs that develop for the first time and last for months, or that change in character in chronic cigarette smokers, are suggestive of bronchogenic carcinoma, it is reasonable to proceed with sputum cytology and bronchoscopy in this setting when cough has not gone away with cessation of smoking for 4 weeks, even when chest radiographs are normal.\(^ {262,264}\)

**Treatment:** The treatment of choice for non-small cell lung cancer is surgical resection.\(^ {265,266}\) However, in a significant majority of patients, this mode of therapy is not feasible because by the time the patient seeks medical help, the neoplasm is unresectable. Surgical resection is generally considered in patients with Stage I, Stage II, and in some cases Stage III disease. Presurgical evaluation should consider pulmonary and cardiac status, general health, and acceptable functional status. In nonsurgical patients and in those with residual tumor in spite of surgical resection, radiation and chemotherapy may be considered. Preoperative radiation is sometimes recommended in certain types of lung cancer. Small cell cancer is usually treated with a combination of radiation and chemotherapy. Bronchoscopic therapy is generally aimed at treatment of obstructing tracheobronchial tumors in patients who are not surgical candidates. Bronchoscopic therapies include laser ablation, intraluminal radiotherapy, photodynamic therapy, tracheobronchial stent placement, cryotherapy, and bougienage. Palliative therapy includes general care of the patient with particular attention to pain control, maintenance of adequate nutrition, and psychological support.

**Summary Statement:**

- Bronchogenic carcinoma is not a common cause of chronic cough (0 to 2%) (Grade II-2). It is very unlikely in never smokers (Grade II-2). It is most likely to occur in present or prior cigarette smokers and patients who have occupational exposures that place them at increased risk for bronchogenic carcinoma.
- Chest radiographs, sputum cytology, and fiberoptic bronchoscopy are the most important initial tests to consider in evaluating for bronchogenic carcinoma as the cause of chronic cough (Grade II-2). The chest radiograph is the most important initial diagnostic test in predicting whether or not a bronchogenic carcinoma is a potential cause of chronic cough. It has been shown to have a positive predictive value of 36 to 38% and a negative predictive value of 100% (Grade II-2). In the context of chronic cough, when the chest radiograph suggests that a bronchogenic carcinoma or an inflammatory pulmonary parenchymal process is present, bronchoscopy has been shown to have a positive predictive value of 50 to 89% and a negative predictive value of 100% (Grade II-2).
- In nonsmokers with chest radiographs that are normal or show nothing more than a stable, inconsequential scar, bronchogenic carcinoma is so unlikely to be the cause of chronic cough that other causes should be preferentially pursued (Grade II-2).
- Epidemiologic data reveal that coughs that develop for the first time and last for months, or that change in character in susceptible groups, are suggestive of bronchogenic carcinoma. In this setting, if cough does not go away with cessation of smoking for 4 weeks, proceed with sputum cytology and bronchoscopy even when the chest radiograph is normal (Grade III).

**Angiotensin-Converting Enzyme Inhibitor-Induced Cough**

**Definition, Prevalence, and Clinical Presentation:** Chronic cough occurs with the administration of ACEIs;\(^ {267,268}\) it is typically described as nonproductive and is associated with an irritating, tickling, or scratching sensation in the throat. Cough appears to be a class effect of these drugs and not dose-related.\(^ {267,269}\) Although this association was originally reported with...
captopril and in the adverse-event reports of early clinical trials, it has since been seen with all the ACEIs in clinical use (Grade II-2, II-3). In patients who experience a cough with one ACEI, cough usually develops when another ACEI is tried. Although the frequency of cough associated with ACEIs has been reported to vary widely from 0.2 to 33%, the true incidence is more likely to be in the region of 10% and probably higher in women, as is all reported cough. The cough from ACEIs does not appear to result in pulmonary dysfunction. In this regard, asthmatics do not seem to be at increased risk for ACEI-induced cough. Chronic cough was reported to be due to ACEIs 0 to 3% of the time in three prospective, descriptive studies (Grade I). Cough has been reported to appear within a few hours of taking a first dose in many patients, but it may not become apparent for weeks or even months. The time course for recurrence and resolution of cough has been prospectively studied in a randomized, double-blind, placebo-controlled investigation (Grade I) in patients who previously experienced an ACEI-induced cough. During the lisinopril rechallenge period, the median time to resolution during the placebo washout period was 26 days (range, 24 to 27.5). 

Pathogenesis: The pathogenesis of ACEI-induced cough is unknown. It is likely that the cough is related to an accumulation of the inflammatory or proinflammatory mediators bradykinin, substance P, and/or prostaglandins and that these mediators in turn increase the sensitivity of the cough reflex. Inevitably, patients with ACEI-induced cough have an increased sensitivity of the cough reflex, which returns to normal on stopping the therapy. Bradykinin and possibly substance P are considered likely to be involved in the pathogenesis since they can be inactivated by angiotensin-converting enzyme and they accumulate in the presence of ACEIs. Recent studies also suggest that the mechanism for this cough in some way involves prostaglandins, mainly through the accumulation of bradykinin in the tissue of the tracheobronchial tree. Evidence supporting this comes from Grade I studies showing that sulindac, nifedipine, and indomethacin attenuated cough associated with ACEI. Nifedipine is a dihydropyridine calcium antagonist that may inhibit prostaglandin synthesis. ACEI-induced cough has been reduced by using the thromboxane antagonist picotamide, which also suggests a role for thromboxanes in the pathogenesis. 

Diagnosis: Because no laboratory test will predict who will have an ACEI-induced cough, the diagnosis should be considered in any patient who has a cough while taking an ACEI (Grade III). While cough due to ACEI typically comes on after variable periods of time after initiation of therapy, patients can present with cough initially due to another condition before initiation of ACEI therapy and have cough subsequently attributed solely to an ACEI when the original cough goes away. Therefore, no matter when cough starts in association with an ACEI, stop the ACEI (Grade III). The diagnosis is confirmed after the drug is discontinued. Cough due to ACEIs will disappear or substantially improve within 4 weeks of discontinuing the drug (Grade I). While oral sulindac, indomethacin, nifedipine, picotamide, and inhaled sodium cromoglycate will provide symptomatic relief in some patients (Grade I), definitive treatment of ACEI-induced cough is discontinuation of the drug.

Psychogenic and Habit Cough

Definition: The habit cough or nervous cough is a throat-clearing noise made by a patient who is often...
withdrawn and self-conscious. Short of a therapeutic trial, it is our opinion that it is hard to distinguish this cough from that of PNDS (Grade III).

Prevalence: Psychogenic cough may be a manifestation of a more severe psychological problem or a habit, but no existing literature provides guidance as to how often this may be the case. Unlike the patient who has a habit cough, patients with psychogenic cough often believe there is a serious chest problem. Psychogenic cough is reported to be relatively common in the pediatric population, but in adults it is an uncommonly reported condition. In 17 published reports, 149 of 153 patients were under 18 years of age. The diagnosis is made in 3 to 10% of children with cough of unknown etiology that persists for more than 1 month.119 Psychogenic cough is slightly more common in girls.

Clinical Presentation: While the literature primarily concerning pediatric patients has suggested that patients with psychogenic cough typically do not cough at night and have a cough with a barking or honking character, it is evident in adults that the presence or absence of these characteristics is not diagnostically helpful. In prospective studies, it has been shown that cough due to a variety of diseases (eg, chronic bronchitis, GERD) is unlikely to occur once patients fall asleep.147,283 and barking or honking coughs can be due to a variety of diseases (eg, bronchiectasis, GERD, PNDS).117 Since there are no distinguishing clinical features or diagnostic tests, psychogenic cough should be considered only after all other possibilities have been excluded.

Pathogenesis: Psychogenic cough may be a form of malingering, especially in adults. In children and adolescents, psychosocial distress such as physical abuse or school phobia can produce a conversion syndrome. Family history may indicate patterning in the child patient (ie, a family member with chronic cough might be a sibling with CF). The child can also have underlying chest disease, analogous to pseudoseizures in an epileptic patient. The cough can follow a respiratory infection but persist long past the time that the child is well. Physiologically, the cough itself can produce airway irritation that predisposes the patient to further cough.

Diagnosis: Psychogenic cough is a diagnosis of exclusion. Patients with chronic cough seek medical attention because the cough adversely affects their quality of life; therefore, every effort should be made to establish a specific, treatable cause of cough (Figure 1).

Treatment: Suggestion therapy is the principal treatment for psychogenic cough in children. A variety of techniques have been successfully employed to facilitate the child being able to hold his/her cough and thus break the cough-irritation cycle. Antitussives can be used as short-term adjunctive therapy to help control the cough. Once the control of cough is established, the symptom resolves completely.

Occasionally a therapeutic trial with anti-inflammatory agents is used to attempt to establish a diagnosis of cough-variant asthma. Inhaled anti-inflammatory agents may help to control chronic airway inflammation. However, any medication given by a caregiver convinced that the therapy will control the cough may, itself, be a form of suggestion therapy. This is speculative, as there are no published data addressing this type of response to specific therapy.

Psychological counseling or psychiatric intervention should be considered for the older patient with presumed psychogenic cough, once an extensive evaluation has failed to reveal another cause of cough.

### Summary Statement:
- Habit cough and psychogenic cough are diagnoses of exclusion (Grade III).
- These diagnoses are made uncommonly in children and rarely in adults.
- While the pediatric literature suggests that the patients with psychogenic cough will have a barking or honking character to their coughs, the presence or absence of these characteristics is not diagnostically helpful in adults (Grade II-2).
- When a psychogenic cough is likely, suggestion therapy, psychological counseling, or psychiatric intervention is appropriate, as is short-term use of nonspecific antitussive therapy (Grade III).

### Chronic Interstitial Pulmonary Disease

**Definition and Prevalence:** Chronic interstitial pulmonary disease is a term encompassing various entities characterized by a diffuse infiltration of the alveolar and/or interstitial spaces with fluid, inflammatory cells (eg, chronic eosinophilic pneumonia), or collagen (eg, idiopathic pulmonary fibrosis). Chronic interstitial disease has not been reported to be a common cause of chronic cough; patients complain more frequently of dyspnea. It is not entirely clear how often the cough is due to the chronic interstitial disease or to the presence of a concomitant disease such as asthma, PNDS, or GERD. The cough associated with chronic interstitial disease, most often nonproductive, has not been specifically studied.

**Pathogenesis:** The pathogenesis of cough in this disease is not known. It may be due to stimulation of cough receptors in Airways of small caliber (small Airways disease is frequently described on biopsy) and/or increased pressure and tension on the Airways during breathing in the presence of decreased lung compliance.

**Diagnosis:** History, physical examination, radiologic evaluation of the chest (particularly chest CT), and blood/serum analyses may suggest the diagnosis. Classifications have been suggested according to the radiologic aspect of infiltrates, such as alveolar filling or primarily interstitial pattern. Pulmonary function tests may help to determine the type of severity of impairment, but transbronchial or open lung biopsy is often required to confirm the diagnosis. BAL may be useful to suggest the diagnosis in some of these pathologic conditions. Concomitant disease, such as asthma or any other condition that may provoke cough, should be considered especially...
when specific therapy for the cause of the chronic interstitial disease is unsuccessful in eliminating cough.

Treatment: Therapy is determined according to the underlying condition. If a cough is severe, antitussive medications may be used to reduce discomfort.

Summary Statement:

- Chronic interstitial disease is an uncommon cause of chronic cough.
- Treatment of cough is based on therapy of the underlying condition. If cough persists despite therapy for chronic interstitial disease, evaluate for the more common causes of chronic cough that may be coexisting before prescribing nonspecific antitussive medications (Grade III).

The Pediatric Patient—Other Etiologies of Cough To Consider

In children, cough accounts for 2 to 3% of all office visits in the United States. Asthma, upper and lower respiratory tract infections, and GERD are the most common causes of acute and chronic cough in children; less common but still important etiologies of cough in young children include congenital anomalies, aspiration, and environmental exposures. In one retrospective study of children referred to an otolaryngologist for evaluation of chronic cough, asthma was the most common etiology (39%), followed by sinusitis (23%), GERD (15%), aberrant innominate artery (12%), psychogenic cough (10%), and subglottic stenosis (7%). No other studies have been published on the spectrum and frequency of chronic cough in children.

Congenital Anomalies: Congenital anomalies of the aortic arch and pulmonary artery that compress the trachea or major bronchi can present with cough associated with stridor or wheezing that is worse with feeding. Causes of vascular rings include a double aortic arch, right-sided aortic arch with left ligamentum arteriosus, anomalous innominate artery, and pulmonary artery sling. Tracheobronchomalacia, either isolated or in association with aberrant great vessels, can cause a recurrent cough that worsens with a lower respiratory tract illness. In children, particularly in young children, small airway obstruction due to a viral infection can produce dynamic collapse of abnormally soft, central airways. An episodic cough that occurs consistently with infection may thus be associated with a congenital lesion, such as an aberrant subclavian artery, that causes focal tracheomalacia with resultant airway compression. Other congenital lesions, such as pulmonary sequestration or bronchogenic cyst, are commonly silent but can lead to persistent cough due to infection or airway compression. Congenital mediastinal tumors may also produce a cough and, if rapidly growing or malignant, may be associated with compression of other mediastinal structures, leading to vocal cord dysfunction or superior vena cava syndrome.

Heart Disease: Acyanotic congenital heart disease may also present as chronic cough in infants. Cough can result from bronchial compression from hypertensive pulmonary arteries, an enlarged left atrium, or narrowing of small airways due to pulmonary edema. Heart lesions that may cause chronic cough associated with wheezing or respiratory distress include a ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, and tetralogy of Fallot.

Foreign Bodies: A foreign body lodged in the airway or esophagus should always be considered when assessing the cause of chronic cough in infants and young children, especially in children between the ages of 1 and 3 years. While most children present within 24 h of the event, 20% of children present more than 1 week after inhaling the foreign body. Food or food material accounts for 80% of the aspirated material, and peanuts are responsible for 50% of all aspirations. Other commonly aspirated foods include hot dogs and candy. Although foreign-body aspiration is more common in the infant and toddler, older children sometimes inhale objects that have been held in the mouth, such as a pen cap. A foreign body in the airway usually causes coughing, although there may be no symptoms at all unless secondary infection develops. In the lower airway, a foreign body can produce either emphysema due to a ball-valve effect and air-trapping, or distal atelectasis due to absorption of the trapped gas. Mobile foreign bodies can produce a paroxysmal cough with cyanotic episodes and stridor secondary to proximal migration and subglottic impaction. In some instances, this leads to fatal airway obstruction and death. Foreign bodies in the esophagus can also produce airway obstruction, dysphagia to solid foods, and death, especially in young children, because the posterior tracheal wall is compliant and opposes to the anterior wall of the esophagus. The presence of cough with a history of potential foreign-body aspiration requires diagnostic and therapeutic rigid bronchoscopy. A retained foreign body or impacted cerumen in the ear or fluid in the middle ear may also cause reflex coughing because of stimulation of Arnold’s nerve, the auricular branch of the vagus.

Aspiration: Poor coordination of swallowing and sucking, disorders of esophageal motility, GERD with regurgitation, and a wide variety of CNS and neuromuscular disorders may result in inhalation of milk or gastric contents into the tracheobronchial tree, causing cough. A history of feeding difficulties or coughing and choking during feeding are highly suggestive of chronic aspiration. Other congenital anomalies, such as tracheoesophageal fistula, laryngeal cleft, or abductor vocal cord paralysis, can cause cough due to aspiration of food, gastric contents, or other foreign matter. Even in normal infants, chronic, small-volume aspiration secondary to overfeeding, bottle propping, dyskinetic swallowing, or GERD can produce chronic cough. Thickened feeds, when used as a therapy for GERD in infants, have also been suggested as a cause of increased cough.

Environmental Factors: Involuntary exposure to parental smoking is a health hazard in infants and is an independent risk factor for serious chest illness prior to 2 years of age. The incidence of chronic cough and...
pneumonia in infants in the first year of life is increased if one parent smokes and is further increased if both parents smoke. More recent studies suggest that passive smoking is a risk factor for cough even in children 5 to 11 years of age. Passive smoking may also affect long-term pulmonary function and has been associated with decreased expiratory flow rates in teenage athletes exposed to parental smoke. This cough frequently disappears when the parents stop smoking. Other environmental exposures, such as exposure to volatile solvents, wood-burning stoves or fireplaces, and kerosene heaters, may also cause or exacerbate a chronic cough in infants. New homes have odors of paint, new furniture, new carpets, and other irritants. Many modern homes are quite dry because of forced-air heating. This can lead to a cough which often occurs with nose bleeds. Astringents in the nose can cause a lipoid pneumonia; when rubbed on the nose or chest, they can increase airway inflammation.

Despite the declining incidence of smoking in adults, the incidence of smoking among youth, particularly adolescent girls, has risen dramatically since the Surgeon General’s report in 1964 on the hazards of smoking. Admission of smoking can be difficult to obtain in this age group. However, since teenagers frequently smoke in confined areas, many young people who smoke experience chronic, mild conjunctivitis. The presence of chronic conjunctivitis in a child with chronic cough should suggest the possibility of smoking as an etiology of the cough.

**Summary Statement:**

- Asthma, upper and lower respiratory tract infections, and GERD are the most common causes of chronic cough in children (Grade II-3 and III).
- Less common but important causes in young children include congenital anomalies, heart disease, foreign bodies, aspiration, and environmental factors (Grade III).
CHAPTER 4. GUIDELINES FOR EVALUATING COUGH

Chronic Cough in the Adult

The cause of chronic cough can be determined in most adult patients; specific therapy will be successful in the majority of patients when chronic cough is evaluated in a systematic manner. A diagnostic approach that systematically evaluates locations of the afferent limb of the cough reflex for diseases that might be causing cough has been utilized in one form or another in 11 published studies.3,4,115-121,310,311 All studies were descriptive in nature; seven were prospective,3,4,115-117,310,311 (Grade II-2), and four were retrospective.3,118-121 (Grade II-3). Ten primarily involved adults, and one118 focused on infants and children. In nine of the studies, the cause was determined from 88 to 100% of the time, leading to successful therapy in 84 to 98% of the patients. In two studies, the cause of cough was determined in 55% and 78%.310 Cough was eliminated in 65% in the latter study. It is not known why these latter two studies yielded results different from those of the other nine studies. Perhaps it was due to the different populations studied or to the use of different diagnostic and therapeutic protocols.

A systematic, diagnostic approach to chronic cough has been validated in immunocompetent patients in multiple prospective and retrospective descriptive studies. No such approach has yet been studied in chronic cough in immunocompromised patients or for acute cough.

Strengths and Limitations of the Anatomic Diagnostic Protocol: One prospective, descriptive study117 (Grade II-2) has shown that the character (eg, paroxysmal, loose and self-propagating, productive, brassy, honking, and barking) and timing (eg, nocturnal, with or after meals, associated with milk ingestion) of cough was not helpful in predicting its cause. Two prospective, descriptive studies3,115 (Grade II-2) revealed the strengths and limitations of testing for diagnosing the cause of chronic cough in adults. The principal strength of diagnostic testing is in ruling out suspected possibilities (Table 8). The principal limitation is that a positive test cannot necessarily be relied upon to establish the diagnosis; a positive test has not been able to consistently predict a favorable response to specific therapy. A positive test, by itself, is not diagnostic of the cause of cough unless a favorable response to therapy is witnessed.

The Capsaicin Cough Challenge: Capsaicin, the pungent extract of red pepper, is a known irritant of nonmyelinated nerves. Interest in its use as a tussive agent stems from investigation of the role of nonmyelinated fibers in bronchial reflexes.312 The mechanism of the challenge has been hotly debated (ie, whether the cough relates to stimulation of myelinated or nonmyelinated fibers). However, this debate has little relevance to the use of capsaicin as a tussive challenge. Unlike some other tussive challenges, the capsaicin challenge seems to be robust and transportable with little requirement for specialist equipment. By having subjects inhale serially increasing concentrations of capsaicin and counting coughs, dose-response curves can be constructed that reflect the sensitivity of the cough reflex. Since the capsaicin cough challenge has not been evaluated other than as a research tool, its sensitivity and precision as a diagnostic test in cough are not known. The Committee does not recommend its use for clinical purposes.

Algorithm for Diagnosing Chronic Cough in Immunocompetent Adults: Based upon a critical and comprehensive review of the literature, the Committee recommends the diagnostic algorithm shown in Figure 1. The section that follows provides guidance in using this algorithm.

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**Table 8—Testing Characteristics of Diagnostic Protocol**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiograph</td>
<td>100</td>
<td>54-76</td>
<td>36-38</td>
<td>100</td>
</tr>
<tr>
<td>Sinus radiograph</td>
<td>97-100</td>
<td>75-79</td>
<td>57-81</td>
<td>95-100</td>
</tr>
<tr>
<td>MIC</td>
<td>100</td>
<td>67-71</td>
<td>60-82</td>
<td>100</td>
</tr>
<tr>
<td>BaE</td>
<td>48-92</td>
<td>42-76</td>
<td>30-63</td>
<td>63-93</td>
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<tr>
<td>Esophageal pH</td>
<td>100</td>
<td>66-100</td>
<td>89-100</td>
<td>100</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>100</td>
<td>50-92</td>
<td>50-89</td>
<td>100</td>
</tr>
</tbody>
</table>

*Data from Irwin et al4 and Smyrnios et al.115 BaE=barium esophagography; Esophageal pH=24-h esophageal pH monitoring; MIC=methacholine inhalation challenge; NPV=negative predictive value; PPV=positive predictive value.

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Diagnostic Caveats in Adults and Recommendations Based Upon Them:

1. Cough due to cigarette smoking or ACEIs should substantially improve or disappear within 4 weeks of cessation or discontinuation of the ACEI.269 Therefore, in the absence of an abnormal chest radiograph, no additional laboratory tests should be ordered until the response to cessation of smoking (Grade II) or discontinuation of the ACEI (Grade I) for 4 weeks has been assessed. In patients who develop cough shortly after beginning to take an ACEI, the chest radiograph can be withheld until response to discontinuation of the drug has been assessed. While drugs other than ACEIs can cause cough (eg, nitrofurantoin; oily oral, nasal, or ophthalmic preparations), these, unlike ACEIs, cause cough by provoking intrapulmonary disease. Since drugs other than ACEIs are almost always associated with an abnormal chest radiograph, they should be suspected when the chest radiograph is abnormal.

2. While chest radiographs will be normal or only show an abnormality consistent with an old and unrelated process (eg, pleural scarring from prior pneumonia) more than 90% of the time, they are useful for initially...
Figure 1. Guidelines for evaluating chronic cough in immunocompetent adults. See text for discussion of the strengths, limitations, and caveats of this protocol. ACEI=angiotensin-converting enzyme inhibitor; BaE=barium esophagography; GERD=gastroesophageal reflux disease; HRCT=high-resolution computed tomography; HX=history; PE=physical examination; PNDS=postnasal drip syndrome.
6. Because the clinical evaluation by history and physical examination has been shown to be unreliable in accurately diagnosing asthma, routine diagnostic testing (eg, spirometry before and after bronchodilator, bronchoprovocation challenge testing, peak flow monitoring) is recommended before treatment to assess for the presence or absence of asthma as the potential cause of cough (Grade II-2).

7. Diagnostic testing for GERD is initially only recommended in patients who do not have upper-GI symptoms of GERD (ie, silent GERD) (Grade III). It is not initially indicated for those patients with cough who complain of sour taste in the mouth, regurgitation, or heartburn on a weekly basis because the frequency of these complaints is, by itself, indicative of GERD.

8. While 24-h esophageal pH monitoring is the most diagnostically useful test for assessing for GERD as the cause of cough, conventional indices used by gastroenterologists to assess for esophagitis may be misleadingly normal.180 Therefore, until future studies provide better guidelines, the test should be read as normal when conventional indices are within the normal range and no suspicious reflux-induced coughs appear during the monitoring session (Grade II-2).

9. Even though barium esophagography is a much less sensitive and specific test than 24-h esophageal pH monitoring in diagnosing GERD as the cause of cough, it may occasionally be singularly useful in this regard.180 For instance, it can reveal reflux to the thoracic inlet at a time when refluxate from the stomach has a pH value similar to that of the normal esophagus, thus preventing its detection in the esophageal pH tracing (Grade III).

10. Since left ventricular failure with passive congestion of the lungs and aspiration from pharyngeal dysfunction due to a variety of neuromuscular diseases have been shown to cause chronic cough less than 3% of the time in prospective studies (Grade II-2), noninvasive cardiac studies and modified barium swallow with videofluoroscopy should be ordered early in the workup only in the proper clinical contexts, or later when cough remains persistently troublesome after other diagnostic considerations for the commonest conditions have been undertaken (Grade II-2).

11. While diagnostic testing is helpful in predicting the cause of chronic cough, the final diagnosis is determined by observing which specific therapy eliminates cough as a complaint. If the evaluation suggests more than one possible cause, therapies should be initiated in the same sequence that the abnormalities were discovered. Since cough can be simultaneously caused by more than one condition, therapy that appears to be partially successful should not be stopped; rather, other therapies should be sequentially added (Grade II-2).

12. The role of empiric therapy in diagnosing the cause of chronic cough has not been rigorously studied. Nevertheless, it is reasonable to
FIGURE 2. Guidelines for evaluating chronic cough in immunocompromised adults. See text for discussion. See legend to Figure 1 for abbreviations.
13. Points to consider to avoid potential pitfalls in assessing response to empiric therapy include the following (Grade III): (a) more than one condition may be contributing simultaneously to the patient’s cough; (b) partially effective treatment for one condition should not be discontinued while additional therapy is added; (c) inhaled medications prescribed for asthma may be making the cough worse; (d) all H₁ antagonists are not equal and the newer, relatively nonsemitic H₁ antagonists will not effectively treat the PNDS of nonhistamine-mediated conditions; (e) it may take up to 2 to 3 months of intensive medical therapy for GERD before the cough due to GERD starts to improve noticeably, and on average it takes 5 to 6 months before the cough disappears; (f) H₂ antagonist therapy alone may be inadequate in successfully treating cough due to GERD; and (g) patients with cough due to GERD may fail to improve with the most intensive medical therapy, and the adequacy of the treatment regimen (and/or the need for surgery) can be assessed by performing 24-h esophageal pH monitoring while the patient is receiving this form of therapy.

Algorithm for Diagnosing Chronic Cough in Immunocompromised Adults: Although the Committee is not aware of any studies that have evaluated chronic cough in this group of patients in a systematic manner, it recommends (Grade III) the protocol shown in Figure 2. This algorithm is specifically designed to avoid the potential pitfall of failing to consider the commonest causes of chronic cough in the presence of seemingly more common diagnostic culprits (eg, P carinii infection in HIV-infected patients). The major difference between this protocol and that recommended for immunocompetent patients is the active assessment by oximetry and blood CD4 counts for the possibility of pulmonary parenchymal disease in the setting of a normal chest radiograph. For example, in the AIDS population, it is unlikely that a clinically significant opportunistic lung infection is present if oxygen saturation with exercise does not fall to 90% or less, or if blood CD4 lymphocyte counts are greater than 200/mm³ (0.200×10⁹/L).

Acute Cough in the Adult

The Committee recommends (Grade III) a clinical approach for the initial evaluation of acute cough. This approach consists of history, physical examination, and the estimated frequency of conditions based upon the epidemiologic data and clinical experience (Table 9).

While there are no published studies on the spectrum and frequency of causes of acute cough, overwhelming clinical experience indicates that PNDS due to upper respiratory tract infections is the most common cause. Therefore, this should be initially considered the most likely cause of acute cough. The most common upper respiratory tract infections leading to acute PNDS include the common cold, acute bacterial sinusitis, which has been estimated to complicate the common cold from 0.5 to 5% of the time, and pertussis. Although pertussis involves the lower respiratory tract during the paroxysmal stage of the illness, it initially presents as an upper respiratory tract infection during the catarrhal stage. Pertussis should be suspected and treated in all patients with acute cough who have been exposed to a close contact with the disease and who present with a cough-vomit syndrome. Acute respiratory infections also commonly cause acute cough or acute worsening of chronic cough in patients with COPD during exacerbations of this disease. Other causes of PNDS, such as allergic rhinitis and environmental irritants, should be considered in the proper historical context.

The diagnosis of the common cold is usually certain when patients present with (1) an acute upper respiratory illness characterized by symptoms and signs referable predominantly to the nasal passages (eg, rhinorrhea, sneezing, nasal obstruction, and PNDS) with or without fever; (2) lacrimation; (3) irritation of the throat; and (4) a normal physical examination of the chest. In this setting, diagnostic testing is not indicated because it is of such low yield. For instance, in immunocompetent patients in this setting, chest radiographs will be normal 97% of the time. On the other hand, when immunocompromised patients, especially those with AIDS or at risk for AIDS, present with acute cough, pneumonia due to a variety of organisms including P carinii and Mycobacterium tuberculosis should be suspected early in the workup, even

<table>
<thead>
<tr>
<th>Causes and Estimated Frequencies of Acute Cough in the Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Common cold</td>
</tr>
<tr>
<td>Acute bacterial sinusitis</td>
</tr>
<tr>
<td>Pertussis</td>
</tr>
<tr>
<td>Exacerbations of COPD</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Environmental irritant rhinitis</td>
</tr>
</tbody>
</table>

Table 9—Causes and Estimated Frequencies of Acute Cough in the Adult
when the physical examination and chest radiograph are normal. In this setting, if oxygen saturation falls to 90% or less with exercise, pneumonia with these organisms as well as other disorders of the lower respiratory tract should be highly suspected; diagnostic studies should be carried out, such as induced sputa and bronchoscopy with BAL and transbronchoscopic lung biopsy.

Clinical predictors of acute and subacute bacterial sinusitis diagnosed by four-view sinus radiographs from a prospective logistic regression model include maxillary toothache, history of colored nasal discharge, poor response to nasal decongestants, abnormal transillumination, and purulent secretion on nasal examination. When all five features are present, the odds of sinusitis rise sharply (likelihood ratio of 6.4), and when none is present, sinusitis is very unlikely (likelihood ratio of 0.1). Similar data do not exist for sinus CT scanning.

Acute cough can also be the presenting manifestation of a potentially life-threatening disease such as pneumonia, congestive heart failure, pulmonary embolism, or conditions that predispose to aspiration. It is especially important to have a high index of suspicion for these disorders in the elderly patient with acute cough, because the classic signs and symptoms of these diseases may be minimal or nonexistent. Because fever is often absent in the elderly patient with pneumonia, a new onset of cough, especially when accompanied by either tachypnea or altered mental status and an abnormal physical examination of the chest, should raise the suspicion of pneumonia and warrant ordering a chest radiograph. It is often not appreciated that approximately 50% of patients with documented pulmonary embolism will complain of cough, and that cough can occasionally be the predominant complaint. Consequently, when patients present with acute cough in association with risk factors for thromboembolic disease, pulmonary embolism must be entertained as a possible diagnosis. Because aspirated material can stimulate the afferent limb of the cough reflex in the large intrathoracic airways, acute cough may be due to any condition that interferes with normal pharyngeal or esophageal swallow is useful to examine for GERD, an esophageal foreign body occludes a large airway. Fiberoptic bronchoscopy is best for suspicious cases, and rigid endoscopy is essential for therapy when a clear-cut history of foreign body is present; bronchoscopy also is useful to obtain specimens for microbiologic culture and for ciliary studies. A barium swallow is useful to examine for GERD, an esophageal foreign body, or a vascular ring.

Pulmonary function testing such as simple spirometry can be performed by most children aged 7 years or older and occasionally by children as young as 5 years. Spirometry with challenge testing pre- and postbronchodilator inhalation can help to diagnose cough-variant asthma. In younger children, a good substitute for spirometry is a therapeutic trial of asthma medication (β-adrenergic agonist with cromoglycate or an inhaled steroid) during which the parents keep a cough diary card. The results of pulmonary function testing are frequently normal in children with cough-variant asthma.

In a child suspected to have lower respiratory tract infection, expectorated sputum (when present) should be sent for stain and culture, including acid-fast and fungus stains, when appropriate. A nasal swab can help diagnose Mycoplasma, pertussis, or Chlamydia, but is of limited value for other lower respiratory infections.

TB skin test results should be recorded and should be done with anergy testing if the child is at increased risk of having TB.

Blood count and differential are rarely useful. Quantitative immunoglobulins can be helpful if recurrent pneumonia is a problem.

A sweat test for CF should be performed whenever the diagnosis is even remotely considered.
Diagnostic Caveats in Children Generated by Consensus (Grade III): Unlike in adults, diagnostic testing is limited in its usefulness in part because many children are unable to cooperate with testing and because positive tests do not necessarily establish a diagnosis or predict a favorable response to specific therapy.

1. Cough due to passive tobacco smoke exposure should improve upon removal from the environment. There is no information on how rapidly improvement should occur.

2. For children with chronic cough, a chest radiograph is useful for ruling out unsuspected lower respiratory tract and cardiac abnormalities. Therefore, a chest radiograph should be obtained in nearly all children with chronic cough. A chest radiograph is probably not needed when PNDS is suspected in children. Consideration should also be given to obtaining a sweat test in children with chronic cough who do not have a clear-cut etiology for their cough. Additional testing is not indicated unless the chest radiograph is abnormal or unless cough persists despite treatment for PNDS, asthma, or GERD.

3. Sinus CT scans are not routinely recommended to evaluate sinusitis. The relationship between PNDS and sinusitis is not as clear in children as it is in adults. Nasal cultures are not useful in guiding therapy.

4. The diagnosis of asthma is best made by diagnostic testing, including spirometric changes after bronchodilator inhalation, bronchoprovocation, or peak flow testing. It is frequently not possible to perform pulmonary function testing in children who are young and unable to cooperate. A characteristic history of asthma triggers and response to therapy become the only routine way to diagnose chronic cough asthma in many children.

5. Since a history of sour taste in the mouth, regurgitation, or heartburn is not frequently present, GERD should be suspected in all cases of cough variant of unknown etiology in children. In these instances, 24-h esophageal pH monitoring may be helpful. A normal study, however, does not rule out nonacid reflux or occasional acid reflux as etiologies for the cough. Cough that occurs simultaneously with reflux events during monitoring is strong presumptive evidence of GERD-associated chronic cough.

6. Congenital anomalies of the cardiorespiratory system are unusual causes of chronic cough in children and are usually suggested by either history or physical examination. The evaluation of these etiologies should be guided by the differential diagnosis.

7. While multiple etiologies of cough are not as well-documented in children as in adults, there is no reason to suspect that there are significant differences. As in adults, therapy should be added sequentially, and additionally when response is partial.

8. Further study is needed to determine the most common etiologies of cough and the response to specific antitussive therapy before specific recommendations can be made in children. The most common etiologies of chronic cough in children appear to be PNDS, asthma, and/or GERD, but further study is needed. Aggressive therapy for PNDS, asthma, and GERD should be rendered before empiric therapy is deemed unsuccessful and further evaluation is undertaken.

9. The Committee recommends an approach to acute cough in children that consists of history and physical examination with determination of the most likely etiology. The most common etiologies in children appear to be the common cold and environmental irritants, but no studies examining other etiologies have been performed.
CHAPTER 5. PHARMACOLOGIC TREATMENT

The treatment of cough can be (1) therapy that controls, prevents, or eliminates cough (ie, antitussive therapy), or (2) therapy that makes cough more effective (ie, protussive therapy).

Antitussive Therapy

Antitussive therapy can be either specific or nonspecific. It is indicated when cough performs no useful function, such as clearing the airways in an infectious pneumonia. Specific antitussive therapy is directed at the etiology (eg, smoking in CB) or presumed operant pathophysiologic mechanism responsible for cough (eg, PND in allergic rhinitis). Nonspecific antitussive therapy is directed at the symptom rather than the underlying etiology or pathophysiology and aims to control rather than eliminate cough; it is indicated when definitive, specific therapy cannot be given either because the etiology of cough is unknown or because definitive therapy has not had a chance to work or will not work (eg, inoperable lung cancer).

Specific antitussive therapy for chronic cough has been reported to have a high rate of success when a systematic diagnostic protocol is used. From the 10 studies in which outcome data are available, specific therapy appears to have a success rate between 68% and 98%. In nine studies,3,4,115-121 the range was 84% to 98%. The one study with a much lower success rate310 used therapeutic regimens that differed considerably from the others. Nonspecific antitussive therapy has a limited role because of the high probabilities that the cause of cough can be determined and specific treatment can be successful. A recently published, extensively referenced, comprehensive, and critical review of this subject5 accurately reflects the analysis of this Committee; consequently, only the more recently published information is referenced separately.322-325

For the infrequent times that nonspecific antitussive therapy is indicated, the Committee recommends (Grade 1) drugs that have been shown to be effective in randomized, double-blind, placebo-controlled studies (Table 10) in humans with pathologic cough. The Committee does not recommend drugs that have been consistently shown to be ineffective or inconsistently found effective (eg, carbocysteine, bromhexine, levopropoxyphene) in randomized, double-blind, placebo-controlled studies, or drugs that have not been similarly, rigorously studied. Agents that fall into the latter category include ammonium chloride, potassium iodide, hydration by the oral and IV

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Patients</th>
<th>Population</th>
<th>Design</th>
<th>Dosing</th>
<th>Results</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium bromide</td>
<td>23</td>
<td>B</td>
<td>RDBPC</td>
<td>40 μg qid, aerosol</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>PI</td>
<td>RDBPC</td>
<td>80 μg qid, aerosol</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>73</td>
<td>CC</td>
<td>RDBPC</td>
<td>6 mg/120 mg bid, po</td>
<td>Decreased cough</td>
<td>1</td>
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<tr>
<td>Guimesal</td>
<td>140</td>
<td>B</td>
<td>RDBPC</td>
<td>500 mg tid, po</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td>Levodropropizine</td>
<td>19</td>
<td>BA</td>
<td>RDBPC</td>
<td>100 mg qid, po</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td>Naproxen</td>
<td>79</td>
<td>Rhinovirus colds</td>
<td>RDBPC</td>
<td>400-500 mg loading dose, then 200-500 mg tid, po</td>
<td>Decreased cough</td>
<td>1</td>
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<tr>
<td>Codeine†</td>
<td>8</td>
<td>B</td>
<td>RDBPC</td>
<td>30-60 mg qid, sd, po</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>91</td>
<td>URI</td>
<td>RDBPC</td>
<td>30 mg qid, po, 4 d</td>
<td>Not effective</td>
<td>1</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>79</td>
<td>TB, CA, PF, B</td>
<td>RDBPC</td>
<td>20 mg bid, po, 3 d</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td>Glucine‡</td>
<td>121</td>
<td>B</td>
<td>RDBPC</td>
<td>60 mg sd, po</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>TB, CA, PF, B</td>
<td>RDBPC</td>
<td>20 mg bid, po, 3 d</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>14</td>
<td>B, S</td>
<td>RDBPC</td>
<td>25-50 mg qid, po, 16 h</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td>Caramiphen</td>
<td>121</td>
<td>B</td>
<td>RDBPC</td>
<td>10 mg qid, po, 10 d</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td>Viminol</td>
<td>24</td>
<td>B</td>
<td>RDBPC</td>
<td>70-140 mg sd, po</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>B</td>
<td>RDBPC</td>
<td>60 mg sd, po</td>
<td>Decreased cough</td>
<td>1</td>
</tr>
</tbody>
</table>

*A*=asthma; *B*=bronchitis; *CA*=cancer; *CC*=common cold; *F*=pneumonia; *PF*=pulmonary fibrosis; *PND*=postinfectious; *RDBPC*=randomized, double-blind, placebo-controlled; *SA*=sarcoidosis; *sd*=single dose; *URI*=upper respiratory infection. Guimesal is a synthetic agent whose chemical structure includes salicylate and guaiacol rings.

†Based upon RDBPC studies, it is reasonable to assume that all narcotics of the phenanthrene alkaloid group are effective. Therefore, only codeine, the prototypical agent, is listed.

‡Racemic glaucine, a generic, centrally acting, nonnarcotic antitussive, to our knowledge is available only in some Eastern European countries.

Readers should be cautioned that the drug marketed in Europe by the trade name Glaucine is not the same drug, and should not be prescribed as an antitussive; it is the β-adrenergic blocker metipranolol.
routes, aromatic chest rubs, theophylline, and benzona-
tate. Studies suggesting efficacy of inhaled fenoterol and
sodium cromoglycate as nonspecific antitussives must also
be regarded as inconclusive because the patient groups
that served as study subjects were not well-characterized
and may have included patients with asthma.

Although topically administered lidocaine (lignocaine)
has an unequivocal, transient antitussive effect during
bronchoscopy, and IV lidocaine will clearly suppress the
persistent, almost uninterrupted cough after awakening
from general anesthesia following bronchoscopy, lidocaine
by either route has not been evaluated in appropriately
designed clinical trials in patients with pathologic cough.
While iodinated glycerol has been inconsistently shown to
decrease cough, it has been removed from the market in
the United States because of potential safety concerns.

**Pharmacologic Protussive Therapy**

Protussive therapy is indicated when cough performs a
useful function and needs to be encouraged (eg, bronchi-
ectasis, CF, pneumonia, postoperative atelectasis). Protus-
tive therapy is treatment that increases cough effective-
ness with or without increasing cough frequency. The
results of subjective studies alone are impossible to eva-
uate since patients may sense that mucus has been
changed by agents that may alter mucociliary factor(s)
when actually there has been no improvement in clearance.
Since it is theoretically possible to change the
consistency of mucus and the volume of expectorated
sputum without improving cough clearance, objective
studies that measure only these parameters are impossible
to evaluate; for instance, the volume of sputum may
increase without improving cough effectiveness because
(1) the patient swallowed less mucus during the study
period; (2) the drug stimulated the production of saliva; or
(3) the drug actually increased the volume of airway
secretions without improving cough effectiveness. There-
fore, protussive therapy can only be considered clinically
useful if it has been shown to increase significantly the
clearance of particles from the lower airways during
coughing in randomized, controlled studies in patients
with pathologic cough.

**Cough Clearance:** Drugs that have been adequately
evaluated for cough clearance in well-designed clinical
studies are listed in Table 11.321 While hypertonic saline
aerosol improved cough clearance in patients with bron-
chitis in two studies, there was no improvement in either
pulmonary function or subjective assessment. In one
prospective, open-label, placebo-controlled, parallel-
group trial in CF patients, ultrasonically nebulized hyper-
tonic saline significantly improved FEV1 (15 vs 2.8%) after
2 weeks; however, cough clearance was not measured.
Moreover, 6 of 58 patients had to withdraw from the
study, one because of severe coughing and one because of
hemoptysis associated with hypertonic saline.324

Amiloride aerosol in patients with CF has been shown
to improve a calculated cough clearability measure (not a
direct measure of cough clearance) without improving
pulmonary function. While aerosolized ipratropium bro-
mine diminished the effectiveness of cough for clearing
radiolabeled particles from the airways in COPD, aerosol-
ized terbutaline following chest physiotherapy significantly
increased cough clearance in patients with bronchiecta-
sis.325

The divergent results with these two different types of
bronchodilators suggest that terbutaline achieved its favor-
able effect by increasing hydration of mucus or enhancing
ciliary beating, and this overcame any negative effects of
bronchodilation on cough clearance (Grade I). If broncho-
dilators result in too much smooth muscle relaxation of
large airways, flow rates can actually decrease, even in
healthy individuals: more compliant large airways can
narrow too much because they cannot withstand dynamic
compression during forced expirations. Although hyper-
tonic saline, amiloride, and terbutaline by aerosol follow-

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Patients</th>
<th>Population Design</th>
<th>Dosing</th>
<th>Results</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonic saline</td>
<td>11</td>
<td>B</td>
<td>RDBPC Aerosol, bid, 3 d</td>
<td>Increased cough clearance</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>B</td>
<td>RDBPC Aerosol, sd</td>
<td>Increased cough clearance</td>
<td>1</td>
</tr>
<tr>
<td>Carboxyethane</td>
<td>16</td>
<td>B</td>
<td>RDBPC 4 g q.d. po, 7 d</td>
<td>Not effective</td>
<td>1</td>
</tr>
<tr>
<td>Mercaptotoanethane sulphonate</td>
<td>11</td>
<td>B</td>
<td>RDBPC 10% aerosol, bid, 3 d</td>
<td>Not effective</td>
<td>1</td>
</tr>
<tr>
<td>Bronhexine</td>
<td>9</td>
<td>B</td>
<td>RDBPC 24 mg tid. po, 14 d</td>
<td>Not effective</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>B</td>
<td>RDBPC 5 mg, IV, sd</td>
<td>Not effective</td>
<td>1</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>15</td>
<td>B, HE</td>
<td>RDBPC 100 mg, po, sd</td>
<td>Not effective</td>
<td>1</td>
</tr>
<tr>
<td>Erdosteine</td>
<td>16</td>
<td>B</td>
<td>RDBPC 300 mg tid, po, 8 d</td>
<td>Increased cough clearance</td>
<td>1</td>
</tr>
<tr>
<td>Amiloride</td>
<td>23</td>
<td>CF</td>
<td>RDBPC 10 mmol/L aerosol, sd</td>
<td>Increased cough clearability†</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>CF</td>
<td>RDBPC 10 mmol/L aerosol, bid 21 d</td>
<td>Increased cough clearability†</td>
<td>1</td>
</tr>
<tr>
<td>Terbutaline plus CPT/FD</td>
<td>8</td>
<td>BR</td>
<td>RDBPC 5 mg aerosol, sd, following</td>
<td>Increased cough clearance</td>
<td>1</td>
</tr>
</tbody>
</table>

*B=bronchitis; BR=bronchiectasis; CF=cystic fibrosis; CPT/FD=chest physiotherapy and postural drainage; HE=healthy elderly; RDBPC=randomized, double-blind, placebo-controlled; sd=single dose
†Cough clearability is a calculated measurement and not a direct measure of cough clearance.
cough clearance (Grade I), or cough clearability in the case of amiloride, their clinical utility remains to be determined in future studies that assess the short-term and long-term effects of these agents on the patient's condition.

Cough Frequency: A number of agents can increase cough frequency with varying success. While these effects have been primarily used to induce cough in animals and human volunteers in order to evaluate the effectiveness of antitussive drugs and better understand the pathogenesis of cough, no therapeutic agent to our knowledge has been studied as a potentially clinically useful protussive agent.

Summary Statement:

- The treatment of cough can be (1) therapy that controls, prevents, or eliminates cough (i.e., antitussive therapy), or (2) therapy that makes cough more effective (i.e., protussive therapy).
- Antitussive therapy can be either specific or nonspecific. Specific therapy is directed at the etiology or operant pathophysiologic mechanism responsible for cough. Nonspecific therapy is directed at the symptom and aims to control rather than eliminate the cough.
- Because of the high probability of being able to determine the causes(s) of cough and prescribe specific treatment that can be successful, there is a limited role for nonspecific antitussive treatment (Grade II-2, II-3). The Committee recommends (Grade III) that nonspecific antitussive therapy be prescribed only when specific therapy cannot be given either because the cause is not known or because specific therapy has not had a chance to work or will not work (eg, inoperable lung cancer).
- Although hypertonic saline, amiloride, and terbutaline by aerosol following chest physiotherapy have been shown to increase cough clearance (Grade I), or cough clearability in the case of amiloride, their clinical utility remains to be determined in future studies that assess the short-term and long-term effects of these agents on the patient's condition. Hypertonic saline in CF patients appears promising.

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APPENDIX

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