Cough Conundrums: A Guide to Chronic Cough in the Pediatric Patient

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PRACTICE GAPS

Cough is a common presenting chief complaint in the pediatric population. Characteristics of cough that are revealed in either the history or physical examination can facilitate diagnosis and management.

OBJECTIVES *After completing this article, readers should be able to:*

1. Manage the common causes of cough, recognizing the underlying mechanics of coughing.
2. Discuss effective and efficient management options based on gathered clinical evidence.
3. Review existing guidelines for the management of chronic cough.
4. Identify when subspecialty referral is appropriate.

CLINICAL CASE

A 12-year-old boy with autism spectrum disorder presents with concerns of progressively worsening wet-sounding cough for 3 weeks that is worse at night and clears throughout the day. He was initially evaluated 2 weeks earlier and given albuterol for possible reactive airway disease. He denies fevers, exercise limitation, or viral prodrome. On examination he is afebrile, with a respiratory rate of 18 breaths/min, heart rate of 100 beats/min, blood pressure of 100/67 mm Hg, and pulse oxygen saturation of 100% on room air. He appears comfortable. Physical examination is remarkable for bilateral upper lobe faint expiratory wheezing and right-sided neck swelling. What is the next step in the management of this patient?

INTRODUCTION

Cough is a source of considerable financial burden on the health-care system, accounting for approximately $29.5 million in annual outpatient visits in the United States. (1) The burden on the individual is equally high, costing caregivers' time and lost wages, school absenteeism, poor sleep quality, and

AUTHOR DISCLOSURE Drs Masson, Kier, and Chandran have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CF	cystic fibrosis
COVID-19	coronavirus disease 19
CT	computed tomography
EVALI	electronic cigarette or vape–related acute lung injury
FEV_1	forced expiratory volume in 1 second
GER	gastroesophageal reflux
OTC	over the counter
PBB	protracted bacterial bronchitis
PFT	pulmonary function testing
UACS	upper airway cough syndrome

sports limitations in those affected. According to Allied Market Research, the global "cough remedies market" for over-the-counter (OTC) medicines in the category of cough and cold is enormous, amounting to an estimated $7.08 billion and estimated to grow to $9.91 billion by 2030. (2)

Considering the burden on the outpatient setting specifically, an Australian multicenter study found that 75% of a cohort of caregivers sought 5 or more physician consultations to determine the etiology and treatment for prolonged coughing. (3) Furthermore, 14% of these sought 15 or more consultations. (3) A mean generic pediatric health-related quality of life score, using the Pediatric Quality of Life Inventory, was also used in this study, and scores were found to be similar to those with other chronic illnesses, such as cardiac disease and diabetes. (3) Reassuringly, quality of life significantly improved with resolution of coughing. (3)(4)

Caregivers often seek to treat disruptive coughing with OTC remedies often consisting of multiple ingredients. Although caregivers hope for cough resolution by administering OTC remedies, OTC remedies mask both the character and severity of the cough and risk significant adverse effects.

Cough is a natural protective mechanism of the body. A strong and efficient cough is needed to mobilize secretions and eliminate foreign entities in the respiratory tract. It is, therefore, important to investigate the underlying reason for cough before suppression.

EPIDEMIOLOGY

When considering 4 major international pediatric guidelines (American, Belgium, British, and Australian), there are some notable differences for determining the duration of chronic cough. The American College of Chest Physicians defines chronic cough as longer than 4 weeks, (5) Belgium guidelines consider chronic cough as longer than 3 weeks, (6) the British Thoracic Society defines chronic cough as longer than 8 weeks, (7) and Cough In Children and Adults, Diagnosis and Assessment, an Australian guideline, considers chronic cough to be longer than 4 weeks in duration. (8) The pediatric age group is also variably defined by age (<15–18 years) depending on the guideline considered. The general rationale across all guidelines takes into consideration the natural process of infectious causes of cough and allows for adequate resolution of the expected acute inflammatory process. Studies suggest that on average 69% of children report coughing with colds, with minimal differences between age groups. (9) Conversely, the prevalence of cough without colds increases with age from 34% in 1-year-olds to 55% in children aged 14 to 17 years. (9) Coughing at night occurs in 25% of children overall. (9) Despite previous meticulous diagnostic protocols and investigation tools, 12% to 42% of chronic cough remains unexplained or refractory. (9) In general, there is consensus that coughing for more than 8 weeks requires evaluation. (5)(6)(7)(8) Chronic cough, for the purposes of this article, is defined as longer than 4 weeks in duration.

PATHOGENESIS OF COUGH

Cough is a powerful and normal protective reflex and is both a physiological mechanism for mucociliary clearance and an essential component of the innate immune system. Healthy children cough 10 to 34 times daily. (10) Cough may be voluntary or reflex initiated. The 3 phases of cough, namely, inspiration, compression, and expiration, are regulated by a sophisticated pathway involving afferent and efferent arms as well as the central pathway. A noxious stimulus sends a signal through the afferent arms to the central pathway, which involves the nucleus tractus solitarius, the brainstem respiratory network (cough center), the subcortex, and the cortex. The central pathway through the efferent arms activates the respiratory muscles, larynx, and pelvic muscles. The cough pathway, which matures throughout infancy, is thought to be regulated by a continuous feedback loop in the afferent arms and the cough center (Fig 1). (11)

CAUSES OF CHRONIC COUGH

In the following sections we discuss chronic cough: common causes (Table 1), uncommon causes (Table 2), and emerging causes (Table 3). Each table lists the diagnosis, risk factors, clinical presentations, characteristics of the cough, evaluation needed, and ensuing sequelae. The most common causes of cough are asthma or asthmalike conditions, postinfectious causes, upper airway cough syndrome (UACS), gastroesophageal reflux (GER), and protracted bacterial bronchitis (PBB). (12) Age is an important factor to consider in diagnosing the etiology of the cough. In infants and children younger than 3 years, PBB and postinfectious causes account for a combined 68% of cases. (12) Conversely, these conditions rarely afflict preschool-age children (3–4 years old), accounting for only 9% of cases. Infectious agents and habit cough predominate in children older than 11 years and in teenagers. (5)(9)

Common Causes of Chronic Cough

Asthma. Asthma is overall the most common cause of chronic cough in the pediatric age group. Asthma is also a

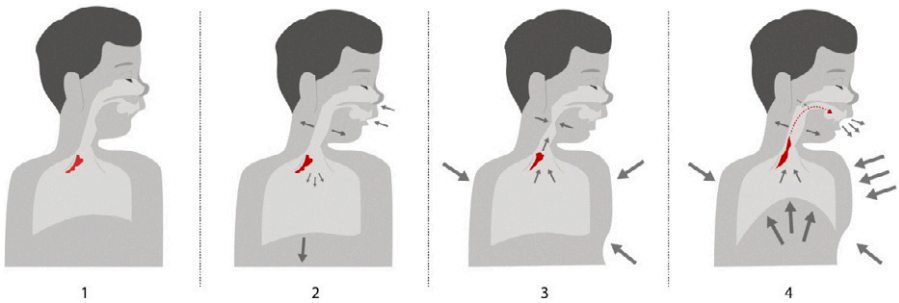

Figure 1. The phases of cough: 1, rest; 2, inspiratory phase (inspiration with glottis open); 3, compression phase (glottic closure and increasing intrathoracic pressures); and 4, cough with glottic opening (increased diaphragmatic pressures and expulsion).

multifaceted disease, characterized by chronic airway inflammation and variable expiratory airflow limitation. Key signs and symptoms of asthma include wheezing, shortness of breath, chest tightness, and cough, which typically vary in intensity over time. (13) Cough usually is nonproductive and occurs in "coughing fits" or "jags" when facing a noxious stimulus. Chronic cough is often a manifestation of persistent airway inflammation. (13) This inflammation perpetuates a cycle of airway hyperresponsiveness, airflow limitation, and disease chronicity. Atopy, refers to the genetic tendency toward the development of an IgE-mediated response to antigens/allergens. Atopy is the strongest predisposing risk factor for developing asthma. (14) Second- and third-hand tobacco smoke continue to be important preventable causes of poorly controlled asthma, and a frequent trigger for exacerbation and reduced lung function. (15)(16) Environmental triggers such as wild fires, cooking smoke, scented products, cleaning agents, and perfumes should be evaluated.

Asthma is very difficult to diagnose in young children because the utility of pulmonary function testing (PFT) is limited. The asthma predictive index has become an invaluable tool in providing insight into which infants/preschoolers with recurrent wheezing will have asthma at school age. A positive asthma predictive index score must include recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (eczema or parental asthma) or 2 of 3 minor criteria (allergic rhinitis, wheezing without colds, or peripheral eosinophilia $\geq$4%). (17)

Clinical diagnosis of asthma remains relatively straightforward based on the presenting symptoms and the patient's response to bronchodilator therapy. PFT performed by experienced personnel typically shows limitation of expiratory airflow (represented by a reduction in forced expiratory volume in 1 second [FEV_1] and/or FEV_1/forced vital capacity) reversed by bronchodilators (FEV_1 increased by 12% after bronchodilator use). Such testing is often normal when the patient is asymptomatic. Per Global Initiative for Asthma and National Heart, Lung, and Blood Institute asthma guidelines, referral to a specialist is indicated when symptoms persist and/or exacerbations occur despite appropriate treatment (18)(19).

Fractional exhaled nitric oxide testing can provide additive information when monitoring asthma control by measuring airway inflammation. This is particularly useful in those with allergic or eosinophilic asthma. This test does not by itself diagnose asthma, but it can provide additional information in determining whether the current treatment plan is objectively effective and whether further tailoring of treatment is required to achieve the best results. (20)

Infectious Causes

Viral Upper Respiratory Tract Infections

A common manifestation of viral upper respiratory tract infections, as well as viral bronchiolitis, is cough. Uncomplicated coughing associated with common viruses typically lasts 10 to 14 days but can last up to 3 weeks. (21) Prolonged coughing beyond this period can occur due to the phenomenon of postinfectious hypersensitivity (see later herein). Common viral etiologies for an upper respiratory tract infection include rhinovirus (30%–50%), influenza (5%–15%), coronaviruses (10%–15%), respiratory syncytial virus (5%), and parainfluenza viruses (5%). (22)(23)(24)

Bacterial

Bordetella pertussis, although overall not a common cause of chronic cough, deserves discussion because treatment is essential in the acute period for those affected as well as close contacts. In nonoutbreak settings, 32% of prolonged cough is due to pertussis. (23) Importantly, the diagnosis needs to be considered even when the classical signs of pertussis are not present to prevent community spread. (21) Cough is characterized as paroxysmal with a terminating inspiratory "whoop." In its early stages, pertussis can present similar to the common cold, with the typical cough occurring at approximately 1 to 2 weeks. In infants, apnea may be the presenting sign requiring hospitalization. (25)

Table 1. Common Causes of Chronic Cough

ORGAN SYSTEM	ETIOLOGY		PRESENTATION	RISK FACTORS	EXAMINATION	COUGH POINTERS	EVALUATION	SEQUELAE
Pulmonary causes	Asthma		Cough, wheeze, exercise intolerance, responsive to SABA, chest pain/tightness	Early viral infections in genetically predisposed individuals, environmental exposures	Wheeze, cough, diminished air entry	Spastic/dry sounding, responds to bronchodilators, cough resolves with empirical trial of inhaled corticosteroids	Allergy testing	Airway remodeling
	Infectious	Viral	Cough, +/- fever, URTI symptoms	Sick contacts	Variable presentation, wet or dry cough, rhonchi, rales	Wet or dry	Nasopharyngeal/sputum PCR	Progression of infection to pneumonia and/or community spread; disease is often self-limited
		Bordetella pertussis	3 stages: catarrhal, paroxysmal, convalescent URTI symptoms, cough, apnea in infants	Sick contacts, unvaccinated	Paroxysmal cough	Cough that terminates with inspiratory "whoop"		
		Mycoplasma pneumoniae	Tracheobronchitis, pharyngitis, malaise, fever, cough, headache	Sick contact exposure	Productive cough, wheeze, rales	Productive, but may be absent		
	Postinfectious hypersensitivity		Persistent cough 3–8 wk after viral illness	Unknown	Coughing without wheeze	Often dry		Self-resolving
	Protracted bacterial bronchitis		Chronic cough >4 wk	Frequent viral illnesses, child care attendance, tracheomalacia, bronchomalacia	Wet coughing	Productive cough, wheezing, worse at night	BAL	Bronchiectasis, 40% recurrence rate
Upper airway causes	Chronic rhinosinusitis/UACS		Headaches, nasal congestion +/– discharge	Chronic allergies, narrow sinuses, deviated septum	Sinus/facial tenderness, nasal congestion	Often dry, sometimes productive if copious nasal discharge	CT sinuses	Nasal polyps, diminished quality of life
GI causes	Gastroesophageal reflux		Choking, gagging, spit-up around feeding, neck/body posturing, regurgitation, epigastric or substernal pain	Prematurity, Developmental delay, poor truncal tone, obesity, correlation with feeds	Voice changes, upper airway sounds, wheezing, tachypnea	Wet or dry cough, worse in supine position	pH probe monitoring	Failure to thrive, recurrent wheezing/pneumonia

BAL=bronchoalveolar lavage, CT=computed tomography, GI=gastrointestinal, PCR=polymerase chain reaction, SABA=short-acting β_2-agonist, UACS=upper airway cough syndrome, URTI=upper respiratory tract infection.

Table 2. Uncommon Causes of Chronic Cough

ORGAN SYSTEM	ETIOLOGY	PRESENTATION	RISK FACTORS	EXAMINATION	COUGH POINTERS	EVALUATION	SEQUELAE
Pulmonary causes	Retained foreign body	History of aspiration, coughing with eating, witnessed or unwitnessed inhalation/ ingestion of food or nonfood item	Young age, developmental delay, young sibling	Focal wheeze or absent breath sounds	Initially dry, may progress to wet if infected	Flexible or rigid bronchoscopy to retrieve	Bronchiectasis
	Cystic fibrosis	FTT, chronic cough, recurrent or chronic bacterial pneumonia, chronic sinusitis, nasal polyps	Family history, absent newborn screen	Failure to gain weight, wheeze, rales or rhonchi, sinusitis, nasal polyps	Wet cough productive of copious thick and sticky sputum	Sweat chloride, sputum culture, bronchoscopy, chest CT	Bronchiectasis, obstructive and progressively restrictive lung disease, transplant
	Ineffective cough	Rhonchi persisting after coughing, weak cough, recurrent pneumonia	Neuromuscular disease, poor muscle tone, developmental delay, young age, postoperative	Poor truncal tone, weak breath sounds, weak cough	Weak cough, asynchronous breathing	MIP and MEP	Chronic lung infections, bronchiectasis
Upper airway causes	Auricular nerve irritation	Chronic cough associated with compression of the Arnold nerve	Postsurgical, chronic allergies	Cough related to ear canal stimulation/ obstruction	Dry	Laryngoscopy	Psychosocial
	Vascular rings/slings	Recurrent wheezing, coughing	Presence of other anatomical abnormalities	Dry coughing, swallowing dysfunction, recurrent wheezing	Dry	Contrast chest CT	If not addressed may cause critical airway obstruction
GI causes	Tracheoesophageal fistula	Cough after feeds	Acquired: tracheal or esophageal surgeries, Congenital: high-risk syndromes	Wet or chronic dry cough, temporal relation to eating/ drinking	Barking cough around feeds	Chest CT, upper endoscopy, or bronchoscopy	Bronchiectasis, chronic pneumonia
Infectious causes	Fungal pneumonia	Low-grade fevers, cough, environmental exposure	Travel or exposure history, neutropenia, hematologic malignancy, HIV, lung transplant, prolonged ICU stay >21 d	Spectrum of wheeze, rhonchi, or rales depending on disease severity	Productive cough		Death in immunocompromised
Other causes	Habit cough	Cough without known triggers, not when sleeping or distracted	Anxiety, depression, stress	Clear lungs	Honking cough		Psychosocial
	Mediastinal masses	Slow worsening	None	Mass effect, lymphadenopathy	Dry or wet cough	Chest CT, MRI chest	Death

CT=computed tomography, FTT=failure to thrive, HIV=human immunodeficiency virus, MEP=maximal expiratory pressure, MIP=maximal inspiratory pressure, MRI=magnetic resonance imaging.

Table 3. Emerging Causes of Chronic Cough

COMMON ETIOLOGY	PRESENTATION	RISK FACTORS	EXAMINATION	COUGH POINTERS	EVALUATION	SEQUELAE
COVID-19 related	Dyspnea, dry cough	Unknown	Normal	Dry		Unknown
EVALI	Cough, nausea, dyspnea chest pain with vape exposure	Vape, especially JUUL brand	Normal	Dry	Noncontrast chest CT	May self-resolve after vape cessation, prolonged dyspnea

COVID-19=coronavirus 2019, CT=computed tomography, EVALI=electronic cigarette/vape–related acute lung injury.

Mycoplasma pneumoniae also is not overall a common cause of respiratory infection, but because it is both quite treatable and communicable, it also should be considered in the differential diagnosis alongside more common causes. Presentation includes tracheobronchitis, pharyngitis, cough, and, sometimes, wheezing. In general, symptoms are mild, lending to the term *walking pneumonia*. Cough is often productive but sometimes absent in children older than 5 years. (26)

Typical bacterial etiologies (*Streptococcus pneumoniae, Haemophilus influenza*) that cause pneumonia generally do not cause prolonged coughing if adequately treated. The strongest predictors of pneumonia in general in children are fever, cyanosis, and increased work of breathing. Bacterial pneumonia generally is associated with crackles (rales) on chest auscultation, focal chest radiographic findings, chest pain, shortness of breath, fever, productive coughing with possible hemoptysis, and ill appearance. After appropriate antibiotic use, coughing resolves within 2 to 3 weeks. (27)

Postinfectious Hypersensitivity. Patients who exhibit coughing more than 3 weeks after the resolution of acute upper respiratory tract infection symptoms may have a postinfectious cough. This occurs in 1 in 10 children who contract viral illnesses such as respiratory syncytial virus and rhinovirus. The chest radiographs are normal, and the cough eventually resolves on its own. This is thought to be due to extensive inflammation and disruption of airway epithelial integrity, making them sensitive to nonnoxious stimuli, thereby lowering the threshold for cough (Fig 2). (25)(26)

When postinfectious cough emanates from the lower airway, it often presents with an excessive amount of mucus secretion accumulation and cough receptor hyperresponsiveness. Antibiotics have no role in the management of postinfectious cough except in the presence of bacterial sinusitis or early pertussis. Although optimal treatment is unclear, the use of inhaled ipratropium may be helpful. Albuterol has not proven to be better than placebo. (25)

Upper Airway Cough Syndrome. UACS, formerly known as postnasal drip, is a broad category that includes allergic and nonallergic rhinitis and chronic rhinosinusitis. Saline sinus rinses can be beneficial. Antibiotics can be used if an acute bacterial cause for sinusitis is suspected, eg, fevers, facial tenderness, headaches, or sinus pain. Cough caused by allergic etiologies improves with intranasal corticosteroids or intranasal or systemic antihistamines. The suspicion of UACS rests on the patient's ability to report the presence of mucus dripping along the posterior pharynx. The finding of mucoid secretions at the posterior pharynx or a cobblestoned appearance of the posterior pharyngeal mucosa is suggestive. Often these patients present with throat clearing or snorting-type coughing. Environmental history is crucial to identify possible allergic triggers. In these patients, allergy testing may be beneficial, and avoidance of exposure to specific allergens is key to management. Empirical use of systemic or intranasal antihistamines with or without a decongestant is both diagnostic and therapeutic. (27)

Gastroesophageal Reflux. GER most likely causes cough by stimulation of an esophageal-bronchial reflex and by irritating the lower respiratory tract by microaspiration. (28) When GER causes cough, there may be no gastrointestinal symptoms up to 50% to 75% of the time. (28) GER, when present, plays a significant role in the control of chronic cough, asthma without allergy, and posterior laryngitis. Twenty-four–hour pH monitoring can help to establish a temporal correlation between cough and GER and is considered to be the most accurate diagnostic method for children with suspected GER. Per the American College of Chest Physicians guidelines, for children 14 years or younger with chronic cough in the absence of underlying lung disease, treatment for GER should not be used without clinical features of GER, such as recurrent regurgitation, dystonic neck or body posturing in infants, or heartburn/epigastric pain in older children. For those 14 years or younger with symptoms and signs, or tests consistent with pathologic GER, treatment with acid-suppressive therapy should be initiated for 4 to 8 weeks along with lifestyle modifications, and their response reevaluated. (28)(29)(30)(31) Lifestyle modifications include

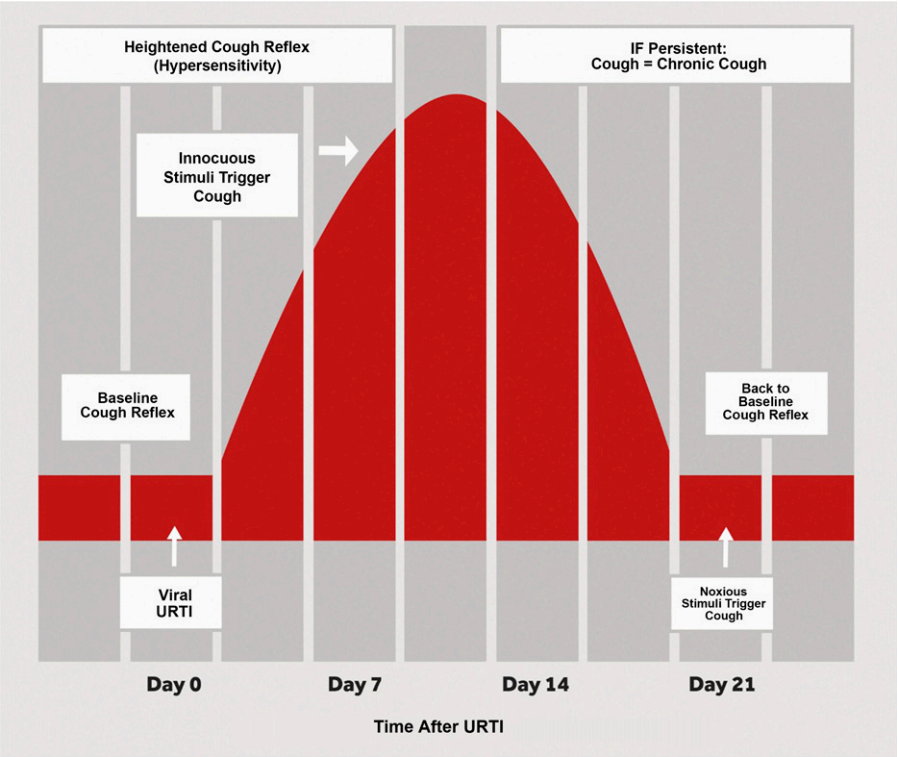

Figure 2. Postinfectious hypersensitivity cough. Following an infectious etiology, the airway becomes more sensitive to cough when exposed to what was previously innocuous stimulus. Cough should resolve within 3 weeks but can persist to a more chronic state during which it lasts for no more than 8 weeks. URTI=upper respiratory tract infection.

weight loss through diet modification if overweight or obese, elevating the head of the bed while sleeping, and meal avoidance 3 hours before bedtime. Barring improvement with these modification, therapy may be initiated via antacids, proton pump inhibitors, or H2 blockers. (32)

Protracted Bacterial Bronchitis. The initial definition of PBB comprised a history of chronic wet cough, a positive bronchoalveolar lavage culture for a known respiratory pathogen, and a clinical response to a 2-week course of oral antibiotics for community-acquired pneumonia. The current criteria for diagnosing PBB is largely clinical and includes a wet cough lasting at least 4 weeks, absence of other findings to identify another cause of the cough, and resolution of the cough with at least 2 weeks of an antibiotic. (33) Chest radiography may be performed to exclude other causes but often does not show any specific signs of PBB. If able to perform lung function testing, airway obstruction without reversibility may be seen. Forty percent of all children with PBB will have a recurrence of 1 or more episodes. In cases of recurrence, referral to a pulmonologist is indicated to perform a flexible fiberoptic bronchoscopy with bronchoalveolar lavage to obtain lower airway cultures for both targeted antibiotic treatment and airway evaluation. Bronchoscopy usually reveals purulent secretions in the airway. Typical pathogens include *Haemophilus influenzae, S pneumoniae,* and *Moraxella catarrhalis.* (33)

The cause of PBB is not known, but because it is commonly seen in younger children (<6 years of age), it may be due to frequent viral illnesses, which cause airway injury and inflammation, thereby making it easier for bacteria to grow and cause infection. Children who attend child care have been known to be at higher risk for PBB. Those with underlying tracheomalacia or bronchomalacia may also be at higher risk because these conditions can lead to trapping of mucus in the airways. (34)

Uncommon Causes of Chronic Cough

Apart from the common causes of cough discussed previously herein, there are uncommon causes of cough that must be considered. Some of these uncommon causes may have "cough pointers," or features of cough that can lead to a potential diagnosis. Knowledge of these pointers may minimize diagnostic evaluation that may otherwise delay the diagnosis and treatment.

Despite these pointers, there are times when a diagnosis may still be elusive. In up to 20% of patients with chronic cough, treatments initiated are not curative, (34)(35) leading the care team to consider more uncommon causes. When

contending with idiopathic chronic cough, the challenge lies in finding the precise mechanism responsible for the troublesome sign and/or symptom so that appropriate therapeutic measures can be initiated efficiently to relieve the cough. Some uncommon causes to consider are retained foreign body, cystic fibrosis, ineffective cough, auricular nerve irritation, vascular rings or slings, tracheoesophageal fistula, mediastinal masses, fungal pneumonia, or habit cough.

Retained Foreign Body. A history of sudden onset of coughing in an otherwise healthy child without evidence of upper respiratory tract infection is highly suspicious for aspiration; however, this history is often absent. (36) The classic triad of new-onset cough, wheezing, and asymmetrical breath sounds is seen in only 16% to 40% of patients. (36) In general, patients with tracheal foreign bodies present with dyspnea and are more easily diagnosed due to acuity and severity of symptoms. (36) Bronchial foreign bodies, which account for 80% to 90% of aspirations, typically are diagnosed later and are more likely to present with partially decreased breath sounds. Partial obstructions can make the diagnosis elusive, resulting in mistaken diagnosis and treatment for presumed upper respiratory tract infections, bronchiolitis, pneumonia, or asthma. In a child with chronic cough, recurrent pneumonias, persistent croup, or asthma that fails standard medical therapy, one should always consider a retained foreign body in the differential diagnosis. Generally, chest radiographs are considered the first diagnostic study. Confirmation is possible, either in the way of finding the radiopaque object or suspecting air trapping, but radiographs cannot be used to exclude the diagnosis. Most foreign bodies aspirated are radiolucent and, therefore, chest radiographs are normal in more than 50% of tracheal foreign bodies and 25% of bronchial foreign bodies. In this way, end-inspiratory and end-expiratory films can be helpful in the more cooperative child. (36) Fluoroscopy and computed tomography (CT) have historically been used as alternatives for diagnosis. (36) CT sensitivity approaches 100%, with the only limitation being the size of the object. However, if clinically suspected, a foreign body aspiration must be ruled out by bronchoscopy for direct visualization. (36)(37)(38)(39)

Cystic Fibrosis. Cystic fibrosis (CF) is an autosomal recessive genetic disease characterized by 2 disease-causing mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which causes the CFTR protein to become dysfunctional, ultimately resulting in the mucus of various organs to become thick, tacky, and difficult to mobilize. CF disease has evolved differently with the advent of extensive genetic testing, newborn screening, and available therapies. Historically, chronic productive cough has previously been a cornerstone sign in this disease. Newborn screening has been an effective means to make this diagnosis early on, but this is not perfect. Sweat chloride testing and genetic testing can adequately diagnose this condition in those with a gamut of signs and symptoms, notably chronic coughing, failure to thrive (growth failure), malabsorption, chronic sinusitis, and recurrent pneumonia. If CF is suspected, referral to a pulmonologist is essential to facilitate both testing and long-term care. Long-term prognosis ultimately depends on the degree of bronchiectasis that has developed secondary to recurrent and chronic pulmonary infections. Intravenous antibiotic treatment is generally required to treat these infections. Lung transplant and/or death have historically been the end points to this disease, but the recent development of CFTR modulators provides hope and optimism for this disease going forward. (40)(41)

Ineffective Cough. Coughing, however natural, may not come easily to patients with surgical incisions, thoracic trauma, respiratory muscle fatigue, or neuromuscular weakness. Mechanisms normally existing in the lower bronchioles and alveoli to maintain airway patency include the mucociliary system, immune system, and lymphatics, which may become compromised either acutely (postoperative recovery) or chronically (spinal cord injury). These systems depend on the strength of the diaphragm and intercostal muscles to generate adequate cough force. When this is lacking, the basic cough cycle is impaired, thereby creating a nidus of infection in the lower airway via retained secretions. Cough in these patients is, therefore, weak and inadequate in clearing secretions. Rhonchi are often heard in the chest after a maximal cough effort. Devices such as cough-assist machines may help to encourage both an adequate inspiratory and expiratory pressure to improve chest clearance, and devices such as chest percussive vests with nebulizer treatments can help to hydrate, break up, and liberate secretions. Assessment of mean inspiratory and expiratory pressures can be helpful to assess diaphragmatic strength in these patients. (42)

Auricular Nerve Irritation. Consideration for other, more unusual causes for coughing may stem outside of the airway, such as in cases of wax or a foreign body in the external ear canal, or in the case of auricular nerve damage during neck injury/surgery, or tumor compression. These pathologies irritate the auricular branch of the vagus nerve, known as the Arnold nerve. Tonsillar size should be assessed in these cases, as hypertrophied tonsillar tissue may impinge on the epiglottis and cause a similar

presentation. This is mostly a diagnosis of exclusion. Treatment is curative with removal of the foreign body. If nerve irritation is due to nerve damage, treatment with gabapentin has been suggested. (43)

Vascular Rings/Slings. Congenitally abnormal configurations/formations of the aortic arch and its major branches can create vascular rings around the trachea and esophagus with varying degrees of compression. (44) One of the most common anomalies is a double aortic arch, where the ascending aorta bifurcates and compresses the trachea and esophagus. (44) Signs and symptoms such as harsh-sounding cough, stridor, dyspnea, and upper respiratory tract infections present initially in early childhood. Vascular rings and slings can be diagnosed with the aid of echocardiography, axial CT, and magnetic resonance imaging. (45) Bronchoscopy may be helpful to determine the extent of airway narrowing and further guide surgical intervention. Surgery is advised for symptomatic patients who have evidence of tracheal compression. (45)

Tracheoesophageal Fistula. Congenital tracheoesophageal fistula (TEF) is a rare condition that occurs in 1 per 3,500 live births. (46) Clinical presentation depends on the type of esophageal atresia. Type C, known by a proximal esophageal pouch and a distal TEF, accounts for 84% of cases. (46) TEF occurs without esophageal atresia (H-type fistula) in only 4%, but it is more common after the neonatal age group. (46) TEF is commonly associated with VACTERL (vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities); Trisomy 13, 21, and 18; and congenital heart lesions. (46) Newborns with esophageal atresia are unable to swallow saliva or milk, and so gaseous distention develops via the TEF. (46) Children who present with late-onset symptoms such as coughing and cyanosis during feeding, recurrent severe bronchitis, and pneumonia are more likely to have an H-type fistula. (46) Dry- or wet-sounding chronic cough, often barking in character due to possible concomitant tracheomalacia, recurrent bronchitis and pneumonia, wheezing, and dyspnea are signs and symptoms often reported. (46) Cough, tachypnea, or increased work of breathing are more prominent around feedings. CT with contrast and flexible fiberoptic bronchoscopy are complementary tools to study airways and their relationships with the vascular structures to guide surgical intervention. Bronchiectasis may also develop as a consequence of repeated lower respiratory tract infections. (46)(47)

Acquired TEF is likewise a rare entity and occurs as a result of trauma, radiotherapy secondary to malignancy, granulomatous infection, and previous surgery of the trachea and esophagus. Signs and symptoms similarly include uncontrolled coughing after swallowing. (46)(47)

Fungal Pneumonia. Fungal respiratory infection occurs either via the inhalation of spores or conidia or by the reactivation of a latent infection. Among fungal infections, aspergillosis, coccidioidomycosis, and histoplasmosis are the most common. Severe disease mostly affects immunocompromised children or children younger than 2 years who may yet have underdeveloped immune systems. Geographic location has typically been used to stratify risk for a fungal pneumonia, particularly around regions where the ground may be disturbed. As it pertains to US geography, coccidioidomycosis is more common in the southwestern regions. Waves of infection occur often during earthquakes or near construction sites. Histoplasmosis is more prevalent in the Mississippi and Ohio River Valley regions, particularly where contaminated bat or bird droppings may be a point of contact. Blastomycosis is more common east of the Mississippi River and has been associated with exposure to ponds and riverbanks. *Cryptococcus neoformans* is associated with pigeon dropping exposure. *Aspergillus fumigatus* is of particular importance for the CF airway, or for children with asthma leading to a hypersensitivity reaction. Allergic bronchopulmonary aspergillosis can be detected via skin testing and serum IgE testing. Cough is typically associated with thick sputum, chest pain, headache, and flulike symptoms. (48)(49)

Habit Cough. Terms such as *psychogenic cough, tic cough, vocal cough,* and *honking cough* have all been used to describe habit cough due to its pathognomonic nature. (46) Characteristics of this cough include a honking quality, lack of a clear trigger, and absence during distraction or sleep. In cases when the presentation is highly suggestive of this diagnosis, further evaluation is often not necessary. When the presentation is not as clear, diagnosis is by exclusion, requiring chest imaging and PFTs to rule out more indolent causes. Suggestion therapy has been the mainstay treatment in children, with the hope that once the control of cough has been established, the sign may completely resolve. Suggestion therapy involves the child taking control of their cough and stifling the cough for longer and longer periods, using slow deep breathing and sips of water to control the urge to cough. This approach and a variety of techniques have been reported as being successful to break the cough-irritation cycle. Other techniques that have been described include self-hypnosis, speech therapy, and behavioral interventions. (50)(51)

Mediastinal Masses. Mediastinal masses may suggest their etiology by their location. These masses may be located in the anterior, middle, or posterior mediastinum. Many of these

masses are asymptomatic and have more indolent courses. Anterior mediastinal masses, which may be lymphoma, teratoma, or thymoma, can present with coughing or dyspnea when the child is supine. The anterior mediastinal location yields masses with the most signs and symptoms and are more readily diagnosed. Middle mediastinal masses may compress blood flow via obstruction of the superior vena cava and sometimes cause airway obstruction. Most often these masses are incidental findings and include bronchogenic cysts, cardiac tumors, cystic hygromas, or vascular abnormalities. Posterior mediastinal masses are rarer yet and include esophageal duplication, meningomyelocele, neuroenteric abnormalities, or neurogenic tumors. Chest radiography and, ultimately, CT of the chest or magnetic resonance imaging can help make the diagnosis. A biopsy is usually needed to confirm and create a treatment plan. (52)

Emerging Causes of Chronic Cough

Coronavirus Disease 2019 Related. The novel severe acute respiratory syndrome coronavirus 2 has proved itself to be a multifaceted pathogen, and although most confirmed pediatric cases present asymptomatically or with mild upper respiratory tract symptoms, there is evidence that a small percentage of cases can progress to acute respiratory distress syndrome or multiorgan system dysfunction. The most common coronavirus disease 2019 (COVID-19) illness signs and symptoms include fever, fatigue, shortness of breath, joint pain, chest pain, cough, and loss of taste or smell. Reports of chronic cough after COVID-19 illness are not yet definitively established. Overall, chronic cough has been evident in only 24.7% of young children (7–10 years) vs 26% of older children (12–17 years). (53)

Electronic Cigarette/Vape–Related Acute Lung Injury. Electronic cigarettes are battery-powered, often handheld devices that heat a liquid that contains nicotine, flavorings, and other chemicals to produce an aerosol, which is then inhaled. The exhaled smoke has been perceived to be water vapor, when it is in fact a collection of fine particles. The e-liquid used in these devices are usually propylene glycol or a vegetable glycerin-based substance with nicotine, a gamut of flavorings, and often other chemicals and metals. One electronic cigarette most often used by adolescents uses a compact device that resembles a USB flash drive and delivers high doses of nicotine equivalent to 20 cigarettes per pod. Tetrahydrocannabinol can be added to electronic cigarettes alone or in conjunction with nicotine. Unfortunately, the market has encouraged illicit dealers to create potentially toxic combinations of substances that often contain vitamin E and cannabinoid oils. Processes such as dabbing or dripping, smoking concentrated tetrahydrocannabinol or nicotine prepared in wax and smoked in a pipe, or inhaling the vapor produced from placing concentrated butane hash oil or nicotine on a hot surface have also become popular.

Ninety-five percent of patients present with respiratory symptoms of cough, chest pain, and shortness of breath, which progress in severity over 1 to 2 weeks. Auscultation is often normal. Nonspecific findings such as leukocytosis, elevated erythrocyte sedimentation rate, and elevated liver enzyme levels have been reported. The chest radiograph is abnormal in most cases, revealing bilateral patchy/diffuse infiltrates. Chest CT commonly exhibits predominantly bibasilar consolidations and diffuse ground-glass opacities. Treatment with antibiotics targeted toward severe community-acquired pneumonia are recommended at the time of presentation. Oral or intravenous corticosteroids can be used. The long-term consequences of electronic cigarette/vape–related acute lung injury are unknown, and so pulmonary function tests, 6-minute walk with pulse oximetry, and CT of the chest may be considered 1 to 2 months after presentation, and followed over time. (54)

CLINICAL CASE FOLLOW-UP

In the previously mentioned case, follow-up chest radiography and subsequent CT of the chest revealed a large mediastinal mass with a midline shift. The neck swelling and cough were considered to be secondary to lymphatic obstruction by the mass, which proved to be a non-Hodgkin lymphoma confirmed by biopsy. After chemotherapy and radiotherapy, the child continues to do well.

CONCLUSION

Cough is a normal protective mechanism of the airway. Prolonged cough most commonly presents after a viral upper respiratory tract infection. Postinfectious hypersensitivity is considered an important etiological factor in the persistence of cough. Many common causes of cough have specific "cough pointers"—types of cough or associations—that can provide clues to diagnoses. Although the respiratory system is the most commonly affected in cases of persistent cough, extrapulmonary causes must be carefully considered in specific situations. In addition to asthma, common causes of prolonged cough include PBB, chronic GER, and UACS. In cases when signs and symptoms persist, it may be worthwhile for the pediatrician to consider uncommon causes of chronic cough, such as retained foreign body, CF, and structural anomalies. Emerging causes such as electronic cigarette/vape–related acute lung injury and COVID-19–related cough are still being fully investigated. A clear

understanding of the pathophysiology and etiology of common causes of cough, a detailed history, careful physical examination, and judicious investigations can most often lead the pediatrician to the right diagnosis and management.

Summary

- According to grade 1 evidence, cough can be normal, but it is important to consider clues in either history or examination that can point to treatable causes. In most patients, cough is related to viral upper respiratory tract infection, and supportive measures alone will be sufficient.
- According to grade 1 evidence, chest imaging should be obtained in the presence of nontraditional history or cough characteristics, lower respiratory tract symptoms, relentless progressive coughing, or hemoptysis.
- According to grade 1 evidence, children with a history of cough with suspicion of foreign body should undergo urgent bronchoscopy.
- According to grade 2 evidence, antihistamines and intranasal corticosteroids are helpful for allergic cough.
- According to grade 1 evidence, over-the-counter cough suppressants are comparable to placebo and may have potential for adverse effects. According to grade 1 evidence, for children 14 years and younger with chronic cough without an underlying lung disease, treatment for gastroesophageal reflux disease should not be used when there are no clinical features of gastroesophageal reflux. According to grade 2 evidence, bronchodilators are not effective and should be avoided in nonasthmatic children.
- According to grade 1 evidence, children should be removed from environmental tobacco smoke or pollutant exposure.

References and teaching slides for this article can be found at https://doi.org/10.1542/pir.2021-005398.

PIR QUIZ

1. A 7-year-old girl with asthma returns to the clinic after yearly evaluation with her pulmonologist who manages her inhaled corticosteroid. She continues to have exacerbations and cough in the late summer during harvesting season. The patient's mother states that the pulmonologist completed pulmonary function testing but in addition completed fractional exhaled nitric oxide testing to evaluate the treatment efficacy of which of the following conditions?
   A. Allergic asthma.
   B. Gastroesophageal reflux disease.
   C. Habit cough.
   D. Postinfectious hypersensitivity.
   E. Protracted bacterial bronchitis.

2. A 5-year-old boy is evaluated in the clinic for cough of 4 weeks' duration. When the cough began 4 weeks ago, it was associated with congestion, fever, and fatigue. These associated symptoms resolved over the following 7 days, but the cough remained persistent. The child has no history of wheezing, allergies, or prolonged respiratory symptoms. There is no secondhand smoke exposure. On physical examination vital signs are all within normal limits, and lungs are clear to auscultation with no focal crackles or wheezes. Which of the following is the most appropriate pharmacotherapy for the cough?
   A. Albuterol.
   B. Amoxicillin.
   C. Clindamycin.
   D. Corticosteroids.
   E. Ipratropium.

3. A previously healthy, fully vaccinated 2-year-old is evaluated for the fourth time for cough in the past 6 weeks. He is afebrile and in no respiratory distress. He has mildly decreased lung sounds in the right lower lobe with no crackles or wheezing. He has completed 2 courses of appropriate antibiotics for community-acquired pneumonia. Albuterol does not seem to improve his cough. Evaluation so far has been limited to viral testing, which is negative. Which of the following chest imaging studies is the most appropriate next step in management?
   A. Computed tomography.
   B. Magnetic resonance imaging.
   C. Radiography.
   D. Positron emission tomography.
   E. Ultrasonography.

4. A 10-year-old girl is evaluated for cough during the past 8 weeks. The parents describe it as a nonproductive cough that sounds like a "honking noise." It is most prevalent when she is resting such as watching television. They do not hear her cough at night. She has had no associated symptoms such as congestion, fever, weight loss, or fatigue. Which of the following is the best next step in management?
   A. Albuterol as needed.
   B. Amoxicillin.
   C. Bronchoscopy.
   D. Chest radiography.
   E. Suggestion therapy.

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5. A 16-year-old is evaluated for cough with associated chest pain during the past 2 weeks. The cough has slowly worsened and it is now difficult to complete daily tasks due to shortness of breath. Lung examination reveals no crackles or wheezing. The patient is afebrile. He denies smoking tobacco but admits to vaping and using e-cigarettes. Laboratory evaluation including a complete blood cell count and complete metabolic panel is significant for elevated white blood cell count and aspartate aminotransferase level. Chest radiography is ordered. The chest radiograph is most likely to show which of the following findings?

   A. Bilateral diffuse infiltrates.
   B. Enlarged cardiac silhouette.
   C. Large pleural effusion.
   D. Lobar consolidation.
   E. Pneumothorax.