Chapter e13: Nonspecific Respiratory Tract Symptoms (with Cough)

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KEY CONCEPTS

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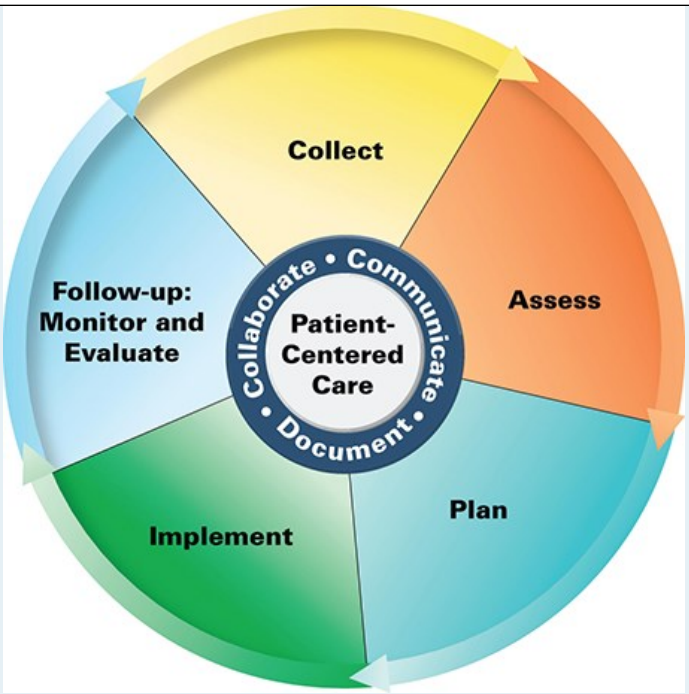
1. Cough is classified as acute, subacute, or chronic based on duration of symptoms.
2. Cough is an essential component for lung health maintenance, but persistent or excessive cough ceases to be protective, is bothersome, and adversely affects quality of life.
3. Although cough is associated with a variety of diseases, the duration of cough helps narrow the potential etiologies for cough symptoms.
4. The presence of dyspnea, red flag symptoms, and/or symptoms suggestive of acute bacterial rhinosinusitis indicates the need for referral to the patient's primary care physician.
5. Treatment trials (eg, intranasal corticosteroids, first-generation antihistamines, treatments for gastroesophageal reflux disease) can help rule out common causes of chronic cough.

PATIENT CARE PROCESS

Patient Care Process for Cough



Collect

- Duration of symptoms, red flag symptoms (see Table e13-5), and the presence and severity of symptoms associated with acute bacterial rhinosinusitis (see Tables e12-6 and e12-7)
- Use validated symptom questionnaires as needed (see text).
- Current medical conditions, family history, and occupational and environmental (eg, pets, carpet/bedding, mold) history
- Tobacco and marijuana use, prior allergies, and immunization history and medications
- Ability to access medications and adherence to current medications

Assess

- Indicators of acute, subacute, or chronic cough (see Table e13-1 and text)
- Red flag symptoms (see Table e13-5) or symptoms associated with acute bacterial rhinosinusitis (see Tables e12-6 and e12-7) indicating need for referral to primary care provider
- Active medical problems associated with chronic cough (see Table e13-2)
- Possibility of cough related to gastroesophageal reflux disease (GERD; see Chapter 50, “Gastroesophageal Reflux Disease”)
- If applicable, estimate creatinine clearance to assess dosing of current or new medications.
- If the patient taking any medications associated with cough (especially ACE inhibitors; see Table e13-4)

Plan*

- Refer to primary care provider for assessment of cough with dyspnea, red flag symptoms (see Table e13-5), or symptoms related to environmental or occupational exposures.
- Smoking cessation interventions in those ready to quit smoking (see Chapter 85, “Substance Use Disorders I: Opioids, Cannabis, and

Stimulants")

- Immunizations if not contraindicated (eg, influenza, pneumococcal, diphtheria, tetanus, acellular pertussis; see Chapter 147, "Vaccines, Toxoids, and Other Immunobiologics")
- Step-up therapy in patients with asthma-related cough to improve symptom control (see Chapter 44, "Asthma")

Implement*

- Patient education
- Recommendations that are within scope of practice
- Document in health record
- Instructions and schedule for follow-up

Follow-up: Monitor and Evaluate

- Reevaluate in 4 to 6 weeks and reassess using validated symptom questionnaires as needed.
- Adherence to care plan
- Adverse drug effects
- Immunizations for those deferred earlier (see Chapter 147)
- For acute or subacute cough that persists for more than 8 weeks (ie, progresses to chronic cough), trial of an oral first-generation antihistamine and/or intranasal corticosteroid
- For chronic cough that does not improve with an oral first-generation antihistamine and an intranasal corticosteroid, refer patient to primary care provider for ruling out asthma and nonasthmatic eosinophilic bronchitis before recommending treatment trial for GERD.
- For GERD-induced cough, improvement in cough may take up to 3 months, even though GERD symptoms may improve within 4 to 8 weeks.
- For ACE-inhibitor–induced cough, cough usually subsides within 8 weeks of discontinuing the medication but may take up to 1 year.

*_*Collaborate with patient, caregivers, and other healthcare professionals.*_

BEYOND THE BOOK

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Create a flow chart that outlines the sequence of therapeutic approaches for the four most common causes of chronic cough. Indicate the name of the medication class that may be used for a therapeutic trial when available as an over-the-counter medication. When a therapeutic trial of an over-the-counter medication is not appropriate, indicate referral to the patient's primary care physician for each of the respective causes of chronic cough.

This activity provides an opportunity for students to practice applying the assess, plan, and implement steps of the patient care process.

INTRODUCTION

Cough is the second most common symptom patients report as the reason for seeking healthcare in ambulatory settings.[1] In addition to occurring as a common symptom associated with respiratory diseases, cough serves as a protective respiratory reflex and also can be initiated voluntarily.[2] Cough is classified as acute, subacute, or chronic based on duration of symptoms (Table e13-1).[3] As a defense mechanism, cough protects the airways from aspiration of foreign substances, expels infectious organisms and harmful environmental insults, and clears excessive mucus secretions.[2,4] However, when cough is excessive or persists, it can be detrimental to patients through adverse consequences such as syncope, urinary incontinence, vomiting, chest pain, rib fractures, sleep disturbances, relationship difficulties, social embarrassment, and depression.[5,6] An increased frequency of cough also adversely affects health-related quality of life.[5]

TABLE e13-1

Classification and Duration of Cough Symptoms

Classifications	Duration (weeks)
Acute	<3
Subacute	3-8
Chronic	>8

Data from Reference 3.

EPIDEMIOLOGY AND ETIOLOGY

The estimated prevalence of chronic cough varies and depends on the epidemiological study design, duration of symptoms used to define chronic cough, and how the data is obtained (eg, diagnosis codes, patient report, physician diagnosis).[7,8] The global prevalence of chronic cough is approximately 10% and the prevalence of chronic cough in the United States ranges between 10% and 15%.[8] Chronic cough is more common in women and more commonly occurs in patients aged 50 to 70 years old.[7,9] Chronic cough is more common in patients who continue to smoke, which may reflect a protective response to inhaled irritants rather than hypersensitive cough.[10] Results from the ACHOO study revealed the burden associated with acute cough and/or cold symptoms. Fifty-two percent of the survey respondents indicated that their daily lives were affected “a fair amount” or “a lot” when they had a cough and/or cold. Participants also reported a decrease of 26% in their perceived productivity when they were experiencing cough and/or cold symptoms, and 45% of respondents reported missing at least 1 day of work or school.[5]

The etiology of cough may occur anywhere within the realm of the vagus nerve, which is the longest nerve of the autonomic nervous system. Therefore, cough may arise from a variety of systems (eg, respiratory, cardiovascular, gastrointestinal).[4] Viral upper respiratory tract infections are the most common cause of acute cough, followed by exacerbations of underlying diseases (eg, asthma, chronic obstructive pulmonary disease [COPD], upper airway cough syndrome [UACS], bronchiectasis) and pneumonia.[2,3] The most common cause of subacute cough is postinfectious cough followed by exacerbations of underlying diseases.[2,4,8] Asthma (including cough-variant asthma), UACS, nonasthmatic eosinophilic bronchitis (NAEB), and GERD are the most common causes of chronic cough in adult nonsmokers with UACS being the most common cause of chronic cough in the United States.[3,11] Additional causes of chronic cough are included in Table e13-2.[3,12]

TABLE e13-2

Causes of Chronic Cough

Common	Less Common	Rare
• Upper airway cough syndrome • Asthma (including cough variant asthma) • Nonasthmatic eosinophilic bronchitis • Gastroesophageal reflux disease	• Medications (especially ACE inhibitors) • Occupational and environmental exposure (especially cigarette smoking) • Chronic obstructive pulmonary disease • Bronchiectasis • Bronchiolitis • Obstructive sleep apnea • Lung cancer • Left ventricular heart failure • Somatic cough syndrome • Tic cough	• Aortic aneurysm • Pulmonary embolism • Aspiration of food and liquids due to oral-pharyngeal dysphagia • *Bordetella pertussis* • Interstitial lung disease (eg, sarcoidosis) • Tuberculosis • Enlarged tonsils • Basidiomycetes fungi • Cervical spondylosis • Heterotopic salivary gland at the base of the tongue • Idiopathic pulmonary fibrosis • External ear disease

Data from References 3,6,13–15.

ANATOMY AND MECHANISMS OF DISEASE

Physiology of Cough

Cough is a host defense mechanism. The cough reflex prevents introduction of particulate matter in the lower airways. The respiratory epithelial cells are covered with beating cilia and mucus. The beating cilia propel the overlying mucous layer upward toward the larynx. When mucociliary clearance is impaired due to damage of cilia (eg, smoking), coughing serves as a compensatory mechanism to help clear aspirated material, excess secretions, and foreign bodies.[16]

The mechanism of a cough is described as the following sequence: (1) inspiration; (2) forced expiration against a briefly closed glottis, which builds intrathoracic pressure; and (3) opening of the glottis with a subsequent rapid expulsion of air.[17,18] Turbulent airflow through the trachea, larynx, and vocal cords during expiration results in the sound of a cough.[2] Physiologically, cough can be described as laryngeal or tracheobronchial. Laryngeal cough is a true reflex stimulated by aspiration of foreign material, and the amount of inspiration may be minimal. Tracheobronchial cough can be initiated voluntarily and occurs distal to the larynx.[18]

A simplified overview of the cough pathway can be described via the following compartments: (1) the afferent arm (from the cough receptors to the respiratory center); (2) the respiratory center; and (3) the efferent arm (from the respiratory center to the respiratory muscles and larynx).[18]

In the afferent arm, cough receptors in the airways are located in the mucosa and submucosa.[14] Cough receptors are differentiated into three groups: (1) rapidly adapting receptors (RARs); (2) slowly adapting receptors (SARs); and (3) C-fiber nociceptors.[19] These cough receptors are located throughout the airways and lung parenchyma and are activated by a variety of triggers (Table e13-3).[20] Both RARs and SARs are considered pulmonary stretch receptors, which regulate the inspiratory and expiratory phases of coughing. Rapidly adapting receptors are relatively insensitive to chemical stimulation, but they are sensitive to mechanical stimulation. Slowly adapting receptors are also believed to be responsible for the inflation reflex, which terminates inspiration and initiates expiration after the lungs are adequately inflated. C-fiber nociceptors are relatively insensitive to mechanical stimulation, but they are sensitive to bradykinin, capsaicin, ozone, nicotine, prostaglandin E2, and other inflammatory mediators and environmental

stimulants.[17,19] Cough receptors have voltage-gated ion channels such as the transient receptor potential vanilloid-1 (TRPV-1) and transient receptor potential ankyrin-1 (TRPA-1), which are found on RARs and C-fiber receptors.[4,17] Cough sensitivity depends on the location of the stimulation and the type of stimulation. For example, the larynx and proximal large airways are more mechanosensitive and less chemosensitive, whereas the peripheral airways are more chemosensitive and less mechanosensitive.[11,19]

TABLE e13-3

Cough Receptor Triggers

Endogenous

- Mucus
- Refluxate
- Inflammation

Exogenous

- Cold air
- Perfume
- Smoke

Cognitive

- Voluntary cough

Data from Reference 20.

Cough sensory input travels from cough receptors to the respiratory center via the vagus nerve. The respiratory center consists of the nucleus tractus solitaris (NTS) and the cortex.[18] Vagal afferent fibers enter the brainstem via the NTS for central processing of afferent input and regulation of cough. The brainstem then controls the duration and intensity of cough. Through cortical processing, patients can sense an irritation or itch in the airways. Then patients can consciously control a cough behavior to satisfy the urge to cough.[19] In summary, the NTS is responsible for a reflex cough, and the cortex is responsible for voluntarily initiating or voluntarily inhibiting a behavioral cough.[18,19]

The efferent arm interacts with the larynx, respiratory muscles, and pelvic sphincters. The larynx and respiratory muscles are responsible for the previously described three phases of the cough mechanism. The activation of pelvic sphincters during a cough helps prevent incontinence during a cough.[18]

Pathophysiology Associated with Increased Cough

Acute and Subacute Cough

Viral Infections

In the acute phase, respiratory viruses cause changes in the function of the epithelial cells, which initiates an immune response. The immune response includes eosinophils, neutrophils, lymphocytes, and cytokines[19] Eosinophils increase sensory nerve responsiveness and release proteins that stimulate C-fiber nociceptors. The inflammatory response from neutrophils can sensitize peripheral airway nerves and stimulate the cough reflex. Lymphocytes release cytokines that also enhance eosinophilic and neutrophilic inflammation Additionally, respiratory viruses also cause a decrease in expression of M2 muscarinic receptors, which normally decrease cough sensitivity.[21] Collectively, these changes increase cough receptor sensitivity even after the respiratory virus is cleared. This helps explain persistent cough and cough hypersensitivity in the subacute phase.[19]

Chronic Cough

Patients with chronic cough may also experience cough hypersensitivity. Cough hypersensitivity syndrome is characterized by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure.[20,18] New onset or exacerbations of asthma or COPD are potential causes of chronic cough (see Chapter 44, "Asthma" and Chapter 45, "Chronic Obstructive Pulmonary Disease").

Upper Airway Cough Syndrome

Upper airway cough syndrome (previously known as postnasal drip syndrome) is a cough reflex related to inflammatory conditions of the nose and sinuses. The pathophysiology of UACS is not well understood. Direct irritation of nasal mucosa and/or mechano- or chemostimulation from a postnasal drip may initiate a cough. Alternatively, airway inflammation of the upper and/or lower airways may increase the sensitivity of the airway nerves, ultimately resulting in enhanced cough responsiveness such that innocuous stimuli promote coughing.[11,19]

Gastroesophageal Reflux Disease

Due to impaired function of the lower esophageal sphincter, acid and other gastric contents move from the stomach to the distal esophagus. In addition to heartburn and regurgitation, patients may also experience cough. After treatment with proton pump inhibitors, some patients may continue to experience cough.[22] This suggests other substances such as bile, pepsin, and other gastric enzymes may induce cough. Patients with GERD and chronic cough also have elevated levels of substance P, which inhibits apoptosis, increases migration, and prolongs the survival of eosinophils.[21]

Smoking

Tobacco smoke is cytotoxic to the ciliated respiratory epithelial cells. Smoking also decreases cough sensitivity. However, cough sensitivity recovers within 2 weeks after smoking cessation.[23] This helps explain why some patients complain of an increase in cough after smoking cessation. Although the frequency of smoking marijuana is significantly less compared to smoking tobacco, the airway inflammation induced by smoking marijuana is similar to smoking tobacco.[23]

Occupational and Environmental Exposure

Patients may be exposed to respiratory irritants such as vapors, gases, dusts, and fumes in their occupations. Additional environmental exposures include emissions from biomass fuel, wood stoves for cooking or heating, air pollution, cleaning products, natural and manmade disasters (eg, volcano ash, wildfires, World Trade Center collapse), and hobbies (eg, glue for making models, paints, home improvement projects).[23]

Medications

Angiotensin-converting-enzyme (ACE) inhibitors are the most likely medications to cause a cough in patients with approximately 20% of patients taking ACE inhibitors complaining of cough.[15] ACE inhibitor–induced cough is thought to be caused by elevations in bradykinin, substance P, and/or prostaglandins. In addition to converting angiotensin I to angiotensin II, ACE catalyzes the breakdown of bradykinin and substance P. Inhalation of bradykinin stimulates a cough, and substance P is a neuropeptide that is released upon stimulation of C-fibers. Since ACE inhibitor–induced cough has been successfully treated with nonsteroidal anti-inflammatory drugs (NSAIDs), prostaglandins may also play a role in the pathogenesis of ACE inhibitor–induced cough.[21] Onset of cough varies among patients and can occur as early as within a few hours of taking an ACE inhibitor to as long as months. After discontinuing the ACE inhibitor, improvement in cough symptoms occurs within days to weeks; however, complete resolution of cough symptoms may take up to three months.[24] If additional treatment to mitigate cough is needed after discontinuing the ACE inhibitor, NSAIDs, theophylline, dihydropyridine calcium channel blockers, ferrous sulfate, or inhaled cromolyn may be considered.[25]

Excipients in inhaled medications may trigger a cough in some patients with asthma or COPD. Changing the inhaler device or using a spacer may help decrease cough for these patients. Some patients may require a 1- to 2-week treatment with oral corticosteroids to mitigate cough hypersensitivity.[22] Table e13-4 includes some additional examples of medications associated with respiratory adverse effects. It is important to note that this is not a comprehensive list (also see Chapter e48, "Drug-Induced Pulmonary Diseases").

TABLE e13-4

Medications Associated with Respiratory Symptoms

	Cough	Dyspnea	Incidence	Mechanism	Treatment (in addition to discontinuing offending medication)
ACE inhibitors	X	X	• 5%-30% (cough) • 4.5% (dyspnea)	Elevations in bradykinin and substance P and/or enhanced acetylcholine-induced contraction of bronchial smooth muscle	NSAIDs, theophylline, dihydropyridine calcium channel blockers, ferrous sulfate, or inhaled cromolyn
Beta blockers		X	0.5%-5.3%	Blockade of beta-2 receptors in bronchial smooth muscle	• Inhaled beta-2 agonists • Use of cardioselective beta blockers when indicated
Amiodarone	X	X	4%-6%	Influx of inflammatory or immune effector cells to the lung and/or lung parenchymal cell injury with subsequent fibrosis	Corticosteroids
Aspirin and NSAIDs		X	4%-25%	Increased leukotrienes and/or increased sensitivity to leukotrienes	Inhaled beta-2 agonists
Sitagliptin	X		5%-6%	Disruption of neuropeptides and/or cytokines that rely on DPP IV for activation or inactivation	Intranasal or inhaled corticosteroids
Inhaled insulin	X	X	26%-29%	Unknown	None known
Opioids	X	X	28%-66%	Activation of the vagus nerve via inhibition of sympathetic outflow, enhance RARs via release of histamine, and/or constriction of tracheal and bronchial smooth muscle	Corticosteroids, dextromethorphan, magnesium sulfate, lidocaine, propofol
Bleomycin	X	X	10%	Fibrosis of alveolar septa and enlargement of the type II alveolar lining cells	Corticosteroids
Methotrexate	X	X	2%-3%	Pleural pulmonary fibrosis	None known
Bromocriptine	X	X	8%-14%	Pleural pulmonary fibrosis	None known
Cholinesterase inhibitors	X	X	1%	Unknown	None known

Data from References 24–27.

PATIENT CARE PROCESS

Collect Information

- How long has the patient experienced a cough?
- Inquire about the presence of red flag symptoms (Table e13-5).
- Inquire about the presence and severity of symptoms associated with acute bacterial rhinosinusitis (Tables e12-6 and e12-7).
- For adults and adolescent patients (>14 years of age), the patient may complete either of the recommended validated cough questionnaires [ie, Cough Quality-of-Life Questionnaire (CQLQ) or Leicester Cough Questionnaire (LCQ)]. For children less than 14 years of age, the parent may complete the Parent Cough-Specific Quality-of-Life Questionnaire (PC-QOL).
- Obtain an active medical problem list.
- Obtain a family history.
- Obtain an occupational and environmental (eg, pets, carpet/bedding, mold) history.
- Ask about tobacco and marijuana use.
- Inquire about history of allergies and adverse effects.
- Obtain immunization history.
- Obtain and document a complete medication list (ie, name, indication, strength, formulation, and dosing schedule of all prescription, nonprescription, and complementary medications).
- Inquire about the patient's ability to access medications with respect to ability to afford medications as well as ability to pick up medications.
- Inquire about the patient's adherence to their current medications.

TABLE e13-5

Red Flag Symptoms with Report of Nonspecific Cough or Other Respiratory Symptoms

- Hemoptysis
- Smoker >45 years of age with a new cough, change in cough, or coexisting voice disturbance
- Adults aged 55-80 years who have a 30 pack-year smoking history and currently smoke or who have quit within the past 15 years
- Prominent dyspnea, especially at rest or at night
- Hoarseness
- Systemic symptoms (ie, fever, weight loss, peripheral edema with weight gain)
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

Data from Reference 3.

TABLE e13-6

Criteria for the Diagnosis of Sinusitis

Major symptoms	• Purulent anterior nasal discharge • Purulent or discolored posterior nasal discharge • Nasal congestion or obstruction • Facial congestion or fullness • Facial pain or pressure • Hyposmia or anosmia • Fever (for acute sinusitis only)
Minor symptoms	• Headache • Ear pain, pressure, or fullness • Halitosis • Dental pain • Cough • Fever (for subacute or chronic sinusitis) • Fatigue

Note: Presence of at least two major symptoms or one major symptom in combination with at least two minor symptoms is the diagnostic criteria for sinusitis.

Data from Reference 29.

TABLE e13-7

Clinical Presentations Indicating Acute Bacterial Rhinosinusitis

Symptom Type	Symptom Characteristics
Persistent symptoms	• Symptoms lasting >10 days without improving
Severe symptoms at onset	• High fever [>102°F (38.9°C)] • Purulent nasal discharge or facial pain lasting at least three consecutive days
Worsening symptoms	• New onset of fever, headache, or increase in nasal discharge following a viral upper respiratory tract infection lasting 5-6 days with some initial improvement

Note: Antibiotics are recommended when a patient presents with any of these symptom types (ie, persistent symptoms, severe symptoms at onset, or worsening symptoms).

Data from Reference 29.

Assess the Patient

- 3 4 3 Is the cough acute, subacute, or chronic? Although all coughs are acute initially, the duration of the cough at the time the patient seeks

help from a healthcare provider aids in identifying a possible diagnosis (Table e13-1). Respiratory tract infections are the most common cause of acute cough. Subacute cough is most likely a postinfectious cough, followed by exacerbations of underlying diseases. There are several causes of chronic cough with asthma, UACS, NAEB, and GERD representing the most common causes of chronic cough in adult nonsmokers. Asthma, UACS, and GERD may present with additional symptoms consistent with the disease (eg, wheezing, rhinitis, and heartburn, respectively), but they may also present in a "silent" form with cough as the only symptom. Cough worsening during the night is suggestive of UACS.

- Does the patient have any red flag symptoms which are potentially life-threatening and require immediate referral to a physician (Table e13-5)?
- Does the patient have dyspnea? Numerous conditions can cause dyspnea, and the assessment of dyspnea should be conducted by the patient's primary care provider (Table e13-8).
- Does the patient meet diagnostic criteria for sinusitis based on the presence of at least two major symptoms or one major symptom in combination with at least two minor symptoms (Table e13-6)? Does the patient's clinical presentation suggest acute bacterial rhinosinusitis (Table e13-7)?
- Does the patient have any active medical problems that are associated with chronic cough (Table e13-2)?
- Does the patient have any family members with a history of allergies? Do any family members smoke?
- Does the patient have any exposure to occupational or environmental contributors to cough? Does the onset of the cough correlate to presence in the work environment? Cough related to an occupational or environmental stimulus may simply be an isolated symptom resulting from exposure to an irritant, or it may be a manifestation of more significant underlying disease.
- If applicable, assess readiness to quit smoking. If cough is present in a child, is the child exposed to secondhand smoke?
- Are any immunizations indicated (eg, influenza, pneumococcal, diphtheria, tetanus, acellular pertussis)?
- Not all patients with GERD-induced cough have gastrointestinal symptoms. Before suspecting GERD-induced cough in patients without heartburn or regurgitation symptoms, the patient should have an unremarkable chest radiograph, and the following conditions should be ruled out: (1) environmental and occupational irritants (including smoking); (2) medication-induced cough; (3) asthma (cough does not improve with short-acting beta-agonist and inhaled corticosteroids); (4) UACS (cough does not improve after a trial of first-generation antihistamines and intranasal corticosteroids); and (5) nonasthmatic eosinophilic bronchitis (evaluate for presence of eosinophils in sputum or cough that does not improve after a trial of inhaled corticosteroids).
- Is the patient able to access and afford their medications and adhere to their current medication regimen?
- Does the patient have an indication for all of their medications? Does the patient have an active medical problem associated with chronic cough that is not optimally treated?
- If applicable, estimate creatinine clearance to assess dosing of current or new medications.
- Is the patient taking any medications associated with cough (especially ACE inhibitors; see Table e13-4 for additional examples)?

TABLE e13-8

Examples of Conditions and Causes of Dyspnea Organized by Physiological Mechanism

Increased respiratory drive (increased afferent input to respiratory centers)	Stimulation of pulmonary receptors (irritant, mechanical, vascular)
	Interstitial lung disease
	Pleural effusion
	Pulmonary vascular disease (eg, thromboembolism, idiopathic pulmonary hypertension)
	Congestive heart failure
	Stimulation of chemoreceptors (conditions leading to acute hypoxemia, hypercapnia, and/or acidosis)
	Impaired gas exchange (eg, asthma exacerbations, COPD exacerbations, severe pulmonary edema)
	Impaired ventilator pump (eg, muscle weakness, airflow obstruction)
	Metabolic acidosis (eg, renal failure, renal tubular acidosis)
	Decreased oxygen-carrying capacity (eg, anemia)
	Decreased release of oxygen to tissues (eg, hemoglobinopathy)
	Decreased cardiac output
	Pregnancy
	Behavioral factors (eg, hyperventilation syndrome, anxiety disorders, panic attacks)
Impaired ventilator mechanics (reduced afferent feedback for a given efferent output)	Airflow obstruction (eg, asthma, COPD, laryngospasm, aspiration of foreign body, bronchitis)
	Muscle weakness (eg, myasthenia gravis, Guillain-Barré syndrome, spinal cord injury, myopathy, post-poliomyelitis syndrome)
	Decreased compliance of the chest wall (eg, severe kyphoscoliosis, obesity, pleural effusion)

Data from Reference 30.

Plan for Treatment or Referral

- When appropriate, coordinate care with the primary care provider and other healthcare team members to reach consensus on the proposed care plan.
- If cough is accompanied with dyspnea, the patient should be referred to their primary care physician for a more extensive patient assessment.

Patients with red flag symptoms should also be immediately referred to their primary care provider for evaluation (Table e13-5).

- If the patient is exposed to environmental or occupational contributors to chronic cough, refer patient to a primary care provider for objective testing (eg, pulmonary function tests, rhinolaryngoscopy, methacholine challenge, sputum cytology, immunologic tests, beryllium lymphocyte proliferation tests).
- If the patient is ready to quit smoking, recommend appropriate nonpharmacotherapy and pharmacotherapy for smoking cessation (see Chapter 86, "Substance Use Disorders II: Alcohol Nicotine and Caffeine").
- If the patient is not moderately or acutely ill, encourage appropriate immunizations if not contraindicated (eg, influenza, pneumococcal, diphtheria, tetanus, acellular pertussis; see Chapter 147).
- If an asthma exacerbation is suspected as the cause of acute, subacute, or chronic cough, stepping up therapy to improve asthma control may be considered (see Chapter 44).

Acute Cough

- If the patient has an acute cough suspected to be related to an acute respiratory tract infection, there are several therapeutic considerations.
  - If acute cough is suspected to be associated with acute bacterial rhinosinusitis, refer patient to their primary care physician for further evaluation and treatment (Tables e12-6 and e12-7; see Chapter 130, "Upper Respiratory Tract Infections").
  - Acute cough from a viral respiratory tract infection is self-limiting with symptoms resolving within 7 days for most patients. For adult patients, a strong body of evidence to support or refute the routine or broad use of over-the-counter medications is lacking (ie, antitussives, expectorants, mucolytics, antihistamines, acetaminophen, NSAIDs). Swallowing associated with the use of lozenges may help suppress cough, and the soothing effect of lozenges, syrups, and honey may mitigate throat irritation. A combination product containing dextromethorphan, doxylamine, acetaminophen, and ephedrine is effective in reducing cough in adults. Dextromethorphan may also be effective in adult patients. Zinc lozenges (>75 mg/day) may reduce the duration of cough symptoms when given within 24 hours of symptom onset. For pediatric patients greater than 1 year old, honey and vapor rubs containing camphorated oils may be useful. Honey may contain *Clostridium botulinum* spores, and an infant's immature digestive system contributes to the development of botulism. Therefore, honey is not recommended until a child is at least 1 year old. Dextromethorphan may provide relief from cough in pediatric patients but is not recommended in patients less than 2 years old. Cough medications containing codeine are not recommended for patients less than 18 years old due to the risk for respiratory adverse effects.

Subacute Cough

- If the patient has a subacute cough suspected to be a postinfectious cough, inhaled ipratropium may help reduce cough symptoms. If cough symptoms continue to adversely affect quality of life after a trial of inhaled ipratropium, inhaled corticosteroids may be considered. For severe cough, a 5 to 7 day course of oral corticosteroids may be considered (eg, prednisone 40 mg once daily for 5 days). If these therapeutic options do not provide adequate relief from cough, centrally acting antitussive medications (eg, codeine, dextromethorphan) may be considered.

Chronic Cough

- 5 If UACS is suspected as a contributing factor of chronic cough, a therapeutic trial of first-generation antihistamines and/or intranasal corticosteroids may be considered (see Chapter e14, "Allergic Rhinitis").
- If the patient has chronic cough suspected to be related to GERD, treatment includes (1) diet modification to promote weight loss in overweight or obese patients; (2) nonpharmacologic treatment such as elevating the head of the bed and avoiding meals within 3 hours of bedtime; and (3) a 2- to 3-month trial of a proton pump inhibitor, H_2-receptor antagonist, or antacid therapy sufficient to control GERD symptoms (see Chapter 50, "Gastroesophageal Reflux Disease"). If the patient is not experiencing symptoms of GERD (eg, heartburn), pharmacotherapy for GERD is not recommended.

- ACE inhibitors should be discontinued since they may increase the severity of cough even when it is caused by other conditions. Angiotensin II receptor blockers (ARBs) serve as an alternative to ACE inhibitors since they have a lower risk of cough.

Additional General Considerations

- Ensure newly initiated medications do not have clinically significant drug–drug interactions with the patient's current medications. Alternatively, recommend dose adjustments or provide patient counseling for drug–drug interactions that can be managed.
- Identify the appropriate setting for follow-up (eg, face-to-face, phone) and schedule follow-up appointment in 4 to 6 weeks.

Implement by Making Recommendations to the Patient

- Provide patient education regarding all elements of the care plan.
- Ensure patient understanding and agreement with the care plan.
- Implement recommendations that are within your scope of practice.
- Communicate the care plan with the patient's healthcare team and provide recommendations to another healthcare team member that is outside your scope of practice.
- Document the patient encounter in the electronic health record.
- Communicate instructions for follow-up and schedule follow-up with the patient (eg, phone, face-to-face).

Follow-up by Monitoring and Evaluating Outcomes

- Patients should be reevaluated in 4 to 6 weeks and reassessed with the cough severity questionnaire (ie, CQLQ, LCQ, or PC-QOL) to evaluate outcomes.
- Assess patient's adherence to the care plan.
- If medications were changed at initial visit, assess for the presence of adverse effects.
- If the patient was not provided immunizations due to a moderate or acute illness at previous visit, encourage appropriate immunizations if not contraindicated and patient is not moderately or acutely ill at follow-up visit (eg, influenza, pneumococcal, diphtheria, tetanus, acellular pertussis; see Chapter 129, "Lower Respiratory Tract Infections").
- In patients with acute or subacute cough that persists for more than 8 weeks (ie, progresses to chronic cough), a trial of an oral first-generation antihistamine and/or intranasal corticosteroid may be recommended (ie, treatment trial for UACS).
- In patients with chronic cough that does not improve with an oral first-generation antihistamine and an intranasal corticosteroid (ie, treatment trial for UACS), refer patient to their primary care provider for ruling out asthma and NAEB before recommending a treatment trial for GERD.
- For GERD-induced cough, improvement in cough may take up to 3 months, even though GERD symptoms may improve within 4 to 8 weeks.
- For ACE inhibitor–induced cough, most patients will experience a reduction in cough within 8 weeks of discontinuing the ACE inhibitor. However, it may take up to 1 year for the cough symptoms to subside in some patients.

Data from References 3,11,15,22–32

CONCLUSION

Cough plays an important function in protecting the airways. However, alterations in this protective mechanism can result in clinically significant problems. There are many medications and a variety of diseases associated with the development of respiratory symptoms. Patients seek help from

healthcare providers when cough symptoms cause significant impairment in functioning and adversely affect their quality of life. Classifying cough based on duration of symptoms is the first step in narrowing potential etiologies for cough. Some patients may present with symptoms that require immediate referral to their primary care provider. Alternatively, other health professionals may help patients select over-the-counter medications to mitigate acute and subacute cough associated with respiratory tract infections, or recommend a therapeutic trial for UACS or GERD in collaboration with the patient's primary care provider.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ARB	angiotensin II receptor blocker
COPD	chronic obstructive pulmonary disease
CQLQ	Cough Quality-of-Life Questionnaire
GERD	gastroesophageal reflux disease
LCQ	Leicester Cough Questionnaire
NAEB	nonasthmatic eosinophilic bronchitis
NSAIDs	nonsteroidal anti-inflammatory drugs
NTS	nucleus tractus solitaris
PC-QOL	Parent Cough-Specific Quality-of-Life Questionnaire
RAR	rapidly adapting receptors
SAR	slowly adapting receptors
TRPA-1	transient receptor potential ankyrin-1
TRPV-1	transient receptor potential vanilloid-1
UACS	upper airway cough syndrome

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SELF-ASSESSMENT QUESTIONS

1. Which of the following symptoms is the second most common reason patients seek healthcare in ambulatory care settings?

   A. Cough

   B. Sneezing

   C. Sore throat

   D. Shortness of breath

2. Which of the following is an adverse consequence that can occur as a result of chronic cough?

   A. Asthma

   B. Irreversible loss of speech

   C. Myocardial infarction

D. Urinary incontinence

3. Which of the following is the most common cause of acute cough?

A. Chronic obstructive pulmonary disease

B. Gastroesophageal reflux disease

C. Heart failure exacerbations

D. Respiratory tract infections

4. Which of the following is the most common cause of subacute cough?

A. Bronchiectasis

B. Respiratory tract infections

C. Smoking

D. Upper airway cough syndrome

5. Which of the following is one of the most common causes of chronic cough in the United States?

A. Heart failure exacerbations

B. Lung cancer

C. Respiratory tract infections

D. Upper airway cough syndrome

6. Which of the following is a potential drug therapy target for new medications aimed at reducing cough?

A. Central alpha-2 receptors

B. Dipeptidyl peptidase-4

C. Peripheral beta-2 receptors

D. Transient receptor potential vanilloid-1

7. Which of the following is responsible for initiating a voluntary cough?

A. C-fiber receptors

B. Cortex

C. Nucleus tractus solitaris

D. Vagus nerve

8. Which of the following antihypertensive medications is most likely to cause cough?

A. Hydrochlorothiazide

B. Lisinopril

C. Metoprolol

D. Valsartan

9. Which of the following medications for the treatment of type 2 diabetes mellitus is most likely to cause cough?

   A. Insulin detemir

   B. Liraglutide

   C. Metformin

   D. Sitagliptin

10. Which of the following symptoms is considered a potentially life-threatening symptom that indicates need for referral to a physician for further evaluation?

    A. Cough

    B. Nasal congestion

    C. Shortness of breath at rest

    D. Sore throat

11. Which of the following is a validated questionnaire that is recommended to use at initial and follow-up appointments to assess health outcomes in adult patients complaining of cough symptoms?

    A. Asthma Quality of Life Questionnaire

    B. COPD Assessment Test

    C. Leicester Cough Questionnaire

    D. Parent Cough-Specific Quality of Life Questionnaire

12. Which of the following combinations of medications is most appropriate for a patient suspected of experiencing chronic cough due to upper airway cough syndrome?

    A. Albuterol inhaler and fluticasone inhaler

    B. Chlorpheniramine tablets and budesonide nasal spray

    C. Dextromethorphan syrup and zinc lozenges

    D. Omeprazole capsules and ranitidine tablets

13. LB is a 38-year-old African American female who complains of chronic cough as her only symptom. She failed to experience a significant improvement in scores on the Cough Quality-of-Life Questionnaire after a therapeutic trial for upper airway cough syndrome. Her primary care provider has ruled out asthma and nonasthmatic eosinophilic bronchitis using spirometry and sputum eosinophil count, respectively. Currently she is not taking any medications, and is not exposed to any environmental or occupational triggers for cough. Which of the following therapeutic trials would be most appropriate for LB?

    A. Albuterol inhaler

    B. Albuterol inhaler and beclomethasone inhaler

    C. Nonpharmacotherapy for gastroesophageal reflux disease (eg, elevating head of bed)

D. Nonpharmacotherapy for gastroesophageal reflux disease (eg, elevating head of bed) and lansoprazole

14. Which of the following clinical scenarios most likely indicates the need for referral to the patient's primary care provider for antibacterial treatment for acute bacterial rhinosinusitis?

    A. A patient with cough, a temperature of 101°F (38.3°C), headache, and nasal congestion for 1 week with some improvement in symptoms

    B. A patient with cough, a temperature of 101°F (38.3°C), nasal congestion, and fatigue for 3 days without improvement in symptoms

    C. A patient with cough, nasal congestion, headache, and fatigue for 2 weeks without improvement in symptoms

    D. A patient with cough, sneezing, nasal congestion, and clear rhinorrhea for 1 week without improvement in symptoms

15. When should patients return for follow-up to evaluate response to therapeutic approaches for the management of a cough that is not attributed to infection?

    A. 1 to 2 weeks

    B. 4 to 6 weeks

    C. 3 to 5 months

    D. 6 to 8 months

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Cough: This is the second most common reason patients report for seeking healthcare in ambulatory care settings, as described in the introduction of the chapter.

2. **D.** Urinary incontinence: Coughing can cause a loss of bladder control, as mentioned in the introduction of the chapter.

3. **D.** Respiratory tract infections: Viral infections of the upper respiratory tract are the most common cause of acute cough. See the "Epidemiology and Etiology" section of the chapter for more information.

4. **B.** Respiratory tract infections: Postinfectious cough is the most common cause of subacute cough. See the "Epidemiology and Etiology" section of the chapter for more information.

5. **D.** Upper airway cough syndrome: Asthma (including cough-variant asthma), upper airway cough syndrome, nonasthmatic eosinophilic bronchitis, and gastroesophageal reflux disease are the most common causes of chronic cough in adult nonsmokers with upper airway cough syndrome being the most common cause of chronic cough in the United States. See the "Epidemiology and Etiology" section of the chapter for more information.

6. **D.** Transient receptor potential vanilloid-1: Cough receptors have voltage-gated ion channels such as the transient receptor potential vanilloid-1. See the Anatomy and Mechanisms of Disease section of the chapter for more information.

7. **B.** Cortex: Cough sensory input travels from cough receptors to the respiratory center via the vagus nerve. The respiratory center consists of the nucleus tractus solitaris (NTS) and the cortex. See the Relevant Anatomy and Mechanisms of Disease section of the chapter for more information.

8. **B.** Lisinopril: As discussed in the Anatomy and Mechanisms of Disease section of the chapter, ACE inhibitors such as lisinopril are the most likely medications involved in causing cough.

9. **D.** Sitagliptin: As listed in Table e13-4, sitagliptin produces cough in about 5% to 6% of patients using the medication for management of diabetes.

10. **C.** Shortness of breath at rest: Cough associated with dyspnea at rest or at night is a red flag symptom that requires medical evaluation. Table e13-5 lists other symptoms that make self-care of cough inadvisable.

11. **C.** Leicester Cough Questionnaire: Adults and adolescent patients (>14 years of age) can complete either the Cough Quality-of-Life Questionnaire

or Leicester Cough Questionnaire to assess health outcomes, as discussed in the Patient Care Process section of the chapter. For children younger than 14 years of age, a parent or caregiver can complete the Parent Cough-Specific Quality of Life Questionnaire.

12. **B.** Chlorpheniramine tablets and budesonide nasal spray: A combination of a first-generation antihistamine and an intranasal corticosteroid is the preferred treatment for upper airway cough syndrome. For more information, see the Patient Care Process section of the chapter.

13. **C.** Nonpharmacotherapy for gastroesophageal reflux disease (eg, elevating head of bed) As discussed in the Patient Care Process section of the chapter, nonpharmacologic interventions should be attempted in patients suspected of having chronic cough associated with GERD, but pharmacotherapy for GERD is not recommended if the patient is not experiencing symptoms of GERD (eg, heartburn).

14. **C.** A patient with cough, nasal congestion, headache, and fatigue for 2 weeks without improvement in symptoms: These and other symptoms listed in Table e13-7 are “red flags” indicating possible acute bacterial rhinosinusitis and making self-care inadvisable. Instead, these patients should be evaluated by a medical professional.

15. **B.** Four to six weeks: As discussed in the Patient Care Process section of the chapter, patients should be reevaluated in 4 to 6 weeks and reassessed with a cough severity questionnaire.