

Cough in the Pediatric Population

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Cough is the most common presenting symptom for medical office visits in the United States. Cough in children is usually related to viral respiratory tract infection and typically resolves spontaneously. Between 35% and 40% of school-age children still cough 10 days after the onset of a common cold, and 10% of preschool children have cough 25 days after respiratory tract infection.¹ In children, cough has been associated with environmental factors, such as outdoor and indoor air pollution, including particulate matter, irritant gases, environmental tobacco smoke exposure, and dampness in the home.² The frequent presentation of cough in children is further complicated by studies documenting that parental reporting of cough in children correlates poorly with objective measurement of frequency, duration, or intensity of cough.³ Cough in children disrupts both the parent's and the child's daily activities and can be associated with impaired quality of life in the child and significant stress in parents that improves with cough resolution.⁴ It is extremely common for parents to treat children with over-the-counter (OTC) cough and cold medications (CCMs) before seeing a health care provider. In a recent survey, approximately 10% of US children were found to be receiving an OTC CCM in any given week. Although OTC CCMs receive Food and Drug Administration (FDA) approval for adults, testing for efficacy and safety in young children has not been adequate,⁵ and inappropriate use of CCMs in children has been documented.⁶ Adverse events associated with use of OTC CCMs do occur and rare infant deaths have been reported. In January 2008, the FDA issued a public health advisory regarding OTC CCM use in children questioning safety and efficacy and whether the clinical benefits justify potential risks;⁷ it now recommends avoiding these medications in children under age 2 years. The FDA also has supported the recent recommendation by the Consumer Health Product Association to avoid OTC CCM use in children under age 4 years. An American Academy of Pediatrics

(AAP) position statement questions the efficacy and safety of these medications in children under age 6 years.

The Cough Reflex

Cough is a protective reflex, a component of normal respiratory physiology that enhances mucociliary function and clears excessive secretions and airway debris from the respiratory tract, as well as a very common symptom of respiratory disease. Cough receptors are located in the respiratory tract from the larynx to the segmental bronchi.⁸ The cough reflex has vagal afferent input, brain stem centralization with cortical modulation, and motor efferent activity involving respiratory muscles. Cough reflex sensitivity (CRS) can be modulated either by disease or pharmacologically. Up-regulation of CRS causes triggering of cough from a relatively nonspecific provocation. Heightened CRS has been demonstrated following viral respiratory tract infections⁹ (postviral or postinfectious cough), as well as in asthma, gastroesophageal reflux disease (GERD), and angiotensin-converting enzyme inhibitor therapy. The prevalence of CRS is similar in prepubertal and early pubertal girls and boys but significantly higher in postpubertal girls and adult women. Using mechanical stimulation, cough can be elicited in 10% of 27-week gestational age preterm infants and up to 90% of full-term infants.¹⁰

Defining Cough in Children

Children cough differently from adults in terms of duration, presentation, and underlying causes. The classification of cough in children reflects these differences.

Normal or Expected Cough

"Normal" children cough. According to objective measurements, healthy school-age children (mean age, 10 years; no respiratory illness in the 4 weeks before the study) typically experience 10 or 11 (and as many as 34) cough episodes/

AAP	American Academy of Pediatrics
ACCP	American College of Chest Physicians
BAL	Bronchoalveolar lavage
CCM	Cough and cold medications
CF	Cystic fibrosis
CRS	Cough reflex sensitivity
CT	Computed tomography
FDA	Food and Drug Administration
FeNO	Fraction of exhaled nitric oxide
GERD	Gastroesophageal reflux disease
ICS	Inhaled corticosteroids
OTC	Over the counter
PBB	Protracted bacterial bronchitis
UACS	Upper airway cough syndrome

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day.¹¹ Sometimes these “normal” cough episodes are prolonged or nocturnal, triggering parental concerns about discomfort and disturbed sleep. Recurrent viral respiratory infections are common in children, particularly in the fall and winter. These may appear to cause persistent cough, but usually the child experiences short breaks between illnesses. Postinfectious cough in normal children may have multiple causes, including heightened CRS. Less than 5% of coughs persisting >8 weeks are believed to be postinfectious (other than pertussis syndromes).¹²

Abnormal Cough

Abnormal cough in children includes cough associated with underlying disease states, as well as ineffective cough from underlying neuromuscular weakness or structural airway abnormalities. Abnormal cough in children can be classified by duration (acute vs chronic); character, quality, and timing (eg, dry vs wet, day vs night); age of child; and etiology (specific vs nonspecific). Overlap among the different categories can make classifying abnormal pediatric cough confusing. To aid in the diagnosis and treatment of the coughing child, the following questions may be helpful:

1. How long has the child coughed? Most adult studies and consensus guidelines define cough as acute (<3 weeks), subacute (3 to 8 weeks) or chronic (>8 weeks).¹³ Most acute and subacute coughs in adults and children are associated with viral upper respiratory tract infection and do not require specific diagnostic evaluation. The definition of chronic or persistent cough in children varies, ranging from 3 to 12 weeks depending on the study or guideline.^{14,15}
2. What is the character of the cough? The character or quality of chronic cough in adults has been shown to be not helpful in predicting specific etiology, and the 2006 American College of Chest Physicians (ACCP) guidelines recommend it not be used in determining etiology in adults.¹³ In contrast, the character or quality of cough in some children is recognizable and reproducible, and may suggest a specific etiology (Table I).
3. Is the cough wet or dry? A moist or wet cough in children is associated with secretions detected on bronchoscopy and can be accurately reported by clinicians and parents.¹⁶ The descriptor “wet” or “moist” cough may be used interchangeably with “productive” cough, even though young children rarely expectorate despite excessive secretions. A recent cross-sectional survey of more than 2000 children age 11 to 15 years found a 7.2% prevalence of chronic productive cough.¹⁷ Chronic productive cough was strongly associated with reports of current asthma symptoms and with environmental tobacco smoke exposure, although specific causes were not investigated.¹⁷ A recent review of chronic wet cough in children without cystic fibrosis (CF) found that the majority of the children had an endobronchial bacterial infection.¹⁸ Chronic wet cough is very rare in children with uncomplicated

Table I. Traditional recognizable cough characteristics at various ages

Cough characteristic	Possible etiology
Infancy	
Barking or brassy	Croup, tracheomalacia/other anatomic abnormalities of respiratory or GI tract
Dry, staccato	Chlamydophilia
Wet	PBB, sinusitis
Childhood	
Barking or brassy	Croup
Spasmodic/paroxysmal (with or without whoop)	Pertussis-like syndrome
Wet (with or without produced sputum)	PBB/sinusitis
Adolescence	
Barking/honking	Habit/psychogenic
Spasmodic/paroxysmal (with or without whoop)	Pertussis-like syndrome
Wet (with or without produced sputum)	Pneumonia/PBB/sinusitis

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asthma. Sinusitis with or without asthma also may cause a wet cough that is responsive to antibiotic therapy. Chronic cough with purulent sputum in children is always pathological, calling for specific assessment for such conditions as CF, non-CF bronchiectasis, and ciliary dysmotility syndromes.

4. Is the cough nocturnal? Nocturnal cough is often cited a hallmark of asthma; however, most objective studies have not confirmed this finding, and parental reporting of nocturnal cough is unreliable compared with objective measurements.^{3,19} As such, other causes of cough should be considered as well. Cough generally is suppressed by sleep, and habit cough most characteristically ceases at night.²⁰
5. How old is the child? Age at onset of cough is important diagnostically; in infants and younger children, greater consideration must be given to anatomic abnormalities of the upper and lower respiratory tracts and the gastrointestinal (GI) tract, as well as possible foreign body aspiration (Table I).

In children, as in adults, cough is subject to psychological influences.¹³ Habit cough is more commonly recognized in children.²⁰ Age also may play a role in the etiology of chronic cough in children. Studies with younger children demonstrate different causes of chronic cough compared with those with predominately older children and teens, who have similar causes as adults.²¹⁻²³

Etiology of Abnormal Pediatric Cough

A previously proposed diagnostic paradigm of specific versus nonspecific cough in children forms the basis of the approach to evaluation and treatment in the 2006 ACCP guidelines.^{13,24} Specific cough is associated with underlying respiratory or systemic disease, and the need for further investigation is typically evident from coexisting symptoms

and signs, radiographs, and laboratory results (**Table II**; available at www.jpeds.com). A frequent (daily) wet cough is the best clinical marker of the presence of a specific cough. Chronic dyspnea and hemoptysis are also historical predictors of specific cough, as are abnormal chest x-ray and auscultation findings.

Nonspecific cough is defined as cough in the absence of other signs and symptoms (**Table II**). Nonspecific cough is “isolated” cough; that is, cough is the sole or predominant symptom and typically is dry. In many cases, nonspecific cough is related to postviral infection and increased cough receptor sensitivity.²⁵ Resolution is spontaneous in the majority of children.²⁶

Specific and nonspecific coughs may have various overlapping causes. In adults, prospective studies have shown that >90% of chronic (>8 weeks) nonspecific coughs can be attributed to 3 predominant causes: upper airway cough syndrome (UACS, previously referred to as postnasal drip syndrome), asthma or eosinophilic bronchitis, and GERD.¹³ Similar data in children are limited. A prospective study in highly selected young children (median age, 2.6 years) referred to a tertiary pediatric respiratory center indicated that UACS, asthma, and GERD accounted for <10% of persistent cough, although 50% of the children had received a diagnosis of asthma before referral.²¹ Wet cough was present in 89% of the children, with a median duration of 6 months. Onset in the first year of life occurred in 62%; environmental tobacco smoke exposure was identified in 43%. The primary cause of cough in this cohort was protracted bacterial bronchitis (PBB), diagnosed in 40%.²¹ The results based on this young tertiary referral population may not be representative of the general pediatric population, however.

A retrospective observational report on chronic cough in young children (mean age, 3 years, 9 months) referred to a European respiratory center also documented PBB as the most common diagnosis.²⁷ A recent prospective study from the United States in older children (mean age, 9.2 years) with chronic cough (persisting for >8 weeks) with no cigarette smoke exposure found similar diagnoses as reported in adult studies: UACS (23%), GERD (28%), asthma (13%) and multiple etiologies (20%).²² A specific cause was found in 90% of cases. Another recent study of similar-aged children (mean age, 8.4 years) presenting to a children’s hospital in Turkey found that the most common causes of cough persisting for >8 weeks were asthma (25%), PBB (23%), UACS (20%), and GERD (5%).²³ The differences in results may reflect differences in patient age as well as in the study populations (**Table III**; available at www.jpeds.com).

Protracted Bacterial Bronchitis

Defined as chronic wet cough, positive bronchoalveolar lavage (BAL), and resolution with antibiotic therapy, PBB is poorly characterized, and data suggest that it is underdiagnosed and often misdiagnosed as asthma.²⁷ Bronchoscopy typically reveals an intense neutrophilic airway inflammatory

response.²⁸ The most common organisms implicated are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. A reasonable alternative approach to avoid invasive bronchoscopy is a trial of antibiotics (eg, amoxicillin and clavulanate for 2 weeks),²¹ but this may not allow for a definitive diagnosis. Adaptive immune function is normal in these children, but preliminary data have shown a marked inflammatory mediator response in BAL fluid and innate immune system activation.²⁸ Further studies of immune system abnormalities in these children are needed.

Gastroesophageal Reflux Disease

GERD is common in infants and children, and aspiration with swallowing in the absence of GERD also may cause cough and other respiratory symptoms in infants.²⁹ Although a high percentage of children with respiratory symptoms have GERD detectable by abnormal esophageal pH, symptoms may be subtle, especially in young children,³⁰ and the specific association between GERD and cough remains controversial.³¹ A positive response to empiric therapy with thickened feedings in infants and an acid-suppressive regimen may be used to support a presumed diagnosis of GERD,³² but lack of cough resolution can be seen with nonacid reflux detectable by impedance measurement.³³ The diagnoses of GERD or asthma are not mutually exclusive, particularly in older children.^{30,34} As many as half of children with asthma and abnormal esophageal pH exhibit few or no obvious symptoms of GERD (eg, heartburn, regurgitation).³⁰

Habit Cough Syndrome

Recognizing habit cough and other functional respiratory disorders, such as vocal cord dysfunction and hyperventilation/sighing dyspnea, is important in pediatric patients. Habit cough, also known as “psychogenic cough,” may be mistaken for asthma, UACS, or another cause of chronic cough. Weinberger et al³⁴ used the term “pseudoasthma” to describe this and other organic and nonorganic disorders misdiagnosed as asthma. The usual presentation of habit cough is a harsh, dry, often honking repetitive cough occurring intermittently throughout the day, often with great frequency. Even though the cough sounds annoying, the child is usually unperturbed (“la belle indifférence”). Yet the cough is often very disturbing to parents, teachers, and other caregivers and may lead to school and social disruption. Characteristically, there is significant improvement with distraction and absence when asleep. The cough is generally reproducible on request.

Habit cough may evolve following upper respiratory tract infection, with an initial brief, wet cough developing into the more characteristic dry, barking cough. The reported frequency of psychosomatic or psychological problems in these patients varies widely; most pediatric patients do not exhibit severe psychopathology. Habit cough occasionally may be difficult to differentiate from tic disorders, even though the vocalization characteristic of Tourette syndrome is usually not present.

Evaluating Chronic Cough in Children

There are no historical features of cough that provide a clear diagnosis in most cases of pediatric chronic, nonspecific cough. Rather than applying a comprehensive battery of tests for chronic cough in all children, most clinicians use clinical pointers in the history and physical examination to target the investigation.

The recommended evaluation of chronic cough is outlined in **Figure 1**. A trial of pharmacotherapy is often used as a diagnostic modality, although spontaneous resolution of cough can necessitate multiple trials to pinpoint the etiology. Recommendations are based primarily on expert opinion, due to the lack of controlled pediatric studies. Thus, the duration of pharmacotherapy trials is empiric, but premature discontinuation can lead to lack of resolution. Children with a prolonged moist cough should be treated initially with an antibiotic for possible PBB or chronic sinus disease. Recurring wet cough after initial clearing with antibiotic treatment is often seen in inadequately treated sinusitis. For children with dry cough, a trial of inhaled corticosteroids (ICS) will address the possible diagnosis of asthma. Certain focused diagnostic tests may be helpful in patients in whom the diagnosis is not secured by history and physical examination, as well as in patients with specific chronic cough (**Figure 2**). Referral to an allergy or pulmonary specialist also is recommended, as shown in **Figure 2**.

A chest x-ray should be obtained in all children with chronic cough. A chest computed tomography (CT) scan without contrast is requisite to support a diagnosis of bronchiectasis or interstitial lung disease. In patients with concomitant persistent upper airway symptoms, a limited CT scan of the sinuses is most helpful when normal to rule out intrinsic sinus disease.³⁵ The results must be interpreted carefully, because abnormal sinus scans are not uncommon in asymptomatic children.³⁶

Spirometry can be performed in most children age >6 years and in some age >3 years with training.¹³ Spirometry with a bronchodilator demonstrating reversible airway obstruction (>12% improvement in forced expiratory volume in 1 second) is helpful in suggesting a diagnosis of asthma. When spirometry is normal, more advanced tests are needed to aid diagnosis. Measurements of airway hyperreactivity, such as the methacholine challenge test, are most helpful when negative; however, a positive airway hyperreactivity test does not necessarily confirm asthma or predict response to therapy. In patients with abnormal pulmonary function who do not respond to a bronchodilator or ICS, bronchiectasis, aspiration, interstitial lung disease, chronic infection, structural airway abnormalities, and cardiac etiologies should be considered.

Measurement of airway inflammation is most reliably performed with induced sputum samples. The findings of >2% eosinophils per high-power field is helpful in supporting a diagnosis of asthma and predicting a response to ICS.³⁷ The measurement of exhaled nitric oxide (FeNO) is helpful

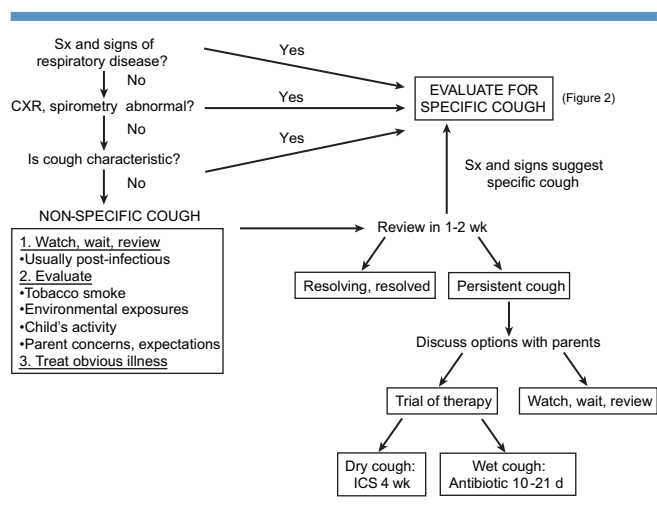


Figure 1. Algorithm for evaluating chronic cough in children

when normal. Kostikas et al³⁸ recently reported FeNO values >19 ppb in young adults as a cutoff point to support a diagnosis of asthma. Similar results have been reported in children. FeNO has been shown to predict response to ICS in adults with chronic cough.³⁹ Chronic cough in children with no history of wheezing, reversible airflow obstruction, or elevated markers of airway inflammation does not support a diagnosis of asthma.

Laboratory studies for chronic cough in children are supportive and can be used to help rule out an infectious

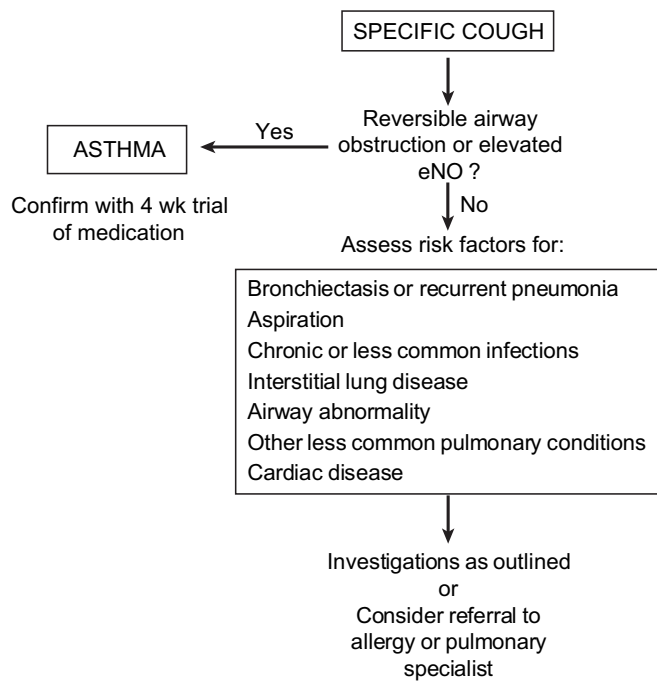


Figure 2. Algorithm for evaluating specific chronic cough in children

etiology, CF, and immunodeficiency. Quantitative immunoglobulins should be measured in all children with persistent cough secondary to recurrent bacterial infections. Flexible bronchoscopy may be used to detect the presence of airway abnormalities, chronic infection, or aspiration with or without retained foreign body; however, bronchoscopy has not been shown to be useful in adults with chronic cough.⁴⁰ A pH probe study to diagnose GER with or without aspiration may be helpful; impedance studies to assess nonacid reflux are increasingly recommended.³³

Treating Pediatric Cough

Children with chronic cough need a different management protocol than adults. Cough in children should be treated according to etiology; however, for chronic nonspecific cough, empiric trials of therapy are frequently used. There is little evidence to support the use of medications for symptomatic relief only in acute cough.¹³

OTC Cough Medications

The published data indicate that OTC cough medications have little, if any, clinical benefit beyond the placebo effect for symptom relief in children.⁴¹ The AAP has advised against using dextromethorphan (as well as codeine) for treating any type of cough.⁴² These medications have been associated with significant morbidity and rarely mortality related to intentional and unintentional ingestion.^{5,6}

Asthma Therapy

Therapy for cough associated with asthma is similar to routine guideline therapy for asthma based on age.⁴³ It is important that the diagnosis of asthma be established, because there are no data to support the empiric use of beta-adrenergic bronchodilators, anticholinergics, theophylline, or leukotriene modifiers for chronic, nonspecific cough in children.¹³

An empiric trial of ICS is recommended in children with an isolated, dry cough for possible asthma. A moderate dose of ICS (200 to 400 $\mu\text{g}/\text{day}$ fluticasone, 400 to 800 $\mu\text{g}/\text{day}$ budesonide or equivalent) is recommended; the use of spacers or nebulizers depends on the patient's age and ability. Recommendations for the duration of therapeutic trials vary from 2 to 12 weeks. Most patients will respond within 4 weeks if proper inhalation technique is used. The presence of more than one cause of cough may delay the response to therapy if all causes are not treated appropriately. It is important to periodically reassess therapy and discontinue it in patients who do not respond. By itself, a response to ICS does not confirm a diagnosis of asthma. Anticholinergic bronchodilators with or without beta agonist have shown limited benefit in patients with cough, and may have some benefit in postinfectious cough.⁴⁴

Therapy for UACS

UACS includes various types of rhinosinus diseases that can induce cough, particularly allergic or nonallergic rhinitis and sinusitis. Tonsillar hypertrophy, causing tissue impingement

on the epiglottis, also has been reported to cause chronic cough in children.³⁴ Unlike in adults, in children antihistamines (administered alone or in combination with decongestants, dextromethorphan, or codeine) have little or no effect on the duration or intensity of acute cough and do not appear to relieve acute nocturnal cough or sleep disturbance associated with nocturnal cough.⁴⁵ ACCP adult cough guidelines recommend first-generation antihistamine therapy as first-line empiric treatment for UACS-related cough, noting that studies have not demonstrated efficacy for newer second-generation antihistamines. Significant improvements in cough in children with allergic rhinitis from treatment with oral cetirizine, terfenadine, and mometasone nasal spray have been reported.⁴⁶⁻⁴⁸ Cough resolution from UACS can take up to 2 to 4 weeks of therapy, depending on the cause (adult data).¹³

GERD Therapy

Data are inconclusive regarding the efficacy of treating chronic nonspecific cough in children with empiric GERD therapy. Meta-analyses have not demonstrated the efficacy of GERD therapy in chronic nonspecific cough in children or adults.³¹ Useful therapies for GERD in children include proton pump inhibitors, prokinetic agents, and H₂ antagonists.³² In adult studies, the response of cough and other extraesophageal manifestations of GERD to therapy can take up to 8 to 12 weeks.¹³ There is increasing recognition of nonacid reflux that does not respond to acid-suppressive therapies.

Antimicrobials

Antibiotic agents appear to have no effect during the short duration of viral upper respiratory tract infections.⁴⁹ In cases with convincing physical evidence of persistent purulent rhinosinusitis or radiographic evidence of paranasal sinus infection with symptom duration >10 days, a course of antibiotics may demonstrate a small benefit in decreasing the duration of cough.⁵⁰ PBB, seen in some young children with chronic cough, is amenable to antibiotic therapy.

Treating Habit Cough Syndrome

Various treatment modalities for habit cough syndrome have been recommended, including self-hypnosis, biofeedback, and suggestion therapy, which has been reported to result in complete cessation of symptoms within 15 minutes.⁵¹⁻⁵³ Suggestion therapy can be conducted by the general pediatrician, but the sessions require much dedicated time with the child.

Conclusion

Cough in children is common, and the majority of cases reflect respiratory infections. Cough is rarely associated with a serious disorder; all children with cough persisting for >8 weeks should be evaluated. A careful history, physical examination, chest x-ray, and spirometry (in an able child) are recommended for all children with chronic cough. If a diagnosis is not evident ("nonspecific" cough), then an approach based

on characterizing the cough as “wet” or “dry” may be helpful. In each case, specific etiology-based treatment is recommended when possible; otherwise, a therapeutic trial is indicated, with ICS for children with dry cough (for possible asthma) and antibiotics for wet cough (for possible PBB or sinusitis). If a trial of medication is used, the treatment should be reviewed within the specified time frame for normal response. If no effect is obvious, the treatment should be stopped and alternative diagnoses considered. Multiple etiologies may need to be treated concomitantly. The treatment of persistent cough in children focuses on etiology; every effort should be made to identify the underlying cause. There is no evidence supporting the use of medications for symptomatic relief of acute or chronic cough in children; some data suggests potentially harmful effects. ■

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Table II. Indicators (signs and symptoms) of specific cough in children based on history and physical examination

- Daily, wet, or productive cough
- Auscultatory findings (wheeze or crackles)
- Chronic dyspnea
- Exertional dyspnea
- Hemoptysis
- Duration >6 months
- Recurrent pneumonia
- Cardiac abnormalities (including murmurs)
- Immune deficiency
- Failure to thrive
- Digital clubbing
- Swallowing problems

Modified with permission.¹³

Table III. Prospective studies of etiology of cough in pediatric patients

	Marchant et al ²¹	Khoshoo et al ²²	Asilsoy et al ²³
Patient population	108; prospective cohort referred to tertiary pediatric respiratory center	40; consecutive presentation to pediatric pulmonary clinic	108; consecutive presentation over 7 months
Setting	Royal Children's Hospital, Brisbane, Australia	West Jefferson Medical Center, New Orleans, LA	Children's Hospital and Research Center, Izmir, Turkey
Age	<18 years (median, 2.6 years)	9.3 years mean	6 to 14 years (mean, 8.4 years)
Definition of chronic cough	>3 weeks (median duration, 6 months)	>8 weeks	> 4 weeks (mean duration, 4 months)
Pertinent history	43% households cigarette smoke exposure; 62% onset cough at age <1 year; 89% wet cough	No cigarette smoke exposure	56% cigarette smoke exposure; 52% wet cough; 30% family history atopy
Evaluation	All: chest x-ray, spirometry in those age >6 years, bronchoscopy/BAL (n = 102) or induced sputum (n = 4), CF evaluation, quantitative IGs, IgE, mycoplasma, and pertussis antibodies Select: HRCT chest, pH probe	All: chest x-ray, PFT, bronchoscopy, methacholine challenge, sweat test, pH/impedance monitoring, allergy testing, quantitative IGs Select: EGD, barium swallow, sinus CT, chest CT, immune evaluation, A1AT testing	All: chest x-ray, PFT Select: Bronchodilator response, chest HRCT, bronchoscopy/BAL, GI scintigraphy, nasal mucosal transport time, sweat test, quantitative IGs, PPD, mycoplasma antibodies
Findings	PBB, 40%; natural resolution, 22%; bronchiectasis, 6%; asthma, 4%; UACS, 3%; GERD, 3%; habit, 1%; idiopathic, 5%; multiple causes, 55%	GERD, 28%; UACS, 23%; asthma, 13%; idiopathic, 10%; infection, 5%; aspiration, 3%; multiple causes, 20%	Asthma, 25%; PBB, 23%; UACS, 20%; GERD, 5%; bronchiectasis, 3%; natural resolution, 2%; TB/ mycoplasma, 2%; congenital malformation, 1%; multiple causes, 19%

PFT, indicates pulmonary function test; HRCT, high resolution chest CT; EGD, esophagogastroduodenoscopy; A1AT, alpha 1 antitrypsin.