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The adult with chronic cough

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Activity Objectives

1. To identify the most common causes of chronic cough in adults.
2. To understand the approach to diagnostic evaluation of chronic cough in adults through therapeutic trials.
3. To understand the association of chronic cough in adults and obstructive sleep apnea.
4. To understand the concept of chronic cough hypersensitivity syndrome and therapeutic approaches.

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CLINICAL VIGNETTE

A 60-year old man presents with a history of chronic cough for 16 months. The cough was present day and night, with little mucus production and some associated feeling of shortness of breath and choking sensation, especially at night. Additional complaints included postnasal drip, runny nose, sensation of mucus in the throat, wheezing, and snoring. The patient was referred for persistent cough with inadequate response to previous treatment prescribed by his primary care physician, including antihistamines, nasal steroid sprays, oral prednisone, antibiotics, and proton-pump inhibitors. Physical examination was unremarkable, with stable vital signs, including heart rate of 80 beats/min (regular), respiration of 16 breaths/min (regular), and blood pressure of 128/78 mm Hg. Height was reported as 68.5 inches and weight as 178 lbs. Spirometric values were measured. Forced vital capacity was 4.52 L (106% of predicted value). FEV_1 was

3.45 L (100% of predicted value). The FEV_1/forced vital capacity ratio was 76%. Forced expiratory flow at 25% to 75% of forced vital capacity was 2.24 L/s (79% of predicted value). Results of chest radiography, computed tomographic scans of the sinuses, and high-resolution computed tomographic scans of the chest were all normal. Fraction of exhaled nitric oxide level was measured at 16 ppb. The patient underwent a methacholine inhalation challenge. FEV_1 was reduced 9% at the highest concentration (25 mg/mL).

Because the patient's symptoms did not improve with therapeutic trials for common disorders causing chronic cough, history and review of systems were revisited. On specific questioning, the patient noted that he has had snoring and restless sleep for many years. The patient's spouse reported that snoring was minimal, and no apnea was observed. However, friends of the patient claimed the patient sounded like a "racing tractor trailer" while asleep. The patient also noted increasing daytime lethargy. He also believed that there might have been an episode of choking while eating chicken at a restaurant a few days before his chronic cough started. This led to consideration of obstructive sleep apnea (OSA) or foreign body aspiration. Pulmonary referral was made, and he underwent bronchoscopy and a sleep study.

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REVIEW

Cough is a normal protective mechanism of the respiratory tract, as well as a very common symptom of respiratory disease. Cough is the most common symptom for which patients seek outpatient medical care. Chronic cough (defined in adults as >8 weeks) has an estimated prevalence of 11% to 20% of the population and results in significant reduction in quality-of-life measures.[E1] The majority of patients with chronic cough are seen by primary care providers, but this is a common complaint of patients seeing allergists. In a 2008 survey of American Academy of Allergy, Asthma & Immunology members, almost one third of the respondents estimated that 20% to 40% of their new patients' chief complaints were due to chronic cough.

Cough receptors are located in the respiratory tract from the hypopharynx and larynx to the segmental bronchi. The cough reflex is initiated when mechanical, inflammatory, chemical, and/or thermal stimuli activate cough receptors connected to vagal afferent nerves. This signal is sent to the brainstem cough center with cortical modulation, and then motor efferent nerves activate respiratory muscles. Cough reflex sensitivity (CRS) can be measured and varies between subjects with age and sex differences. Heightened CRS or lower CRS thresholds can be seen in a number of conditions and disease states with increased cough, including after respiratory tract infection (after infectious cough). CRS and airway hyperreactivity (AHR) are independent physiologic processes and respond to different pharmacologic agents. Bronchodilators and inhaled corticosteroids affect AHR but not CRS.

In adults cough is classified by duration into acute (<3 weeks), subacute (3-8 weeks), and chronic (>8 weeks). This classification is useful in considering the causes of cough because postinfectious cough is estimated to last up to 8 weeks, and therefore evaluation for patients with chronic cough should be reserved for those with cough persisting greater than 8 weeks. In an immunocompetent nonsmoking adult with normal chest radiographic results who is not taking angiotensin-converting enzyme (ACE) inhibitor medication, the underlying cause of chronic cough in most patients will be due to one or a combination of the following: (1) asthma syndrome (asthma, cough-variant asthma, or nonasthmatic eosinophilic bronchitis [NAEB]), (2) upper airway cough syndrome (UACS; formerly called postnasal drip syndrome), or (3) gastroesophageal reflux disease (GERD). Up to 25% of the time, more than 1 diagnosis will be operative and will need to be treated concurrently.[E1] In adults the timing and character of the cough (ie, day vs night or wet vs dry) have not been shown to be predictive of the cause.

Published algorithms have suggested diagnostic empiric trials of therapy targeting the 3 most common causes of chronic cough in adults.

Asthma syndrome

Asthma is characterized by chronic or recurrent respiratory symptoms associated with airway inflammation and variable airflow obstruction. In most patients symptoms include wheeze, dyspnea, and/or cough. In asthmatic patients followed over 9 years, worsening cough was seen as the highest predictive indicator for the development of severe asthma.[E2] In some patients determined to have asthma, cough is the sole or predominant symptom, and this is called cough-variant asthma. Because of possible pathophysiologic differences, patients with cough-variant asthma are thought to represent a different phenotype from those with classic asthma.

A third cough-predominant eosinophilic airway disorder was first described by Gibson et al[E3] as eosinophilic bronchitis and is now called NAEB. These are nonsmoking patients with eosinophilic airway inflammation, normal chest radiographic and spirometric results, and no evidence of variable airflow obstruction.

Table E1 contrasts the clinical and pathophysiologic features of these 3 closely related airway eosinophilic syndromes. Mast cells located in airway smooth muscle differentiate classic asthma and cough-variant asthma from NAEB and are associated with the development of AHR. The mechanism of cough in patients with classic asthma, cough-variant asthma, or NAEB is not well understood. Bronchoconstriction can mechanically stimulate airway afferent nerves to induce cough. However, many patients without asthma or airway obstruction will cough during a methacholine challenge, and therefore other mechanisms are also involved.[E4] Some studies have demonstrated increased CRS in patients with classic asthma and cough-variant asthma versus that seen in healthy control subjects and show improved CRS with asthma treatment. Sputum eosinophil counts and cough frequency independently predict asthma control, implying that coughing is not just a reflection of airway inflammation.[E5] Cellular inflammation might be responsible for cough through influence on afferent nerves. Increased concentrations of mediators in induced sputum and bronchoscopic bronchoalveolar lavage fluid, including prostaglandin E_2 and bradykinin, might be involved in the activation of airway nerves.[E6] The specific role of airway mucus hypersecretion in triggering symptoms such as cough is unclear. Lougheed et al[E4] have proposed altered pulmonary mechanics and small airway function as possible pathophysiologic differences between classic asthma, cough-variant asthma, and NAEB. In nonasthmatic subjects a deep inspiration minimizes or prevents bronchoconstriction to inhaled constricting agents, such as methacholine. In asthmatic patients this bronchoprotective effect is diminished or absent. Preservation or loss of the bronchoprotective effect of a deep inspiration might be a pathophysiologic difference between classic asthma, cough-variant asthma, and NAEB.

In adult nonsmokers with chronic cough, multiple prospective studies have shown that asthma or cough-variant asthma is among the most common causes (24% to 29%).[E1] In another study of adults with chronic cough, NAEB was found to be the cause in 13% of cases.[E1]

Treatment for cough-variant asthma conforms to National Asthma Education and Prevention Program Expert Panel Report 3 asthma guideline therapy. Asthma therapy should be initiated in patients with chronic cough with associated wheezing, evidence of variable airflow obstruction, or both. A response with decrement or resolution of cough can take up to 6 to 8 weeks with appropriate therapy. In patients without a response and in the absence of wheezing but with normal spirometric results, other diagnostic tests should be done. Bronchoprovocation testing has been used in patients with chronic cough to diagnose underlying asthma. Direct bronchoprovocation with methacholine challenge testing has a positive predictive value of only 60% to 80% but a negative predictive value of close to 100%, and therefore it is helpful to eliminate asthma as the cause of the chronic cough.[E1]

A new indirect bronchial challenge test, mannitol bronchoprovocation, is now available for clinical use. Indirect challenge tests, such as mannitol bronchoprovocation, are more specific but less sensitive for a diagnosis of asthma. A positive mannitol challenge result is more reflective of active airway inflammation

that is likely to respond to inhaled corticosteroids. Mannitol challenge, like other osmotic and indirect bronchoprovocation tests, has a specific tussive effect, possibly because of stimulation of afferent sensory nerves. Cough is the most common side effect seen during mannitol challenge. This tussive effect is independent of the bronchoconstrictive effect, suggesting different physiologic mechanisms mediated through distinct pathways. Preliminary studies in patients with chronic cough without asthma have measured cough sensitivity elicited by mannitol without a bronchoconstrictive effect, but this has not been standardized or validated. A coughing response to mannitol without the defined bronchoconstrictive effect is not diagnostic of asthma.

Exhaled nitric oxide (eNO) testing has been compared with methacholine challenge testing in patients with chronic cough, with variable results. In one study an eNO level of greater than 35 ppb in patients with chronic cough had a sensitivity of 95% and a specificity of 80% in predicting response to inhaled steroid therapy.[E7] NAEB is diagnosed in patients with chronic cough who have sputum eosinophilia or increased eNO levels without AHR or variable airflow obstruction. NAEB responds to inhaled corticosteroids, and therefore response to treatment does not differentiate asthma from NAEB.

UACS

Postnasal drainage (PND) is defined as the posterior drainage of secretions from the nose or paranasal sinuses into the pharyngolaryngeal area, presumably caused by rhinosinus disease. Normally, adults produce 20 to 30 mL of nasal mucus daily, which is either expectorated or swallowed with saliva. Very often, patients will complain of the sensation of secretions in the back of the throat, leading to throat clearing, coughing, or both. Often, patients might not be able to expectorate mucoid material, and it can be difficult to differentiate patients with PND from patients with globus sensation. This sensation can also be associated with GERD/laryngopharyngeal reflux (LPR) or other esophageal diseases and can also be a manifestation of a somatoform disorder. It is unclear why only a minority of patients with rhinosinus disease have chronic cough.

In studies of patients with chronic cough, 20% to 40% has been found to be due to a variety of rhinosinus diseases, including allergic and nonallergic rhinitis and chronic rhinosinusitis with or without nasal polyps, as well as anatomic abnormalities of the nose and sinuses.[E1] Tonsillar enlargement in both children and adults has also been reported as a cause of chronic cough, and OSA as a cause of chronic cough can be considered part of UACS.

Mechanical stimulation of cough receptors located in the hypopharynx and larynx either directly or indirectly through inflammatory mediators has been proposed as a mechanism of cough in patients with UACS. Heightened CRS has also been proposed, and this increased CRS can be seen in some patients with allergic rhinitis.

The treatment of UACS is based on the underlying upper airway disorder. Some authors have suggested that first-generation antihistamines are preferred for cough caused by UACS because they might directly inhibit CRS.[E1] However, successful treatment of allergic rhinitis with either second-generation oral or topical antihistamines or topical nasal steroids has been shown to reduce associated cough.[E8,E9] In a small pilot study of adult patients presenting with PND and shown not to have asthma or GERD, 28 days of topical nasal therapy with fluticasone, azelastine, and ipratropium bromide was associated with significant improvement in cough, anterior nasal discharge, and endoscopic nasal inspection.[E10] Also, empiric proton-pump inhibitor therapy has been shown to improve chronic cough and hoarseness in adults whose primary complaint was PND.[E11]

GERD

Gastroesophageal reflux refers to the backflow of stomach contents into the esophagus. Transient episodes of gastroesophageal reflux are physiologic and can occur up to 50 times per day not associated with symptoms. GERD refers to a spectrum of pathologic clinical manifestations, both esophageal and extraesophageal. LPR refers to extraesophageal manifestations of GERD, when gastric contents reach the larynx and pharynx. A number of symptoms are reported with LPR, including chronic cough, throat clearing, hoarseness, globus sensation, and vocal cord dysfunction (VCD).

GERD can potentially stimulate cough by means of irritation of the larynx or bronchi through gross aspiration, microaspiration, or gaseous irritation or through an esophageal-bronchial reflex initiated in the esophageal mucosa. pH-monitoring studies have a poor positive predictive value of response of chronic cough to proton-pump inhibitor therapy.[E12] Other nonacid gastric contents (nonacid esophageal reflux disease), including pepsin and other digestive enzymes, can also initiate cough. Combined pH and impedance monitoring can detect acid and nonacid reflux. Recent studies correlating the temporal relationship of acid and nonacid reflux with cough have shown that equal numbers of patients with chronic cough have cough preceding reflux as those with reflux preceding cough.[E13] Patients with reflux preceding cough have a heightened CRS, possibly indicating heightened central nervous system sensitization, which could cause cough in response to physiologic levels of gastroesophageal reflux. Most patients with chronic cough have no more GERD than healthy subjects in terms of numbers of reflux events, acidity, or extension into the proximal esophagus, larynx, or pharynx.[E14]

Up to 75% of patients who were found to have GERD-induced cough do not have symptoms of heartburn or acid indigestion. Endoscopy is typically not helpful, and most patients with chronic cough and GERD do not have evidence of esophagitis. Previous small observational studies and trials of GERD medical therapy in patients with chronic cough suggested a possible mild response. More recent randomized controlled trials and a recent meta-analysis did not shown any correlation between empiric GERD medical therapy in chronic cough in adults or children,[E12] which is similar to recent studies of proton-pump inhibitor therapy and asthma. There might be a subgroup of responders to proton-pump inhibitor therapy, and lifestyle changes to minimize reflux can be helpful in some patients. Extraesophageal manifestations of GERD, including chronic cough, often persist beyond the resolution of esophageal symptoms (heartburn), and therefore trials of therapy can require up to 2 to 3 months. There is nothing specific about the character of chronic cough that is diagnostic for GERD. Laryngoscopy can be valuable in supporting the diagnosis of LPR, but caution is advised in interpreting the findings because sometimes chronic cough itself can cause edema and inflammation of the vocal cords and other changes in the larynx.

Cough and sleep

Normal physiologic cough is diminished at night. Both REM and non-REM sleep suppress cough. The biological mechanisms

for this are poorly understood. Possibilities include dampening of tussive stimuli, cortical inhibition or loss of cortical input, and/ or increased cough reflex threshold in sleep. Gastroesophageal reflux and microaspiration into the airways, both potent stimuli of cough, are also decreased at night.[E15] In adult patients with chronic cough, approximately 50% report sleep disruption caused by cough. The absence of nocturnal cough has been said to be most characteristic of psychogenic or habit cough, but almost all patients with chronic cough have decreased frequency at night.

Recent studies in adults have demonstrated that cough can be the sole manifestation of OSA and can be effectively treated with continuous positive airway pressure (CPAP). In a survey of 108 adults with sleep-disordered breathing (SDB), 33% had chronic cough.[E16] Female sex, nocturnal heartburn, and rhinitis were risk factors for cough caused by SDB. Body mass index, respiratory disturbance index, Epworth Sleepiness Scale, dyspnea, or snoring did not discriminate those with cough caused by SDB. In a recent retrospective report from the United States, 44% of adults presenting with chronic cough were found to have OSA.[E17] On presentation of these patients with chronic cough, OSA was not commonly suspected and could not be identified from the clinical characteristics of the cough.

Possible mechanisms of OSA-associated cough include apnea causing increased transdiaphragmatic pressure and leading to lower esophageal sphincter insufficiency, GERD, and cough. Airway inflammation from epithelial injury associated with OSA can also be operative. Increased sputum neutrophilia has been reported in patients with cough associated with OSA. Upper airway inflammation from epithelial injury associated with OSA could also be causative because these patients can have increased rhinitic symptoms.

Other causes and treatment

In the absence of an obvious diagnosis, initial assessment includes chest radiography, spirometry, and discontinuing smoking and ACE inhibitor therapy. ACE inhibitor–induced cough is said to account for up to 2% of chronic cough in adults. This cough can take up to 4 weeks for resolution. Angiotensin II receptor blocker therapy has not been associated with cough. Some patients experience increased cough after stopping cigarette smoking caused by normalization of the diminished CRS associated with chronic smoke exposure that desensitizes cough receptors in the airway epithelium. This increased cough usually lasts just a few weeks. Bronchiectasis and interstitial pulmonary disease, including pulmonary fibrosis, can also present with chronic cough. Lung cancer has been found to be the cause of chronic cough in less than 2% of all patients presenting with chronic cough.[E1]

Empiric trials of therapy are often used as diagnostic modalities. The therapy must be continued for sufficient time to be diagnostic, depending on the underlying potential cause (Table E2). Treat multiple potential causes when suspected. After initial diagnostic tests and empiric courses of therapy have been tried, in patients with persistent cough, other investigations can be considered depending on associated clinical symptoms, including computed tomographic scans of the sinus and chest, pulmonary function testing with diffusion capacity, bronchoprovocation testing, and bronchoscopy with assessment of airway inflammation and appropriate treatment, depending on the findings.

In more recent studies of patients with chronic cough, up to 40% of patients are not found to have a definable underlying cause and have been labeled as having idiopathic cough.[E18] This has been given different names, including the chronic cough hypersensitivity syndrome. The features of this syndrome include female predominance, minimal or no sputum production, 1 or more sensory cough reflex triggers (ie, cold air, speech, or odors), urge to cough (tickle or itch) localized to the throat area (laryngeal hypersensitivity), and significant adverse effect of cough on quality of life.

There are overlapping possible mechanisms for chronic cough hypersensitivity syndrome, all of which emphasize laryngeal hypersensitivity:

(1) Postviral vagal neuropathy: a laryngeal sensory neuropathy after an antecedent viral illness of undetermined time lag. Motor nerve branches, sensory nerve branches, or both can be involved, leading to cough and/or laryngospasm, vocal cord paresis, globus sensation, or odynophonia. Medical treatments have included gabapentin, pregabalin, amitriptyline, and botulinum toxin type A.

(2) Laryngeal dysfunction with chronic cough and throat clearing: causing chronic laryngeal irritation, which, along with other inflammatory and irritant stimuli, can predispose the larynx to become hypersensitive to external stimuli and trigger paradoxical VCD during inspiration. This can lead to shortness of breath and clinically be mistaken for asthma or present primarily with cough as a protective mechanism, opening the glottic constriction occurring during VCD. Behavioral therapy and speech pathology or voice therapy have been shown to be very effective.

(3) Irritable larynx syndrome: measured by histamine inhalation challenge demonstrating paradoxical vocal cord adduction measured as a decrease in inspiratory flow rate (laryngeal hyperreactivity). Laryngeal hyperreactivity is proposed as a marker of upper airway involvement irrespective of the trigger of chronic cough and can be followed as an objective tool to evaluate response to therapy.

THE CASE REVISITED

At the time of the bronchoscopy, the patient had marked narrowing of his airways with expiration and some mild areas of erythema. The trachea was diffusely erythematous. Gram staining and cultures indicated normal respiratory flora. Cytology indicated features of both atypical squamous metaplasia and atypical cells consistent with reactive changes.

Bronchoalveolar lavage fluid showed predominance of neutrophils and macrophages. No foreign body was seen.

Nocturnal polysomnography was performed. The first part of the test lasted a total of 168 minutes, with total sleep time of 131 minutes and a sleep efficiency of 78%. The patient's sleep onset was normal at 10 minutes. Sleep architecture through the first portion of the night consisted of only stage 1 and 2 sleep, with no REM sleep observed. Frequent respiratory events interrupted sleep, with an apnea/hypopnea index of 55.9 events per hour, a respiratory effort–related arousal index of 39.4 per hour, and a combined respiratory disturbance index of 95.3 events per hour. The lowest oxygen saturation was 83%. Cardiac rhythm was normal through the study. No significant periodic limb

movements, bruxism, or REM behavior disorder were noted in the first portion of the night.

In the second portion of the night, the patient was started on nasal CPAP and was titrated to 12 cm of water pressure. This pressure appeared to be optimal in the lateral and supine positions. In the second portion of the night, there were increased limb movements at 21.6 events per hour.

The study was consistent with severe OSA syndrome and periodic limb movement disorder. The patient was started on a trial of nasal CPAP at 12 cm of water pressure.

The patient returned in 4 weeks, noting that when nasal CPAP was used consistently, the cough resolved completely.

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TABLE E1. Airway eosinophilic syndromes associated with cough

	Classic asthma	Cough-variant asthma	NAEB
Symptoms	Dyspnea, cough, wheeze	Cough predominant	Cough often associated with upper airway symptoms
Atopy	Common	Common	Same as general population
AHR	Yes	Yes/? less sensitive	No
CRS	Normal	Normal/increased	Increased
Wheeze threshold	↓	↑	↑↑
eNO	Usually ↑	Usually ↑	↑
Mast cells in airway smooth muscle	+	+	−
Response to bronchodilator	Good	Good	Absent
Response to steroid	Good (eosinophilic)	Good	Good
Subepithelial thickening	+	+	+
Decrease in lung function	+	±	±
Bronchoprotective effect of deep inspiration	Absent	Impaired	? Preserved

TABLE E2. Therapeutic trials: When to expect response

Smoking cessation	Up to 4 wk
ACE inhibitor discontinuation	Up to 4 wk
Postnasal drip syndromes	Up to 2-4 wk
Asthma	Up to 6-8 wk
GERD	Up to 8-12 wk
Eosinophilic bronchitis	Up to 3-4 wk