CHEST

Managing Chronic Cough as a Symptom in Children and Management Algorithms

CHEST Guideline and Expert Panel Report

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BACKGROUND: Cough is one of the most common presenting symptoms to general practitioners. The objective of this article is to collate the pediatric components of the CHEST chronic cough guidelines that have recently updated the 2006 guidelines to assist general and specialist medical practitioners in the evaluation and management of children who present with chronic cough.

METHODS: We reviewed all current CHEST Expert Cough Panel's statements and extracted recommendations and suggestions relating to children aged ≤ 14 years with chronic cough (> 4 weeks duration). Additionally, we undertook systematic reviews to update other sections we considered relevant and important.

RESULTS: The eight recent CHEST guidelines relevant to children, based on systematic reviews, reported some high-quality evidence in the management of chronic cough in children (eg, use of algorithms and management of wet/productive cough using appropriate antibiotics). However, much evidence is still inadequate, particularly in the management of nonspecific cough in the community.

CONCLUSIONS: The recommendations and suggestions related to the management of chronic cough in the pediatric age group have been based upon high-quality systematic reviews and are summarized in this article. Compared to the 2006 Cough Guidelines, there is now high-quality evidence for some aspects of the management of chronic cough in children. However, further studies particularly in primary health care are required.

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KEY WORDS: children; cough; evidence-based medicine; guideline; treatment

ABBREVIATIONS: AHR = airway hyper-responsiveness; ARI = acute respiratory infection; CHEST = American College of Chest Physicians; CS = inhaled corticosteroids; CXR = chest radiograph; FB = flexible bronchoscopy; FENO = fractional exhaled nitric oxide; GER = GI gastroesophageal reflux; GERD = gastroesophageal reflux disease; OTC = over-the-counter; PBB = protracted bacterial bronchitis; PCR = polymerase chain reaction; QoL = quality of life; RCT = randomized controlled trial; URTI = upper respiratory tract infection; Xpert MTB/RIF = automated real-time nucleic acid amplification technology for rapid and simultaneous detection of TB and rifampin resistance

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Summary of Recommendations and Suggestions

1. For children aged ≤ 14 years, we suggest defining chronic cough as the presence of daily cough of more than 4 weeks in duration (Ungraded Consensus-Based Statement).[1]

2. For children aged ≤ 14 years, we recommend that (a) common etiologies of chronic cough in adults are not presumed to be common causes in children and (b) their age and the clinical settings (eg, country and region) are taken into consideration when evaluating and managing their chronic cough (Grade 1B).[2]

3. For children aged ≤ 14 years with chronic cough, we recommend using pediatric-specific cough management protocols or algorithms (Grade 1B).[1]

4. For children aged ≤ 14 years with chronic cough, we recommend taking a systematic approach (such as using a validated guideline) to determine the cause of the cough (Grade 1A).[1]

5. For children aged ≤ 14 years with chronic cough, we recommend basing the management or testing algorithm on cough characteristics and the associated clinical history such as using specific cough pointers like presence of productive/wet cough (Grade 1A).[1]

6. For children aged ≤ 14 years with chronic cough, we recommend that a chest radiograph and, when age appropriate, spirometry (pre and post β_2 agonist) be undertaken (Grade 1B).[1]

7. For children aged > 6 years and ≤ 14 years with chronic cough and asthma clinically suspected, we suggest that a test for airway hyper-responsiveness be considered (Grade 2C).[1]

8. For children aged ≤ 14 years with chronic cough, we recommend not routinely performing additional tests (eg, skin prick test, Mantoux, bronchoscopy, chest CT); these should be individualized and undertaken in accordance to the clinical setting and the child's clinical symptoms and signs (Grade 1B).[1]

9. For children aged ≤ 14 years with chronic cough, we suggest undertaking tests evaluating recent *Bordetella pertussis* infection when pertussis is clinically suspected (Ungraded Consensus-Based Statement).[1]

Remarks: CHEST guidelines[3] suggested that clinicians consider cough could be considered caused by pertussis if there is post-tussive vomiting, paroxysmal cough or inspiratory whoop.

10. For children aged ≤ 14 years with chronic cough, we recommend basing the management on the etiology of the cough. An empirical approach aimed at treating upper airway cough syndrome due to a rhinosinus condition, gastroesophageal reflux disease and/or asthma should not be used unless other features consistent with these conditions are present (Grade 1A).[1]

11. For children aged ≤ 14 years with chronic cough, we suggest that if an empirical trial is used based on features consistent with a hypothesized diagnosis, the trial should be of a defined limited duration in order to confirm or refute the hypothesized diagnosis (Ungraded Consensus-Based Statement).[1]

12. For children aged ≤ 14 years with chronic cough, we suggest that clinical studies aimed at evaluating cough etiologies use validated cough outcomes, use a-priori defined response and diagnosis, and take into account the period effect, and undertake a period of follow-up (Ungraded Consensus-Based Statement).[2]

13. For children aged ≤ 14 years with chronic cough, we suggest that exacerbating factors such as environmental tobacco smoke exposure should be determined and intervention options for cessation advised or initiated (Ungraded Consensus-Based Statement).

14. For children aged ≤ 14 years with chronic cough, we suggest that parental (and when appropriate the child's) expectations be determined, and their specific concerns sought and addressed (Ungraded Consensus-Based Statement).

15. For children aged ≤ 14 years with chronic (> 4 weeks duration) wet or productive cough unrelated to an underlying disease and without any other specific cough pointers (eg, coughing with feeding, digital clubbing), we recommend 2 weeks of antibiotics targeted to common respiratory bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) targeted to local antibiotic sensitivities (Grade 1A).[4]

16. For children aged ≤ 14 years with chronic (> 4 weeks duration) wet or productive cough unrelated to an underlying disease and without any other specific cough pointers (eg, coughing with feeding, digital clubbing) and whose cough resolves within 2 weeks of treatment with antibiotics targeted to local antibiotic sensitivities, we recommend that the diagnosis of PBB be made (Grade 1C).[4]

17. For children aged ≤ 14 years with chronic (> 4 weeks duration) wet or productive cough unrelated to an underlying disease and without any other specific cough pointers (eg, coughing with feeding, digital clubbing), when the wet cough persists after 2 weeks of appropriate antibiotics, we recommend treatment with an additional 2 weeks of the appropriate antibiotic(s) (Grade 1C).[4]

18. For children aged ≤ 14 years with chronic (> 4 weeks duration) wet or productive cough unrelated to an underlying disease and without any other specific cough pointers (eg, coughing with feeding, digital clubbing), when the wet cough persists after 4 weeks of appropriate antibiotics, we suggest that further investigations (eg, flexible bronchoscopy with quantitative cultures and sensitivities with or without chest CT) be undertaken (Grade 2B).[4]

19. For children aged ≤ 14 years with PBB with lower airway (BAL or sputum) confirmation of clinically important density of respiratory bacteria (≥ 10^4 cfu/mL), we recommend that the term 'microbiologically-based-PBB' (or PBB-micro) be used to differentiate it from clinically-based-PBB (PBB without lower airway bacteria confirmation) (Grade 1C).[4]

20. For children aged ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and with specific cough pointers (eg, coughing with feeding, digital clubbing), we recommend that further investigations (eg, flexible bronchoscopy and/or chest CT, assessment for aspiration and/or evaluation of immunologic competency) be undertaken to assess for an underlying disease (Grade 1B).[4]

21. For children aged ≤ 14 years with chronic cough (> 4 weeks duration) without an underlying lung disease, we recommend that treatment(s) for GERD should not be used when there are no GI clinical features of gastroesophageal reflux such as recurrent regurgitation, dystonic neck posturing in infants or heartburn/epigastric pain in older children (Grade 1B).[5]

22. For children aged ≤ 14 years with chronic cough (> 4 weeks duration) without an underlying lung disease, who have symptoms and signs or tests consistent with gastroesophageal pathological reflux, we recommend that (a) they be treated for GERD in accordance to evidence-based GERD-specific guidelines[6,7] (Grade 1B) **and (b) acid suppressive therapy should not be used solely for their chronic cough** (Grade 1C).[5]

23. For children aged ≤ 14 years with chronic cough (> 4 weeks duration) without an underlying lung disease, with GI gastroesophageal reflux (GER) symptoms, we suggest that they be treated for GERD in accordance to evidence-based GERD-specific guidelines[6,7] for 4 to 8 weeks and their response reevaluated (Ungraded Consensus-Based Statement).[5]

24. For children aged ≤ 14 years with chronic cough (> 4 weeks duration) without an underlying lung disease, if GERD is suspected as the cause based on GI symptoms, we suggest following the GERD guidelines[6,7] for investigating children suspected for GERD (Ungraded Consensus-Based Statement).[5]

25. For children with chronic cough (> 4 weeks) after acute viral bronchiolitis, we suggest that the cough be managed according to the CHEST pediatric chronic cough guidelines, asthma medications not be used for the cough unless other evidence of asthma is present, and **inhaled osmotic agents not be used**[8] (Ungraded Consensus-Based Statement).

26. For children with chronic cough, we suggest that the presence or absence of night time cough or cough with a barking or honking character should not be used to diagnose or exclude psychogenic or habit cough (Grade 2C).[9]

27. For children with chronic cough that has remained medically unexplained after a comprehensive evaluation based upon the most current evidence-based management guideline, we recommend that the diagnosis of tic cough be made when the patient manifests the core clinical features of tics that include suppressibility, distractibility, suggestibility, variability, and the presence of a premonitory sensation whether or not the cough is single or one of many tics (Grade 1C).[9]

28. For children with chronic cough, we suggest (a) against using the diagnostic terms habit cough and psychogenic cough and (b) substituting the diagnostic term tic cough for habit cough to be consistent with the DSM-5 classification of diseases because the definition and features of a tic capture the habitual nature of cough and (c) substituting the diagnostic term somatic cough disorder for psychogenic cough to be consistent with the DSM-5 classification of diseases (Ungraded Consensus-Based Statement).[9]

29. For children with chronic cough, we suggest that the diagnosis of somatic cough disorder can only be made after an extensive evaluation has been

performed that includes ruling out tic disorders and uncommon causes and the patient meets the DSM-5 criteria for a somatic symptom disorder (Grade 2C).[9]

30. For children with chronic cough, diagnosed with somatic cough disorder (previously referred to as psychogenic cough), we suggest non-pharmacological trials of hypnosis or suggestion therapy or combinations of reassurance, counselling, or referral to a psychologist and/or psychiatrist (Grade 2C).[9]

31. For patients with cough in high TB prevalence countries or settings, we suggest (a) that they be screened for TB regardless of cough duration (Grade 2C)[10] **and (b) the addition of active case finding to passive case finding because it may improve outcomes in patients with pulmonary TB** (Ungraded Consensus-Based Statement).[10]

32. For patients with cough and at risk of pulmonary TB but at low risk of drug-resistant TB living in high TB prevalence countries, we suggest that XpertMTB/RIF testing, when available, replace sputum microscopy for initial diagnostic testing, but CXRs should also be done on pulmonary TB suspects when feasible and where resources allow (Ungraded Consensus-Based Statement).[10]

33. For patients with cough suspected to have pulmonary TB and at high risk of drug-resistant TB, we suggest that XpertMTB/RIF assay, where available, replace sputum microscopy but sputum mycobacterial cultures, drug susceptibility testing and CXRs should be performed when feasible and where resources allow (Ungraded Consensus-Based Statement).[10]

34. For patients with cough with or without fever, night sweats, hemoptysis, and/or weight loss, and who are at risk of pulmonary TB in high TB prevalence countries, we suggest that they should have a CXR if resources allow (Ungraded Consensus-Based Statement).[10]

35. For children aged ≤ 14 years with chronic cough and suspected of having OSA, we suggest that they are managed in accordance to sleep guidelines (Ungraded Consensus-Based Statement).[2]

36. For children aged ≤ 14 years with non-specific cough, we suggest that if cough does not resolve within 2 to 4 weeks, the child should be re-evaluated for emergence of specific etiological pointers (Table 1) (Ungraded Consensus-based Statement).

37. For children aged ≤ 14 years with non-specific cough, we suggest when risk factors for asthma are present, a short (2-4 weeks) trial of 400 μg/day of beclomethasone equivalent may be warranted, and these children should always be re-evaluated in 2 to 4 weeks (Ungraded Consensus-based Statement).

38. For children with acute cough, we suggest that the use of over the counter cough and cold medicines should not be prescribed until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).[11]

39. For children with acute cough, we suggest that honey may offer more relief for cough symptoms than no treatment, diphenhydramine, or placebo, but it is not better than dextromethorphan (Ungraded Consensus-Based Statement).[11]

40. For children with acute cough, we suggest avoiding using codeine-containing medications because of the potential for serious side effects including respiratory distress (Ungraded Consensus-Based Statement).[11]

Introduction

The 2006 CHEST cough guideline[12] initiated the world's first pediatric-specific guideline.[13] This concept is similar with evidence-based guidelines for other common childhood conditions (eg, for gastroesophageal reflux disease),[6] asthma and pneumonia. For chronic cough, common pediatric etiologies[2] are different from those in adults as are outcome assessments (eg, cough-specific quality of life [QoL] tools[14]). This is not surprising as, while the physiology of the respiratory system in children and adults share similarities, there are also distinct differences between prepubertal children and adults that include maturational differences in airway, respiratory muscles and chest wall structure, sleep-related characteristics, respiratory reflexes and respiratory control.[15-17] In the physiology of cough, sex differences in cough sensitivity are well recognized in adults[18] but are absent in prepubertal children.[19-21] In contrast to adults, cough sensitivity in children is instead influenced by airway caliber (FEV_1) and age.[20] Plasticity or adaptability of the cough reflex has been shown to be related to age in animals[22] and it is reasonable to speculate that age-related maturation also occurs in human's cough reflex.[23] Additionally, in young children, the medical history is limited to parental perception.

Here, we present a summary of recently published, cough-related, pediatric-specific CHEST recommendations and suggestions, a management pathway and other updated aspects of the 2006 cough

TABLE 1] Pointers to Presence of Specific Cough[a]

Abnormality	Examples of etiology
Symptoms or signs	
Auscultatory findings	Wheeze–see below Crepitations–any airway lesions (from secretions) or parenchyma disease such as interstitial disease
Cardiac abnormalities	Associated airway abnormalities, cardiac failure, arrhythmia
Chest pain	Arrhythmia, asthma
Choked	Foreign body inhalation
Dyspnea or tachypnea	Any pulmonary airway or parenchyma disease
Chest wall deformity	Any pulmonary airway or parenchyma disease
Digital clubbing	Suppurative lung disease
Daily wet/productive cough	Protracted bacterial bronchitis, suppurative lung disease, recurrent aspiration, atypical infections, TB, diffuse panbronchiolitis
Exertional dyspnea	Any airway or parenchymal disease
Facial pain/purulent nasal discharge	Chronic sinusitis (protracted bacterial bronchitis), primary ciliary dyskinesia
Feeding difficulties	Any serious systemic including pulmonary illness, aspiration
Growth failure	Any serious systemic including pulmonary illness such as cystic fibrosis
Hoarse voice/stridor	Laryngeal cleft/problems, airway abnormalities
Hemoptysis	Suppurative lung disease, vascular abnormalities
Hypoxia/cyanosis	Any airway or parenchyma disease, cardiac disease
Neurodevelopmental abnormality	Aspiration lung disease
Recurrent pneumonia	Immunodeficiency, atypical infections, suppurative lung disease, congenital lung abnormalities, trachea-esophageal H-type fistulas
Recurrent infections	Immunodeficiency
Previous history of chronic lung or esophageal disease (eg, neonatal lung disease, esophageal atresia)	Multiple causes (eg, second H-type fistula, bronchiectasis, aspiration, asthma)
Wheeze–monophonic	Large airway obstruction (eg, from foreign body aspiration, malacia and/or stenosis, vascular rings, lymphadenopathy, and mediastinal tumors) TB should be considered in selected settings (eg, high prevalence or HIV)
Wheeze–polyphonic	Asthma, bronchiolitis obliterans, bronchiolitis
Tests	
Chest radiograph (other than peribronchial changes) or spirometry abnormality	Any cardiopulmonary disease

[a]As the causes of chronic cough encompasses the entire spectrum of pediatric pulmonology and extrapulmonary diseases, this list outlines the more common symptoms and signs and is not exhaustive.

guideline, all based upon high-quality systematic reviews.[13] However, many of the questions addressed in the systematic reviews did not contain high-quality studies and/or evidence. Nevertheless, compared to the 2006 guideline, there is now high-quality evidence for some aspects of the management of chronic cough in children, reflected in the Grades within each recommendation (ie, 16 recommendations are Grade 1). This general guideline does not substitute for sound clinical judgement, requires appropriate adaptations in population settings where disease patterns are different (eg, where parasites are prevalent[24]), and is not intended to be used as a definitive protocol for the management of all children with a coughing illness.

Methods

We reviewed all updated cough CHEST Expert Cough Panel guidelines. We included data directly relevant to treating children with chronic cough (ie, research and public health excluded). These systematic reviews and guidelines, based on a protocol,[25] used the GRADE framework that includes the Delphi approach for voting by a panel with patient representation.

Additionally, to ensure that all important topics from the 2006 guidelines were updated, we undertook additional searches (using the strategy in e-Table 1). Relevant articles published in English between January 2004 (date of last search from previous guideline[13]) and up to 25th April 2019 were identified from PubMed and references in publications and authors' collection. The search, topics and results were undertaken by a single author (A. B. C.) (e-Table 1).

Defining Chronic Cough in Children

The 2006 guideline[13] defined pediatric chronic cough as cough duration > 4 weeks in children aged < 15 years. Our updated systematic review found no studies that addressed the question whether the cough management or testing algorithm should differ depending on the duration of chronic cough.[26] Because cough can spontaneously resolve within 4 weeks, we do not advocate using medications or investigating (other than with simple tests such as spirometry and a chest radiograph) all children at the 4-week timepoint.[27] The duration of greater than 4 weeks is recommended for reasons previously outlined.[28,29] One such reason is to ensure that all children with chronic cough are carefully assessed and not quickly dismissed as a post-viral cough. This is particularly important in children, as chronic cough may be due to a serious underlying condition (eg, inhaled foreign body) and earlier diagnoses, and treatment results in less damage. Indeed, a serious potentially progressive underlying respiratory illness (bronchiectasis, aspiration lung disease, or cystic fibrosis) was documented in 18% of 346 children in a multicenter study that used a cough algorithm.[29] Also, published studies that systematically assessed outcomes of individual children at a children's specialist hospital who had acute cough that persisted for > 4 weeks found a new and serious chronic lung disease (eg, chronic pneumonia, bronchiectasis) in up to 30.8% of children.[30,31] Thus, in the current CHEST guideline, duration of cough remains the same but the age was adjusted from < 15 years to ≤ 14 years.

1. For children aged ≤ 14 years, we suggest defining chronic cough as the presence of daily cough of more than 4 weeks in duration (Ungraded Consensus-Based Statement).[1]

Evaluating Children With Chronic Cough

The 2006 guideline[13] recommended that evaluation be aimed at defining the etiology of the chronic cough. This entails performing a thorough clinical assessment, a chest radiograph (CXR) and/or spirometry (see below) followed by deciding whether any investigations and/or treatment are appropriate and/or required. The belief that common etiologies of pediatric chronic cough differ from adults was supported through a systematic review that found moderate level evidence.[2] The review also described that etiologies were setting and age dependent that is not surprising as common etiologies in resource-poor countries are likely different (eg, TB, parasitic disease) from resource-rich countries.

2. For children aged ≤ 14 years, we recommend that (a) common etiologies of chronic cough in adults are not presumed to be common causes in children and (b) their age and the clinical settings (eg, country and region) are taken into consideration when evaluating and managing their chronic cough (Level 1B).[2]

Using an Algorithm

The steps in the algorithm in the 2006 guideline[13] were based on individual studies, and/or expert opinion, with no published data yet available on using an algorithmic approach for pediatric chronic cough. High-quality evidence, now available in a systematic review,[26] described that using children-specific cough management protocols improves clinical outcomes. Randomized controlled trial (RCT) findings were consistent with those derived from cohort studies. Because the highest evidence for the best type of pathway to be used was based on the CHEST guideline,[13] it is the one recommended here.

Clinical History and Examination: For clinical practical reasons, pediatric cough has been divided into specific cough (ie, usually associated with an underlying disease) and non-specific cough (Fig 1). The approach when using a chronic cough algorithm (Figs 2, 3) is dependent on the presence of cough characteristics, clinical history, physical examination, CXR and spirometry findings.[1,32] Spirometry can usually be reliably performed in children aged > 6 years and in some children > 3 years if trained pediatric personnel are utilized.[33]

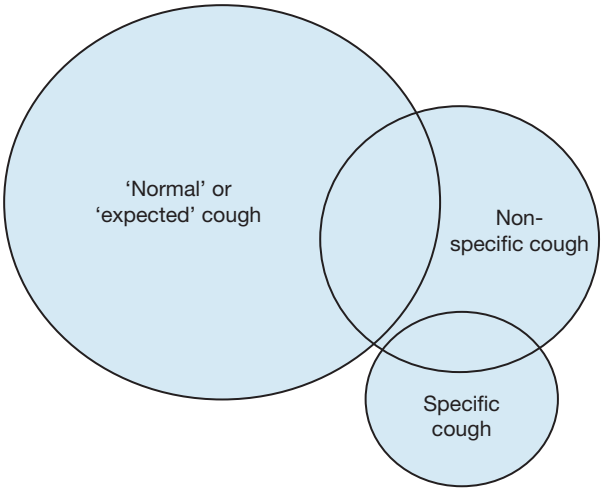

Figure 1 – *Classification of types of cough in children. 'Expected cough' refers to coughing illness reflective of common upper respiratory viral infections in an otherwise child where the cough duration is usually < 2 weeks but may be longer in a small minority.*

Children with chronic cough need to be carefully evaluated for:

- Symptoms and signs of an underlying respiratory or systemic disease (Table 1). The presence of any specific cough pointer indicates an etiology of chronic cough. When any of these symptoms and signs are present, the cough is referred to as 'specific cough.' Other than for wet cough caused by protracted bacterial bronchitis (PBB; see section below) and polyphonic wheeze related to asthma, the presence of any of these symptoms suggests that the cough is likely indicative of an underlying disorder that requires further investigations. The type and depth of these investigations depend on clinical findings. Diagnoses that need to be considered include bronchiectasis, retained foreign body, aspiration lung disease, atypical respiratory infections, cardiac anomalies and interstitial lung disease, among others.
- In some children, the quality of cough is recognizable and suggestive of specific etiology (Table 2).[34-41] This significantly differs from adults where detailed questioning of the characteristics and timing of cough were not diagnostically useful.[42]
- Non-specific cough is more likely to resolve without specific treatment.[27] It is characterized by a dry/non-productive cough in the absence of specific cough pointers with normal CXR and spirometry.
- Contributing exacerbating factors such as tobacco smoke exposure (see below) and parental expectations should also be evaluated, irrespective of the underlying etiology.

After investigations (if necessary), some children may be found to have an underlying serious abnormality.[43] However, in most children, cough is most likely related to a non-serious etiology[44] or may spontaneously resolve as evidenced in the placebo arms of RCTs[45-47] and cohort studies.[48-50] At first presentation, specific cough overlaps with non-specific cough and the latter overlaps with 'expected cough' (Fig 1). Thus, children with a chronic cough should be reevaluated until a diagnosis is found with resolution of the cough (if possible). Management guidelines for pneumonia[51] and other acute infections[52,53] as well as that associated with underlying respiratory (eg, bronchiectasis[54] and asthma[55]) and systemic disorders can be found elsewhere. The following four recommendations are based on systematic reviews[26] that we previously published.

3. For children aged ≤ 14 years with chronic cough, we recommend using pediatric-specific cough management protocols or algorithms (Grade 1B).[1]

4. For children aged ≤ 14 years with chronic cough, we recommend taking a systematic approach (such as using a validated guideline) to determine the cause of the cough (Grade 1A).[1]

5. For children aged ≤ 14 years with chronic cough, we recommend basing the management or testing algorithm on cough characteristics and the associated clinical history such as using specific cough pointers like presence of productive/wet cough (Grade 1A).[1]

6. For children aged ≤ 14 years with chronic cough, we recommend that a chest radiograph and, when age appropriate, spirometry (pre and post β_2 agonist) be undertaken (Grade 1B).[1]

Although spirometry and CXR are suggested, neither are sensitive (ie, absence of abnormality does not imply absence of disease) but both are specific (presence of abnormality implies presence of disease). This was shown in two studies,[27,56] with the more recent study (326 children with chronic cough presenting for the first time to pulmonologists[27]) demonstrating an infinite positive likelihood ratio for both tests.

Investigations in Addition to CXR and Spirometry: The role of the many other tests for evaluating lung disease is beyond the scope of this guideline, as it would encompass the entire spectrum of pediatric respiratory illness and tests. The sections below are limited to a review of available data where the yield (ie, significant abnormalities present) of tests used to

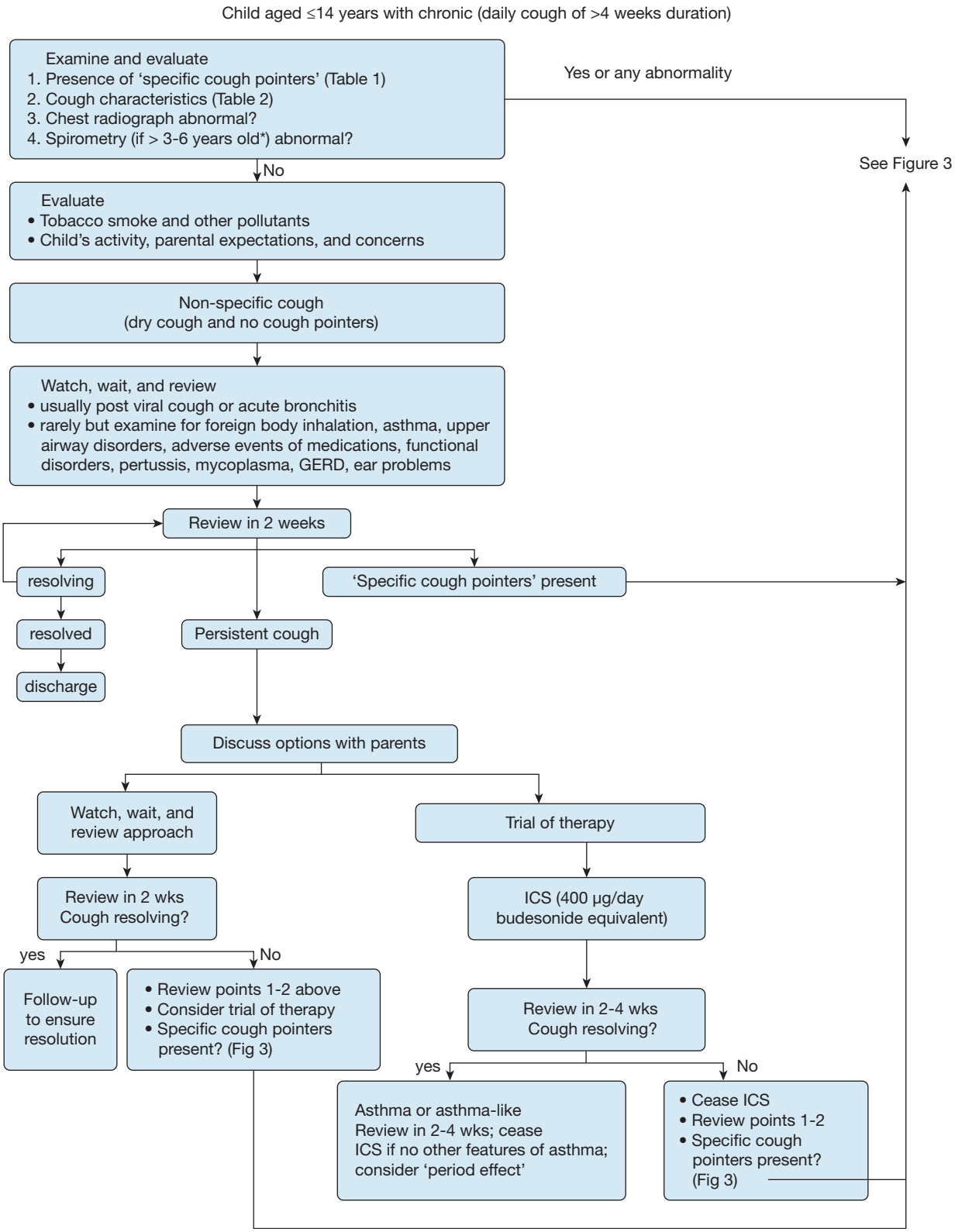

Figure 2 – *Approach to a child aged ≤ 14 years with chronic cough. Children aged > 14 years should be managed as outlined in adult guidelines but there is no good evidence when the age cutoff should be. The algorithm should be read with the accompanying text. *Spirometry can usually be reliably performed in children aged > 6 years and in some children > 3 years if trained pediatric personnel are present.*[33] *GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroids.*

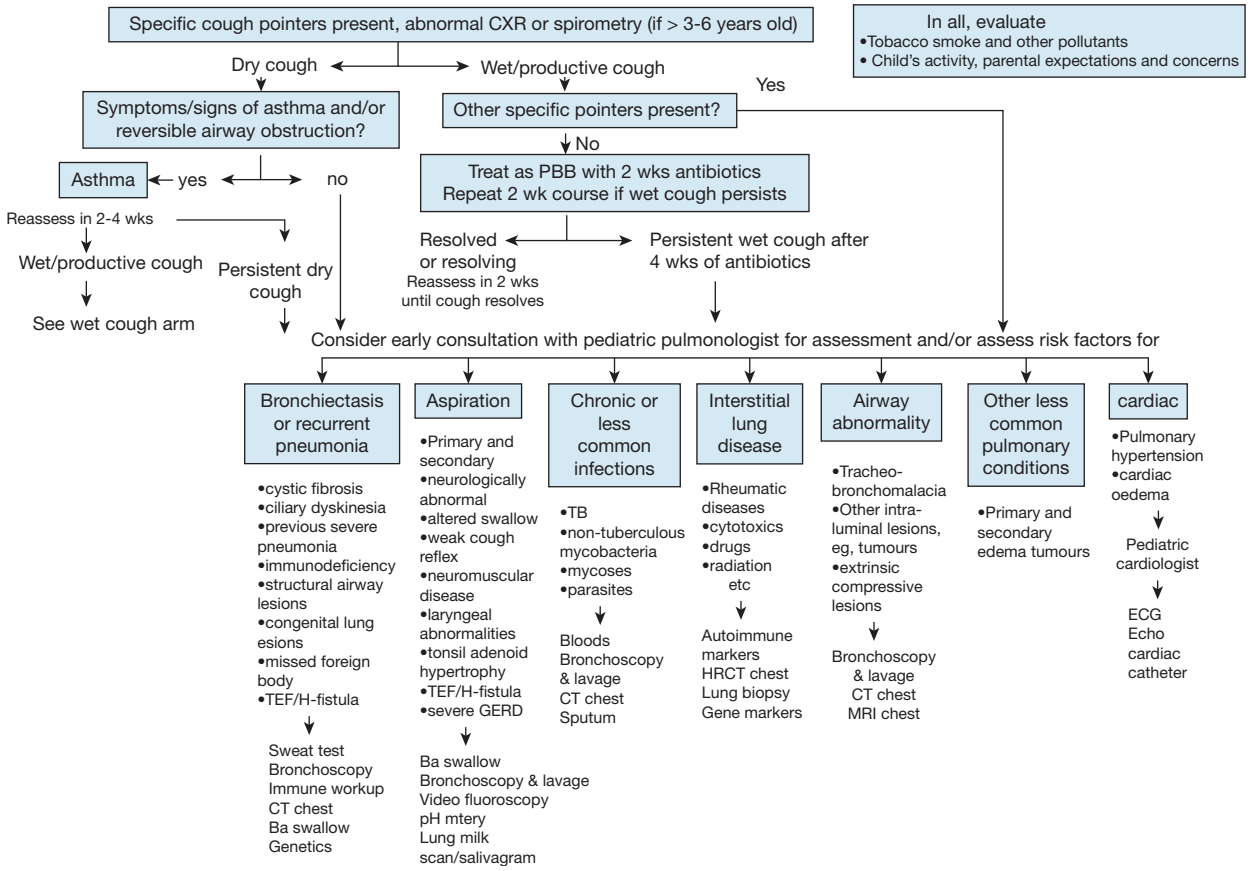

Figure 3 – *Approach to a child aged ≤ 14 years with chronic specific cough (ie, cough associated with other features suggestive of an underlying pulmonary and/or systemic abnormality). CXR = chest radiograph; HRCT = high-resolution CT; PBB = protracted bacterial bronchitis; TEF = tracheal-esophageal firstula. See Figure 2 legend for expansion of other abbreviation.*

investigate chronic cough in children has been evaluated.

Other Lung Function Tests: The interest in lung function tests with respect to chronic cough is predominantly to differentiate asthma (see asthma section) from cough that resolves spontaneously. Readers are referred to updated pediatric specific evidence-based guidelines for asthma.[55] In brief, tests for airway hyper-responsiveness (AHR; direct or indirect) in children are not as straightforward as they are for adults for diagnosing asthma.[55] Further, AHR in children may occur temporarily post-infections[50] and with allergic rhinitis. Also, demonstration of AHR in a child with isolated cough may not be helpful in predicting the later development of asthma[57] or the response to asthma medications.[46] In the single RCT that examined the utility of AHR and response to inhaled salbutamol and inhaled corticosteroids (ICS) for children with isolated recurrent cough (median cough was 8 weeks),[46] AHR presence could not predict the efficacy of inhaled salbutamol and corticosteroids (beclomethasone 400 μg/day) for cough frequency or cough sensitivity. Nevertheless, as asthma is common:

TABLE 2] Classical Recognizable Cough in Children

Cough Characteristic	Suggested Underlying Etiology or Contributing Factor
Barking or brassy cough	Croup,[34] tracheomalacia,[35] habit cough[36]
Cough productive of casts	Plastic bronchitis[37]
Honking	Psychogenic[38]
Paroxysmal (with/without whoop)	Pertussis and parapertussis[39,40]
Staccato	Chlamydia in infants[41]

7. For children aged > 6 years and ≤ 14 years with chronic cough and asthma clinically suspected, we suggest that a test for airway hyper-responsiveness be considered (Grade 2C).[1]

Fractional exhaled nitric oxide (FENO) is increasingly advocated as a biomarker for eosinophilic-related lung disease, predominantly asthma.[58] However, in the interpretation of studies involving FENO levels in patients, clinicians need to be cognizant of the many factors that influence these levels beyond clinical disease. These include variability among devices (limits of agreement is up to 10 ppb),[59,60] ethnicity,[61] height,[62] age,[62] recent dietary intake, atopy and tobacco exposure. For example, using the American Thoracic Society recommended cutoff to define presence of clinically important eosinophilic inflammation in children (levels $>$ 35 ppb in children aged $\leq$ 12 years; $>$ 50 ppb when $>$ 12 years),[58] a systematic review found five studies where $\geq$ 5% of healthy people from non-Caucasian ethnic groups had FENO results above the age-specific inflammatory ranges.[61] Further, although the four recent major documents regarding FENO's utility in the diagnosis and routine use of FENO[55,59,63,64] have similarities, there were substantial discrepancies including the cutoffs for age and FENO values for defining abnormality.

Studies[65-69] from the updated search relating FENO to cough are summarized in e-Table 2. The value of FENO levels in the absence of symptoms of classical asthma (recurrent wheeze and/or dyspnea that responds to β_2 agonist) is yet to be defined for the assessment of chronic cough in children. Additionally, there are conflicting data on FENOlevels in children with cough presumed related with 'upper airway cough syndrome' with one study reporting elevated FENO[70] and another[67] reporting no elevation in levels. Thus, using FENO levels alone for diagnosing and managing children with chronic cough without other cough pointers is yet to be clearly defined.

Heightened cough sensitivity (eg, to inhaled capsaicin) occurs in most coughing illness in children, documented in recurrent persistent cough,[20] and cough dominant asthma.[71] Unlike in adults, the so-called 'cough hypersensitive syndrome' is an inappropriate term in children as the heightened sensitivity resolves upon treatment.[71] A study based on 100 children with chronic cough and 100 control subjects also supported the absence of "cough hypersensitive syndrome" in children, in contrast to adults.[72] An updated summary of clinical studies (e-Table 3) suggests that tests for cough sensitivity are currently non-diagnostic and of limited use for research purposes.

Chest and Sinus CT Scans: An updated search on CT scans to evaluate children in children with chronic cough found only studies that were part of a previous CHEST systematic review[73] (e-Table 1). Chest CT scans using fine collimation of $<$ 1 mm (ie, high-resolution CT scan), the current 'gold standard' for evaluating small airways structural integrity, is more sensitive than spirometric indices.[74,75] Previous classical high-resolution CT scan techniques consisted of thin slices with few slices (ie, spaced every 10-20 mm) while current CT scans with $\geq$ 64 multidetector rows (MDCT) uses both fine collimation finely spaced (every 1-2 mm). The latter has greater sensitivity for small airway diseases (eg, bronchiectasis).[76]

A study of paranasal sinus CT findings in children with chronic cough ($>$ 4 weeks) described that abnormalities were found in 66%.[77] However, these findings had to be interpreted in the context that they may be transient and there are high rates (18-82%) of incidental sinus abnormalities in asymptomatic children undergoing head CTs[78] or sinus radiograph.[79,80] In a prospective study, 50% of 137 children aged $<$ 13 years had sinus CT scans consistent with sinusitis but all were asymptomatic.[78] In asymptomatic children, the presence of haziness (a radiological sign for sinusitis) in conventional sinus radiograph is 52% and in digital radiograph paranasal sinus Water views is 75%.[79] Symptoms (rhinorrhea, nasal congestion, sniffling, and postnasal drip) commonly associated with a sinus abnormality may not relate with paranasal sinus CT scans abnormality.[77] The American Academy of Pediatrics acute bacterial rhinosinusitis guideline recommends undertaking sinus CT only when orbital or central nervous complications are suspected (ie, not routinely).[81] Likewise, the Infectious Diseases Society of America[82] also does not recommend routine radiological assessment. In the USA Otolaryngologists' consensus for chronic rhinosinusitis,[83] specific recommendation for CT scan was only before considering endoscopic sinus surgery.

Flexible Bronchoscopy (FB) and BAL and Cellular Assessment: The usefulness of FB depends on the child's medical history and available expertise. Indications for FB in children with chronic cough include (a) suspicion of airway abnormality or inhaled foreign body, (b) localized changes on radiology of the chest, (c) evaluation of aspiration lung disease, and (d) lavage for microbiological, cellularity and other purposes. Chronic cough in children is often an indication for FB (11.6% of the 1233 in one European series[84]); but, the yield was unreported. Among children suspected of having bronchiectasis, one study found that FB and BAL altered management in 42% of the 56 children.[85] Another

study[86] reported abnormal FB in 8 of 18 (23%) but their cough characteristics were not reported and most did not have 'chronic non-specific cough'; with CXR abnormal in 28%, while some had muco-purulent secretions with BAL showing infection and neutrophilia.[86] A retrospective aero-digestive clinic-based study[87] (thus children very likely had specific cough) described abnormal FB findings in 42% of children with chronic cough (e-Table 4).

In children with untreated unexplained persistent cough, a study described that only a minority (3 of 23) of children had asthma-type airway inflammation.[88] Induced sputum of children enrolled from a community-based survey of children with wheeze, cough, recurrent chest colds and control subjects, found elevated eosinophils (> 2.5%) in all children with wheeze and AHR,[89] but only in half of the children with wheeze alone.[89] Other airway cell differentials were similar in all three symptom groups, and sputum and eosinophil cationic protein levels did not differ among the groups.[89] The authors concluded that "wheeze is a good discriminator for the presence of eosinophilic bronchitis, and that persistent cough and recurrent chest colds without wheeze should not be considered a variant of asthma."[89] Airway specimens are generally useful for microbiology and airway differential cellularity. However, the latter is not as definitive as in adults with chronic cough where therapy is directed based on airway eosinophilia or neutrophilia.[90]

In reviewing research regarding testing, readers should be aware that in studies without control subjects, a positive test in an entire cohort of children with the symptom of interest needs to be interpreted with caution because the test may also be positive in asymptomatic children. Further, patient discomfort, adverse events and costs need to be considered when undertaking further investigations. For example, obtaining a CT scan needs to be balanced against the reported increased lifetime cancer risk, which is age and dose dependent. Although relatively negligible and lower with newer CT protocols, children have 10 times increased risk compared to middle aged adults.[91] For a single CT examination of 200 mA, lifetime attributable cancer mortality risk is 1 in 1000 to 2500 for a 2.5-year-old child.[91] Thus, while chest CTs and to a much lesser extent sinus CTs have a definite role in the evaluation of a child with cough, these should rarely be performed unless other symptoms are present and ideally with prior consultation with a pediatric respiratory specialist.

8. For children aged ≤ 14 years with chronic cough, we recommend not routinely performing additional tests (eg, skin prick test, Mantoux, bronchoscopy, chest CT); these should be individualized and undertaken in accordance to the clinical setting and the child's clinical symptoms and signs (Grade 1B).[1]

9. For children aged ≤ 14 years with chronic cough, we suggest undertaking tests evaluating recent *Bordetella pertussis* infection when pertussis is clinically suspected (Ungraded Consensus-Based Statement).[1]

Remarks: CHEST guidelines[3] suggested that clinicians consider cough could be considered caused by pertussis if there is post-tussive vomiting, paroxysmal cough or inspiratory whoop.

Treatment and Evaluation of Treatment

General

A systematic review[26] found that most children in all the studies received treatment that was specific for the underlying etiology (rather than an empirical approach based on treatment of gastroesophageal reflux disease [GERD], upper airway cough syndrome due to a rhinosinus condition or asthma). The following are recommended/suggested:

10. For children aged ≤ 14 years with chronic cough, we recommend basing the management on the etiology of the cough. An empirical approach aimed at treating upper airway cough syndrome due to a rhinosinus condition, gastroesophageal reflux disease and/or asthma should not be used unless other features consistent with these conditions are present (Grade 1A).[1]

11. For children aged ≤ 14 years with chronic cough, we suggest that if an empirical trial is used based on features consistent with a hypothesized diagnosis, the trial should be of a defined limited duration in order to confirm or refute the hypothesized diagnosis (Ungraded Consensus-Based Statement).[1]

12. For children aged ≤ 14 years with chronic cough, we suggest that clinical studies aimed at evaluating cough etiologies use validated cough outcomes, use a-priori defined response and diagnosis, and take into account the period effect, and undertake a period of follow-up (Ungraded Consensus-Based Statement).[2]

In addition to etiology-based management, it is prudent that children with chronic cough receive common management interventions outlined below.

Cessation of Exposure to Environmental Tobacco Smoke and Other Environmental Pollutants

In the management of any child with cough irrespective of the cause, attention to exacerbating factors is encouraged. The American Academy of Pediatrics tobacco policies[92] address tobacco exposure, control, cessation and e-cigarettes with statements that include "Health care delivery systems should facilitate the effective prevention, identification, and treatment of tobacco dependence in children and adolescents, their parents, and other caregivers." The negative impact of indoor and outdoor pollution on children's lung health is indisputable[93,94]; but, there are no RCTs that have examined the effect of cessation of environmental tobacco smoke or other toxic environmental exposure on children's cough. A single report was found on cessation of parental smoking as a successful form of therapy for the children's cough.[95]

13. For children aged ≤ 14 years with chronic cough, we suggest that exacerbating factors such as environmental tobacco smoke exposure should be determined and intervention options for cessation advised or initiated (Ungraded Consensus-Based Statement).

Physician and Parental Expectations

In addition to addressing pollutants, the general management of children with chronic cough includes providing education and addressing expectations. The former includes providing information on when to seek further medical advice. Although often unrecognized by doctors, chronic cough causes a high health-care burden and impairs the QoL of children[96] and their parents.[29,97] Single[97,98] (n = 190) and multicenter[29] (n = 346) studies involving children presenting for the first time to respiratory specialists with chronic cough found that: (a) approximately 80% had seen > 5 doctors for their cough; (b) their QoL was as poor as those with other chronic diseases (eg, cardiac and GI diseases); and (c) approximately 12% had a serious underlying illness (eg, bronchiectasis).

Addressing expectations in any condition is important.[99] Providing parents with information on the expected length of time until resolution of acute respiratory infections may reduce anxiety in parents, the need for using medications and additional consultation.[100,101] Appreciation of specific concerns and anxieties, and an understanding of why they present are thus important when caring for children. QoL is often determined by expectations rather than experience.[102] Parental and professional expectations as well as doctors' perception of patients' expectations influence consulting rates and prescription of medications.[103-105] Use of cough medications and presentation to doctors were less likely in children with higher educated mothers, as described in a prospective cohort of children studied from birth.[106] Hutton and colleagues described that "parents who wanted medicine at the initial visit reported more improvement at follow-up, regardless of whether the child received drug, placebo, or no treatment."[107] Physicians should be cognizant that "a parent navigating the Internet for information on the home management of cough in children will no doubt find incorrect advice among the search results."[108]

Concerns of parents presenting to family doctors in the United States for their children's cough can be extreme and include: fear of child dying from choking, asthma attack or cot death, and permanent chest damage.[109] Other concerns parents expressed included disturbed sleep and relief of discomfort.[109] For parents of children presenting to a specialist respiratory clinic in Australia, the greatest burdens were feelings of frustration, upset, sleepless nights, awakened at night, helpless, stressed, and sorry for child.[97] Items most bothersome to these parents were not knowing the cause of cough, serious illness, child not sleeping well, and the cough causing damage.[97] Paying attention to these items will likely ensure parents do not feel dismissed by health professionals. Items that impacted on children aged 8 to 12 years were hating their cough, annoyance, feelings of frustrations, being tired, limitation of their activities and disturbing others.[96]

Educational input is most successful when it addresses the child's specific condition. Exploring and understanding concerns of parents is initially required. Written information without discussion provides only modest benefit in changing perceptions and behavior.[110] One RCT that involved sending booklets and sheets including information on minor respiratory tract infections, found that while patients felt more confident managing their minor illness, the effect on subsequent attendance with a minor illness was only modest.[111] Another RCT examined the effect of a pamphlet and a videotape promoting the judicious use of antibiotics and found that their simple educational effort was successful in modifying parental attitudes regarding the use of antibiotics. They also concluded "information about specific childhood conditions may be more effective in changing attitudes than more general information about antibiotic usage."[112]

14. For children aged ≤ 14 years with chronic cough, we suggest that parental (and when appropriate the child's) expectations be determined, and their specific concerns sought and addressed (Ungraded Consensus-Based Statement).

Chronic Cough Associated With Specific Etiologies

Wet Cough and PBB: The validity of wet cough in young children in clinical practice has been confirmed.[4] In older children who can expectorate, productive cough is the preferred term. The presence of chronic wet/productive cough leads to a divergent pathway within the algorithm[32] (Fig 3). The evidence using antibiotics for a chronic wet cough when there no other symptoms and signs (eg, dysphagia or digital clubbing) suggesting PBB, is now strong.[73] While many questions remain, PBB as a clinical entity is also now widely accepted.[73,113-115]

15. For children aged ≤ 14 years with chronic (> 4 weeks duration) wet or productive cough unrelated to an underlying disease and without any other specific cough pointers (eg, coughing with feeding, digital clubbing), we recommend 2 weeks of antibiotics targeted to common respiratory bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) targeted to local antibiotic sensitivities (Grade 1A).[4]

16. For children aged ≤ 14 years with chronic (> 4 weeks duration) wet or productive cough unrelated to an underlying disease and without any other specific cough pointers (eg, coughing with feeding, digital clubbing) and whose cough resolves within 2 weeks of treatment with antibiotics targeted to local antibiotic sensitivities, we recommend that the diagnosis of PBB be made (Grade 1C).[4]

17. For children aged ≤ 14 years with chronic (> 4 weeks duration) wet or productive cough unrelated to an underlying disease and without any other specific cough pointers (eg, coughing with feeding, digital clubbing), when the wet cough persists after 2 weeks of appropriate antibiotics, we recommend treatment with an additional 2 weeks of the appropriate antibiotic(s) (Grade 1C).[4]

18. For children aged ≤ 14 years with chronic (> 4 weeks duration) wet or productive cough unrelated to an underlying disease and without any other specific cough pointers (eg, coughing with feeding, digital clubbing), when the wet cough persists after 4 weeks of appropriate antibiotics, we suggest that further investigations (eg, flexible bronchoscopy with quantitative cultures and sensitivities with or without chest CT) be undertaken (Grade 2B).[4]

19. For children aged ≤ 14 years with PBB with lower airway (BAL or sputum) confirmation of clinically important density of respiratory bacteria (≥ 10^4 cfu/mL), we recommend that the term 'microbiologically-based-PBB' (or PBB-micro) be used to differentiate it from clinically-based-PBB (PBB without lower airway bacteria confirmation) (Grade 1C).[4]

Chronic productive purulent cough is always pathological, reflective of conditions such as bronchiectasis, diffuse panbronchiolitis[116] and aspiration. The workup usually involves detailed evaluation that includes the spectrum of available investigations to outline structure and function of the respiratory system as well as evaluation for immunological causes and to exclude cystic fibrosis and other underlying systemic abnormalities. These investigations may include chest CT scans, flexible bronchoscopy, barium swallow, video fluoroscopic evaluation of swallowing, echocardiography, complex sleep polysomnography, and nuclear medicine scans. When bronchiectasis is suspected, children should be evaluated using an appropriate pathway.[113]

20. For children aged ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and with specific cough pointers (eg, coughing with feeding, digital clubbing), we recommend that further investigations (eg, flexible bronchoscopy and/or chest CT, assessment for aspiration and/or evaluation of immunologic competency) be undertaken to assess for an underlying disease (Grade 1B).[4]

GERD: Unlike in adults,[117] GERD is not commonly identified as the cause of pediatric chronic cough.[2] Indeed in children, there is little current convincing evidence that GER is a common cause of isolated chronic cough (ie, without GI-related GERD symptoms). However, proving causality is difficult[118,119] for several reasons that include the absence of a gold standard diagnostic tool for the diagnosis of GERD in infants and children.[6,7] Also, there are a wide array of possible interventions for GERD and some of these may result in more potential harm than benefit (eg, surgery[120] and proton pump inhibitors[121,122]).

Our systematic review on chronic cough related to GERD[5] found a paucity of high-level evidence. Data from pediatric GER-specific evidenced-based guidelines from the UK National Institute for Health and Care Excellence[7] and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition[6] were consistent with findings of CHEST guidelines[1,2] undertaken prior to the cough GERD-specific guideline.[5] In summary, the CHEST panelists recommended that: (i) treatment(s) for GERD should not be used when there are no GI clinical features of GERD; and (ii) pediatric GERD guidelines should be used to guide treatment and investigations. Specific recommendations/suggestions were:

21. For children aged ≤ 14 years with chronic cough (> 4 weeks duration) without an underlying lung disease, we recommend that treatment(s) for GERD should not be used when there are no GI clinical features of gastroesophageal reflux such as recurrent regurgitation, dystonic neck posturing in infants or heartburn/epigastric pain in older children (Grade 1B).[5]

22. For children aged ≤ 14 years with chronic cough (> 4 weeks duration) without an underlying lung disease, who have symptoms and signs or tests consistent with gastroesophageal pathological reflux, we recommend that (a) they be treated for GERD in accordance to evidence-based GERD-specific guidelines[6,7] (Grade 1B) **and (b) acid suppressive therapy should not be used solely for their chronic cough** (Grade 1C).[5]

23. For children aged ≤ 14 years with chronic cough (> 4 weeks duration) without an underlying lung disease, with GI GER symptoms, we suggest that they be treated for GERD in accordance to evidence-based GERD-specific guidelines[6,7] for 4 to 8 weeks and their response reevaluated (Ungraded Consensus-Based Statement).[5]

24. For children aged ≤ 14 years with chronic cough (> 4 weeks duration) without an underlying lung disease, if GERD is suspected as the cause based on GI symptoms, we suggest following the GERD guidelines[6,7] for investigating children suspected for GERD (Ungraded Consensus-Based Statement).[5]

Bronchiolitis: Although bronchiolitis is one of the most common acute lower respiratory tract infections in very young children, there are few data specific to chronic cough post-bronchiolitis.[8] Thus, CHEST guidelines for chronic cough related to bronchiolitis consisted only of suggestions from ungraded consensus-based statements.

25. For children with chronic cough (> 4 weeks) after acute viral bronchiolitis, we suggest that the cough be managed according to the CHEST pediatric chronic cough guidelines, asthma medications not be used for the cough unless other evidence of asthma is present, and inhaled osmotic agents not be used[8] (Ungraded Consensus-Based Statement).

Somatic Cough Syndrome and Tic Cough: Since publication of the CHEST guidelines on somatic cough syndrome and tic cough,[9] recent pediatric data primarily emanating from retrospective studies suggest that the 'habit cough' label is used[36,123] and this was considered appropriate by a minority of the panelists. However, the DSM-5 classification of psychiatric and psychological disorders no longer recognizes the habit or psychogenic terms and neurologists prefer to consider a 'habit cough' a vocal tic disorder. Because these children respond to the same behavioral interventions that are used for a tic disorder, we continue to use the same terms in this summary that we recently published.

26. For children with chronic cough, we suggest that the presence or absence of night time cough or cough with a barking or honking character should not be used to diagnose or exclude psychogenic or habit cough (Grade 2C).[9]

27. For children with chronic cough that has remained medically unexplained after a comprehensive evaluation based upon the most current evidence-based management guideline, we recommend that the diagnosis of tic cough be made when the patient manifests the core clinical features of tics that include suppressibility, distractibility, suggestibility, variability, and the presence of a premonitory sensation whether or not the cough is single or one of many tics (Grade 1C).[9]

28. For children with chronic cough, we suggest (a) against using the diagnostic terms habit cough and psychogenic cough and (b) substituting the diagnostic term tic cough for habit cough to be consistent with the DSM-5 classification of diseases because the definition and features of a tic capture the habitual nature of cough and (c) substituting the diagnostic term somatic cough disorder for psychogenic cough to be consistent with the DSM-5 classification of diseases (Ungraded Consensus-Based Statement).[9]

29. For children with chronic cough, we suggest that the diagnosis of somatic cough disorder can only be made after an extensive evaluation has been performed that includes ruling out tic disorders and uncommon causes and the patient meets the DSM-5 criteria for a somatic symptom disorder (Grade 2C).[9]

30. For children with chronic cough, diagnosed with somatic cough disorder (previously referred to as psychogenic cough), we suggest non-pharmacological trials of hypnosis or suggestion therapy or combinations of reassurance, counselling, or referral to a psychologist and/or psychiatrist (Grade 2C).[9]

Common precipitating or perpetuating factors of children with somatic cough syndrome/tic were school phobia and fear of rejection and need for attention.[124] However, associated psychopathology has been reported to be rarely diagnosed.[125] While somatic cough syndrome is more common in adolescents, tic habitual cough occurs in younger children[126] and more commonly in boys.[127] The mean age of diagnosis for tic cough ranges from 4 to 18 years.[126,128,129] In 140 children diagnosed with this disorder over a 20-year period, 58% were male.[128] In a Swedish community-based study using DSM-III criteria, 0.3% were girls and 0.7% were boys in children aged 7 to 15 years.[127] Treatment of tic and somatic cough disorders range from simple explanation, suggestion therapy,[36,123,128,130] hypnosis and biofeedback, to management of Tourette's disorder.[125,126]

TB: In settings where TB is prevalent, differentiating it from the many causes of chronic cough is difficult especially in young children who are unable to expectorate. Furthermore, the consequence of not treating TB is substantial for the child, family and community.[10] Here, we highlight CHEST[10] recommendations/suggestions directly related to patient treatment (ie, not public health) and those without HIV.

31. For patients with cough in high TB prevalence countries or settings, we suggest (a) that they be screened for TB regardless of cough duration (Grade 2C)[10] **and (b) the addition of active case finding to passive case finding because it may improve outcomes in patients with pulmonary TB** (Ungraded Consensus-Based Statement).[10]

32. For patients with cough and at risk of pulmonary TB but at low risk of drug-resistant TB living in high TB prevalence countries, we suggest that XpertMTB/RIF testing, when available, replace sputum microscopy for initial diagnostic testing, but CXRs should also be done on pulmonary TB suspects when feasible and where resources allow (Ungraded Consensus-Based Statement).[10]

33. For patients with cough suspected to have pulmonary TB and at high risk of drug-resistant TB, we suggest that XpertMTB/RIF assay, where available, replace sputum microscopy but sputum mycobacterial cultures, drug susceptibility testing and CXRs should be performed when feasible and where resources allow (Ungraded Consensus-Based Statement).[10]

34. For patients with cough with or without fever, night sweats, hemoptysis, and/or weight loss, and who are at risk of pulmonary TB in high TB prevalence countries, we suggest that they should have a CXR if resources allow (Ungraded Consensus-Based Statement).[10]

Cough Post-infections, Pertussis, Mycoplasma, and Other Infections: Post-viral cough is a term that refers to cough after the acute upper respiratory tract infections (URTIs). In contrast to the hospital settings,[2] cough post viral URTIs is likely the most common cause of chronic cough in children in the community. When a child who has not fully recovered from a URTI-related cough acquires a subsequent URTI, the coughing illness may seem prolonged. The mean annual incidence of total respiratory illness per person year ranges from 5.0 to 7.95 in children aged < 4 years to 2.4 to 5.02 in children aged 10 to 14 years.[131] Following URTIs, acute cough typically resolves within 1 to 3 weeks but 10% may cough for $>$ 20 to 25 days.[132,133] However, there are few data on the pathophysiology or natural history post-viral chronic cough beyond 25 days[132]; none of these studies followed these children individually to look at their diagnostic outcomes. The first study[30] to determine the outcomes of children who present for an acute respiratory illness was based in a specialist hospital. In the follow-up of 839 children, 627 (75%) coughed for < 7 days and 171 (20%) for $>$ 28 days.[30] Of those with chronic cough ($>$ 28 days), a new and serious illness (eg, bronchiectasis, aspiration) was found in the 36 of the 117 children who were clinically reviewed.[30]

Other infections such as pertussis and mycoplasma can cause chronic cough. Pertussis should be suspected, especially if the child has had a known contact with someone with pertussis even if the child is fully immunized, as partial vaccine failure is an emergent

problem.[134] Pertussis, pertussis-like and mycoplasma infections classically cause cough associated with other symptoms; pertussis cough is usually spasmodic[135] and mycoplasma may be associated with other symptoms of a respiratory infection such as pharyngitis. Wheezing is not classically associated with pertussis but one study concluded that wheezing should not be used to exclude pertussis in children with chronic cough.[136] These infections may present as chronic cough without any associated symptoms[39] especially in the presence of process modifiers such as antibiotics and vaccination.[135,137] The pediatric components of the CHEST pertussis guideline[3] only included suggestions/recommendations relating to acute cough. The median duration of cough in unvaccinated (for pertussis) children aged < 6 years was 52 to 61 days and 29 to 39 days for vaccinated children.[135]

Data for *C pneumoniae* and *M pneumoniae*[138] as the causes for chronic cough in children are less robust. In a prospective childhood vaccine study, evidence of *C pneumoniae, M pneumoniae, B parapertussis,* and *B pertussis* was sought in children (aged 3-34 months) if the child or household member coughed for > 7 days. In total, 115 etiological agents were identified in 64% (99/155) of episodes with cough for < 100 days.[39] The most common single agent was *B pertussis* in 56% (64/115), with a median cough period of 51 days, followed by *M pneumoniae* in 26% (30/115), mean cough period of 23 days, *C pneumoniae* in 17% (19/115), 26 days, and *B parapertussis* 2% (2/115).[39] Other microbial studies were not performed and other possible etiologies of cough were not considered. A factor that needs to be considered when analyzing such results is determining whether the infectious agent isolated is truly the cause of the cough. In a cohort of 1211 children,[139] polymerase chain reaction and enzyme immunoassay (PCR-EIA) for detection of *C pneumoniae* on throat swabs were done and repeated until PCR-EIA was negative. The percentage of asymptomatic infections was very high (54% of all positive PCR-EIA).[139]

Asthma: CHEST did not undertake a specific systematic review on chronic cough related to asthma in children. Current child-specific asthma guidelines caution against diagnosing asthma based on the symptom of cough alone because while "almost all children with asthma have intermittent cough, wheeze and/or exercise-induced symptoms, only about a quarter of children with these symptoms have asthma."[55] Given the large number of publications on asthma, our updated search subsequent to the 2006 guideline[13] was limited to RCTs (see present supplement). Three Cochrane reviews[140-142] addressed the question. Although these reviews were > 10 years old, our recent search did not identify any new RCTs. Therefore, our CHEST recommendations/guidelines related to asthma stated above were not changed.

Although there is little doubt that children with asthma may present with cough, most children with isolated cough do not have asthma.[143-145] Cough in children associated with asthma without a co-existent respiratory infection is usually dry.[55] Using ambulatory tracheal sounds monitoring for 72 hours in 90 children, a study examined the diagnostic relevance of spontaneous cough in children with asthma and found that the sensitivity and specificity of cough as a marker for wheeze was poor at 34% and 35%, respectively.[146] An asthma-like transient clinical syndrome may occur post respiratory syncytial viral bronchiolitis,[147] *M pneumoniae*[148] and other lower acute respiratory infections (ARIs).[50]

When airway profiles have been examined in children with isolated chronic cough, the studies have shown very few children with airway inflammation consistent with asthma.[88,89,149] Marguet and colleagues concluded that "chronic cough is not associated with the cell profiles suggestive of asthma and in isolation should not be treated with prophylactic anti-asthma drugs."[149] Similarly, Gibson et al,[89] in a study of children in the community concluded, "persistent cough and recurrent chest colds without wheeze should not be considered a variant of asthma." Several other studies also support McKenzie's annotation[143] that highlighted the problem of over-diagnosis of asthma based on the symptom of cough alone. A cross-sectional community study of 1178 children also reported that persistent cough (> 3 weeks) in the absence of wheeze differs in important respects from classic asthma and resembles the asymptomatic population and concluded that "cough variant asthma is probably a misnomer for most children in the community who have persistent cough."[150]

Eosinophilic Bronchitis and Allergy: In children, eosinophilic bronchitis (e-Table 2) is not well-defined, in contrast to adults where it is a well-recognized cause of adult chronic cough. Likewise, 'allergic cough' is a poorly defined condition even in adults and its relationship to childhood cough probably represents an overlap with asthma, allergic rhinitis and adenoid tonsillar hypertrophy.[151] There is little doubt that atopy is increased in children with asthma but in children without asthma, findings regarding cough and atopy are

inconsistent with reports of increased atopy (or diseases associated with atopy) in children with cough described[152,153] as well as the absence of influence of atopy[45,46,154] (e-Table 5). Using various markers of atopy (eg, skin prick test, radioallergosorbent test, or specific IgE tests) are unlikely to determine children with cough who will respond to asthma therapies. In children with atopy, cough sensitivity is not elevated (e-Table 3).

Upper Airway Disorders: Cough is included in the symptom complex of both acute (> 10 days)[81,82] and chronic (> 90 days)[83] rhinosinusitis. However, whether cough is actually related to sinusitis is controversial. In both conditions, the recommended first-line treatment is antibiotics (amoxicillin[81] or amoxicillin-clavulanate[82] for 7-10 and 20[82] days, respectively). It is argued whether the relationship between nasal secretions and cough is more likely linked by common etiology (infection and/or inflammation causing both) or due to clearing of secretions reaching the larynx. The common bacterial pathogens in sinusitis are identical to those in PBB[113,155] and to date, no studies have undertaken FB in children with acute or chronic sinusitis to determine if the chronic cough is related to lower airway infection.

Pediatric studies have reported 'upper airways cough syndrome' whereby none were RCTs and most treated with antibiotics (e-Table 6). A single RCT on adolescents and adults (n = 245) with allergic rhinitis using cough as an outcome measure showed that the daytime cough difference between the active treatment arm (mometasone furoate) and placebo was significant ($P = .049$).[156] In comparison, a larger difference between groups was found for nasal symptoms and there was no difference in nighttime cough.[156] There are no RCTs on therapies for upper airway disorders on younger children with non-specific cough. Updated guidelines for managing allergic rhinitis are available but there are no data specific for cough.[157,158]

Anatomical Airway Abnormalities and Cough: Chronic cough is common in children with airway lesions,[159] where reports of up to 75% of children with tracheomalacia related to vascular anomaly had persistent cough at presentation.[160] Studies that have looked specifically at PBB and tracheo-bronchomalacia have found coughing rates of up to 74% retrospectively[161] and 68% prospectively,[162] although the prospective study also found rates of 53% in their control group.[162] Children with airway malacia are often misdiagnosed with asthma.[163] The relationship between airway lesions and cough is not straightforward. Systematic reviews[164,165] of available studies show it remains unclear if one condition is antecedent to the other. The prevalence of airway lesions in asymptomatic children is unknown and how the symptom of cough relates to airway lesions can only be postulated. Airway malacia impedes clearance of secretions[166] and it is plausible that the prolonged cough in these children relates to a bronchitic process distal to the lesion. Indeed, a prospective study[167] on children with malacia found increased likelihood of respiratory illness frequency, severity, significant cough and a tendency for delayed recovery but neither the site nor severity of malacia had a dose effect on respiratory illness. Although persistent cough is listed as an indication for FB,[84,168] its role in those with isolated chronic cough has yet to be defined prospectively.

Chronic Nocturnal Cough: The major problem in using the symptom of nocturnal cough alone is the unreliability and inconsistency of its reporting when compared to objective measurements.[169-171] Several studies have reported the unreliability of nocturnal cough reporting in children with asthma,[169] which is not surprising in light of the poor agreement between subjective and objective assessment of nocturnal cough (Cohen's kappa of 0.3).[170] However, when the ability to detect change rather than whether cough was present or absent (agreement) was measured, parents' report correlated with objective cough counts in detection of change in scores.[45,171]

Nocturnal cough is often used as a direct indicator of asthma, as children with asthma are often reported to have troublesome nocturnal cough, but a community-based study found that only a third of children with isolated nocturnal cough (absence of wheezing, shortness of breath or chest tightness) had an asthma-like illness.[154]

Objective nocturnal cough counts in children hospitalized with asthma were higher than children with other illness.[172] However, to date there are no studies that have objectively documented that nocturnal cough is worse than daytime cough in children with unstable asthma. In a group of children with asthma reported to have troublesome cough, a median of only 6 cough episodes per night was documented.[173] By comparison, 46 children considered well by parents and attending school (age, sex, and season matched to children with recurrent cough) coughed 0 to 57 cough episodes per night (median of 0).[174] Also, nocturnal cough is independently associated with reduced socio-economic

indices in schoolchildren.[175] Increased nocturnal cough has also been reported with GER and snoring disorders[176] in children. Studies involving nocturnal cough need to be interpreted acknowledging that children's nocturnal cough poorly correlates with objective measures[170,171,177] and of biased reporting of respiratory symptoms.[178]

Medications and Adverse Events: Chronic cough has been reported as a side effect of angiotensin converting inhibitors (ACEI),[179] asthma medications immediately after inhalation,[180] psychostimulant medications (eg, dextroamphetamine resulting in new onset tics),[181] etanercept[182] and complication of chronic Vagus nerve stimulation.[183] In one review, only one of the 51 (2%) children treated with an ACEI (enalapril) developed a chronic cough[184]; yet, another study reported cough in 7 of the 42 (16.7%) children.[179] In children, cough associated with ACEIs resolves within days (3-7 days) after withdrawing the medication,[179,185] and may not recur when the medication is recommenced.[179]

Inhalation of Foreign Body: Although presentations are usually acute, chronic cough can also be the presenting symptom in a previously missed foreign body inhalation. Cough is the most common symptom in most series on foreign material inhalation (up to 88%),[186,187] but not all.[188] Other dominant symptoms included decreased breath sounds and wheezing (45%).[186,187] A history of a choking episode should always be sought in children with chronic cough as missed foreign body results in long-term pulmonary damage.[186,189] However, as aspiration may be unwitnessed, a negative history does not rule out this cause. A normal CXR does not exclude foreign body inhalation.

Otogenic causes-Arnold's ear-cough reflex: In approximately 2.3% to 4.2% of people (bilateral in 0.3%-2%), the auricular branch of the Vagus nerve is present and the Arnold's ear-cough reflex can be elicited.[190-192] The prevalence of Arnold's ear-cough reflex in children with chronic cough is similar to that in healthy children.[72] This is in contrast to adults where the prevalence of the reflex is 11-fold higher in adults with chronic cough compared to healthy adults and adults with respiratory disease without cough.[72] The reflex can be elicited by palpation of the postero-inferior wall, palpation of the antero-inferior wall of the external acoustic meatus (ear canal) or mechanical stimulation of the ear canal with insertion of cotton-tip applicator 3 to 5 mm for 2 to 3 seconds.[72,190,192] Because of the presence of this reflex, the ears should always be examined in patients with chronic coughs and any foreign material or structure such as a hair resting on the ear drum should be removed. However, in our experience, this is a very rare cause of childhood chronic cough (e-Table 7).

Other Conditions: Many respiratory and non-respiratory conditions can cause cough. It is not possible to review all causes. However, with the increasing interest in sleep medicine, CHEST undertook a systematic review of OSA and cough.[2]

35. For children aged ≤ 14 years with chronic cough and suspected of having OSA, we suggest that they are managed in accordance to sleep guidelines (Ungraded Consensus-Based Statement).[2]

Management of Non-specific Cough

As mentioned above, treatment of chronic cough in children should be based on etiology. However, sometimes, a 'trial of therapy' is appropriate and if used, it is imperative that the children are followed up and medications ceased if there is no effect on the cough within an expected timeframe (ie, it is important to evaluate 'time to response'). Here, we present a summary of possible treatments for non-specific cough in children, the time to response and level of evidence (Table 3).[5-7,45-47,73,140-142,156,193-215] Based on previous systematic reviews on cough etiology (asthma is a commonly reported etiology in some settings)[2] and cough pathways[26] and in addition to suggestions 10-12, we have the following suggestions:

36. For children aged ≤ 14 years with non-specific cough, we suggest that if cough does not resolve within 2 to 4 weeks, the child should be re-evaluated for emergence of specific etiological pointers (Table 1) (Ungraded Consensus-Based Statement).

37. For children aged ≤ 14 years with non-specific cough, we suggest when risk factors for asthma are present, a short (2-4 weeks) trial of 400 μg/day of beclomethasone equivalent may be warranted, and these children should always be re-evaluated in 2 to 4 weeks (Ungraded Consensus-Based Statement).

Asthma-based Therapies

In treating non-specific cough with asthma medications, new research since the 2006 guideline[13] identified three Cochrane reviews[140-142] that described no benefit from ICS (beclomethasone 400 μg/day) or β_2 agonist, or no appropriate studies. Another previously reported Cochrane review found no evidence to support the use

TABLE 3] Summary of Therapies Used for Non-specific Cough as Reported in Literature Based on Controlled Trials

Therapy	Time to Response[a]	Level of Evidence	Data Limitation and Considerations
Anti-histamines			Adverse events (especially with H1 antagonist)
Acute cough	1 wk	Systematic review (with OTC medications[193])	Non-beneficial from 3 RCTs in children
Chronic cough	2 wk	Systematic review[194]	Non-beneficial in systematic review.[194] Single small study showed benefit by 2 wk of treating allergic cough in children with pollen allergy with cetirizine[195]
Anti-microbials (for chronic wet/productive cough)	2 wk	Systematic reviews and meta-analysis[73]	Some may require 4 wks[73]
Asthma type therapy			
Cromones	2 wk	Systematic review[196]	Single open trial only[197]
Anti-cholinergics	4 wk	Systematic review,[198] single case series[199]	No trials in children. Case series unclear
Inhaled corticosteroids	2-4 wks	RCTs,[45,46] systematic review[141]	Small benefit if any, adverse event
Oral corticosteroids	Not relevant	No RCTs	No RCTs, adverse events[200]
Beta-2-agonist			Adverse events[47]
Acute cough	Not relevant	Systematic review[201]	Non-beneficial
Chronic cough		Systematic review,[140] RCT[46]	Non-beneficial
Theophylline	1-2 wk	Observational studies[202-204] Systematic review[205]	No RCTs, adverse events
Leukotriene receptor antagonist		Systematic review[142]	No trials in children
GERD therapy			
Motility agents	Not relevant	Single controlled trial[206]	No benefit, adverse events, systematic review on metoclopramide[207] showed no benefit for GER but cough was not an outcome measure
Acid suppression	Not relevant	Systematic reviews[5-7]	Adverse events
Food thickening or anti-reflux formula	1 wk	Systematic review,[5] RCTs[208,209]	Inconclusive data; one reported increase in cough[208] and a second reduction[209]
Head positioning	Not relevant	Systematic review[207]	No benefit, systematic showed no benefit for GER and cough was not an outcome measure[210]
Fundoplication		No data	No RCT, adverse events
Herbal anti-tussive therapy		No data	No RCTs
Nasal therapy			
Nasal steroids	1-2 wk	RCT[156]	Mainly adults and older children (> 12 y) in RCT, beneficial when combined with antibiotics for sinusitis[211,212]
Other nasal sprays		No data	No RCT, adverse events
Over the counter			Adverse events[214,215]
Acute cough	Not relevant	Systematic review[11,193]	Honey maybe beneficial, other OTC medications were non-beneficial
Chronic cough		Systematic review for codeine[213]	No studies
Physical therapies steam, vapor, rubs		No data	No RCTs, adverse events eg, burns

No data = no pediatric data.
GER = GI gastroesophageal reflux; OTC = over-the-counter; RCT = randomized controlled trial.
[a]Time to response = expected reduction in cough severity if treatment is effective, as reported by trialists.

of anti-cholinergics for non-specific cough in children.[198] We did not find any RCTs on use of oral steroids for non-specific cough in children. In cough associated with pertussis, dexamethasone provides no significant benefit for the symptomatic relief of cough.[216] Even in children with wheeze (without asthma), one RCT in 200 children (1-5 years) found that oral steroids conferred no benefit[217] but were instead associated with a non-significant increase in hospitalizations ($P = .058$).

If a trial of asthma therapy is warranted, we suggest using 400 μg/day equivalent of budesonide or beclomethasone as this dose is effective in the management of most childhood asthma and adverse events occur on higher doses.[218,219] We suggest reassessment in 2 to 4 weeks as the earlier studies in adults and children that used non-steroid based medications for asthma for the era (ie, theophylline,[202] terbutaline and major tranquillizers[220]) reported that cough related to asthma completely resolved by 2 to 7 days.[202-204,220] Cough unresponsive to ICS should not be treated with increased doses of ICS. If the cough resolved with ICS use, clinicians should still be aware that the child does not necessarily have asthma and the child should be re-evaluated off asthma treatment as resolution of cough may occur with the period effect (spontaneous resolution)[221] or a transient effect responsive to ICS use.

A Cochrane review found an absence of evidence (in contrast to evidence of absence) for the use of cromones for non-specific cough in children (no RCTs).[196] Cromoglycate and nedocromil reduces cough associated with asthma[222,223] and in children born prematurely.[224] A single open, single arm trial with inhaled nedocromil reported significant reduction in cough scores from 30 to 15 per week after 2 weeks of treatment with 4 mg qid with no additional benefit in the subsequent 4 weeks.[197] A summary of data on the therapeutic effects of nedocromil on inflammation and symptoms reported that "the effect on asthmatic cough was significant within 24 hours" and cough symptom scores improved by $>$ 30% by day 2.[222]

Theobromine, a methylxanthine present in cocoa, is a promising anti-tussive but an adult-based RCT found no significant superiority in those randomized to theobromine compared to placebo.[225] One non-placebo RCT involving children with acute cough reported that an herbal syrup was superior to an over-the-counter (OTC) medication containing theophylline and diphenhydramine.[226] We did not identify any new pediatric studies involving methylxanthines for chronic cough since the Cochrane review.[205] Old observational studies involving oral theophylline described that the chronic cough resolved within 2 weeks (Table 3).

OTC Cough Medications

The previous 2006 CHEST guidelines[12,13] highlighted the lack of efficacy and potential morbidity and mortality of OTC medications for young children. In the following months, FDA issued a warning for not using these OTC medications in young children[227] and manufacturers voluntarily re-labeled these OTC products "do not use in children under 4 years of age."[228] In 2018, FDA altered the labeling for prescription opioid cough and cold medicines to limit their use to adults $\geq$ 18 years.[229] Other than honey, the updated systematic review[193] concluded that OTC cough medications have little, if any, benefit in the symptomatic control of acute cough in children but importantly, preparations containing anti-histamine and dextromethorphan were associated with adverse events. Thus, using OTC medications has to be balanced with adverse events, which includes reported death from toxicity in young children.[214,230] CHEST's advice on the use of OTC for chronic cough in children is the same as for acute cough due to the common cold.

38. For children with acute cough, we suggest that the use of over the counter cough and cold medicines should not be prescribed until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).[11]

39. For children with acute cough, we suggest that honey may offer more relief for cough symptoms than no treatment, diphenhydramine, or placebo, but it is not better than dextromethorphan (Ungraded Consensus-Based Statement).[11]

40. For children with acute cough, we suggest avoiding using codeine-containing medications because of the potential for serious side effects including respiratory distress (Ungraded Consensus-Based Statement).[11]

Anti-histamines

In contrast to data in adults, the efficacy of anti-histamines in relieving cough in children is minimal, if at all. Data on anti-histamines combined with other medications as part of OTC medications were summarized above. A recent review of utility of anti-histamines in children did not recommend its use for chronic cough in children.[231] A Cochrane review on anti-histamines for prolonged non-specific cough

included three therapeutic and two safety RCTs.[194] The two larger therapeutic studies described no significant difference between the two groups (significant improvement in both the intervention and the placebo/placebo-like arms). In the RCT with the smallest sample size, cetirizine (a second-generation anti-histamine) was significantly more efficacious than placebo in reducing chronic cough in children associated with seasonal allergic rhinitis, and the effect was seen within 2 weeks of therapy.[195] Combined data from the safety evaluation studies revealed a non-significant difference between groups (OR, 1.6; 95% CI, 0.7 to 3.82) for cough as an adverse event but the trend favored the placebo arm.[194] A Cochrane review of symptomatic treatment of cough related to pertussis also found no significant benefit for diphenhyramine.[232]

Conclusions

Child-specific cough guidelines should be used for children aged ≤ 14 years and these differ from adults as the etiological factors and treatments in children are sometimes different from adults. While the majority of coughing illness in children is reflective of expected childhood respiratory infections, the cough may also be signifying a serious disorder. Thus, all children with chronic cough should have a thorough clinical review to identify pointers suggestive of an underlying respiratory and/or systemic illness.

Cough in children should be treated based on etiology and there is no evidence for using medications for symptomatic relief of cough. If medications are used, children must be followed up and medications ceased if there is no effect on the cough within an expected timeframe. Evaluation of time to response is important. Irrespective of diagnosis, environmental influences should be discussed and managed accordingly. Cough negatively impacts the QoL of both the child and parents; education regarding when to look into and explore parental expectations and fears are often valuable in the management of cough in children.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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