CHEST

Etiologies of Chronic Cough in Pediatric Cohorts

CHEST Guideline and Expert Panel Report

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BACKGROUND: There is no published systematic review on the etiologies of chronic cough or the relationship between OSA and chronic cough in children aged ≤ 14 years. We thus undertook a systematic review based on key questions (KQs) using the Population, Intervention, Comparison, Outcome format. The KQs follow: Among children with chronic (> 4 weeks) cough (KQ 1) are the common etiologies different from those in adults? (KQ 2) Are the common etiologies age or setting dependent, or both? (KQ 3) Is OSA a cause of chronic cough in children?

METHODS: We used the CHEST Expert Cough Panel's protocol and the American College of Chest Physicians (CHEST) methodological guidelines and Grading of Recommendations Assessment, Development, and Evaluation framework. Data from the systematic reviews in conjunction with patients' values and preferences and the clinical context were used to form recommendations. Delphi methodology was used to obtain consensus.

RESULTS: Combining KQs 1 and 2, we found moderate-level evidence from 10 prospective studies that the etiologies of cough in children are different from those in adults and are setting dependent. Data from three studies found that common etiologies of cough in young children were different from those in older children. However, data relating sleep abnormalities to chronic cough in children were found only in case studies.

CONCLUSIONS: There is moderate-quality evidence that common etiologies of chronic cough in children are different from those in adults and are dependent on age and setting. As there are few data relating OSA and chronic cough in children, the panel suggested that these children should be managed in accordance with pediatric sleep guidelines. CHEST 2017; 152(3):607-617

KEY WORDS: cough; evidence-based medicine; pediatrics

ABBREVIATIONS: CHEST = American College of Chest Physicians; GERD = gastroesophageal reflux disease; ILD = interstitial lung disease; KQ = key question; PBB = protracted bacterial bronchitis; PC-QOL = parent cough-specific quality of life; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL = quality of life; RCT = randomized controlled trial; UACS = upper airway cough syndrome

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Summary of Recommendations and Suggestions

1. For children aged ≤ 14 years, we recommend that common etiologies of chronic cough in adults are not presumed to be common causes in children (Level 1B).

2. For children aged ≤ 14 years with chronic cough, we recommend that their age and the clinical settings (eg, country and region) are taken into consideration when evaluating and managing their chronic cough (Level 1B).

3. For children aged ≤ 14 years with chronic cough, we suggest that clinical studies aimed at evaluating cough etiologies use validated cough outcomes, define response and diagnosis a priori, take into account the period effect, and undertake a period of follow-up (Ungraded consensus-based statement).

4. For children aged ≤ 14 years with chronic cough and suspected of having OSA, we suggest that they are managed in accordance with sleep guidelines (Ungraded consensus-based statement).

Chronic cough is a common reason for parents to seek specialist evaluation for their children. In children, chronic cough is associated with impaired quality of life,[1] multiple physician visits,[2] and adverse effects from inappropriate use of medications.[3] Recent studies[1,4,5] and systematic reviews[6,7] have found that using cough algorithms or pathways leads to earlier diagnosis and improved clinical outcomes, such as shorter duration of cough and increased quality of life. Thus, the updated American College of Chest Physicians (CHEST) guidelines recommended using pediatric-specific cough pathways when managing children with chronic cough.[8] Pediatric-specific chronic cough management pathways are different from those used in adults. The reasons for the difference include assessment of outcomes and the maturational aspects of immunity and physiology of the respiratory system (thus affecting aspects such as cough sensitivity[9]) from childhood to adulthood, as well as the most common etiologies of chronic cough.[10]

In adults, although common etiologies are somewhat dependent on continent (United States and the United Kingdom differ from Japan[11]), the most common etiologies identified include asthma or "cough variant asthma," gastroesophageal disease (GERD), upper airway cough syndrome/postnasal drip syndrome, chronic bronchitis, and idiopathic causes.[11,12] The frequency of the first three listed etiologies led to recommendations of empirical treatment for these conditions when managing adults with chronic cough.[13] In contrast, empirical therapy is not advocated for children in either the previous[14] or current[8] CHEST cough guidelines.

However, to date, there is no systematic review on the common etiologies of chronic cough in children in which children were systematically evaluated for the various possible causes of cough. Hence using the Population, Intervention, Comparison, Outcome framework, we performed systematic reviews to address key questions (KQ) relating to etiologies of cough in children. Given the recent interest in sleep and cough in adults with chronic cough,[15] one of the KQs specifically addressed this association. The 3 KQs addressed were:

KQ 1: In children with chronic (> 4 weeks) cough, are the common etiologies different from those in adults?

KQ 2: In children with chronic (> 4 weeks) cough, are the common etiologies age or setting dependent, or both?

KQ 3: Is OSA an etiology of chronic cough in children? If so, when should OSA be considered a cause of chronic cough in children?

In this paper, we present the systematic reviews for the KQs noted, a summary of the evidence, and the formulated recommendations based on these findings using CHEST's cough guidelines methods and framework.[16]

Methods

We undertook the systematic reviews based on the protocol[16] established by selected members of the CHEST Expert Cough Panel. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting. The KQs were framed by this paper's main authors.

Study Identification and Eligibility Criteria

Searches for the systematic reviews were undertaken externally by librarians (Nancy Harger, MLS, and Judy Nordberg, MLS) from the University of Massachusetts Medical School using the search strategies outlined in e-Appendix 1. We included only studies published in English. Duplicates found between Scopus and PubMed searches were identified and removed by the librarians before sending the abstracts to the two authors (A. C., J. O.) who reviewed the abstracts.

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For KQ1 and KQ2, we specifically excluded epidemiology association papers and studies aimed at evaluating a single etiology as the cause of chronic cough, for example, protracted bacterial bronchitis,[17] tobacco[18] and other environmental exposures,[19] or pertussis/selected infections.[20]

For the CHEST cough guidelines, it was determined a priori that the age cutoff for pediatric and adult components was 14 years. However, to ensure that all relevant studies were captured, we searched for studies that included participants up to 18 years of age. The age cutoff for the child-based vs adult-based protocols is further discussed later.

Data Extraction and Quality Assessment

The two reviewers independently reviewed all abstracts and fully agreed on which full-text articles to retrieve to assess for potentially eligible studies. It was planned that disagreements that could not be resolved by consensus would be adjudicated by a third reviewer (R. I.), but there were no disagreements. Data were extracted by a single author (A. C.) and checked by a second author (J. O.). For cohort studies, we reported on the study's setting, number enrolled and completing the study, inclusion and exclusion criteria, as well as other factors (Table 1[21-32]) we considered important for interpretation of studies on chronic cough specific to the KQs. These factors included a definition for diagnoses, how cough was measured and resolution defined, and whether or not the period effect was considered a priori. Reasons for these factors, considered quality factors for pediatric cough studies, are published elsewhere.[33]

Recommendation Framework

We used a standard method[16] per previous pediatric recommendations[8] and as stipulated by the CHEST Guideline Oversight Committee (e-Appendix 1) using the CHEST's Grading of Recommendations Assessment, Development and Evaluation framework. When there was insufficient evidence for diagnosis and management recommendations, the panel placed great emphasis on patient values, preferences, ease and cost of tests, and availability of potential therapies. The panel also made several suggestions for future research.

Results

The search results and PRISMA diagrams for all KQs are presented in e-Figures 1 and 2.

KQs 1 and 2: Summary of Evidence and Interpretation

Fourteen studies were included in the systematic review for these KQs: 10 were prospective studies and four were retrospective (Table 1, e-Fig 1). Among the prospective studies, the sample size ranged from 40 subjects[27] to 563 subjects,[34] whereas that of retrospective studies was smaller, ranging from 38 subjects[35] to 63 subjects.[36]

The prospective studies were undertaken in several different countries encompassing affluent (Australia[1,28] and United States[27]) and less affluent settings (Turkey,[22,31,34] India,[26] and Pakistan[30]), and the children were enrolled from medical clinics (pediatrics, pulmonology, and allergy). In contrast, all but one[37] of the retrospective studies were based in otolaryngology clinics, and all but one study[1] were single-center studies.

The most common ascribed etiologies for chronic cough in the prospective studies varied (Table 1). This is not surprising, as the settings of these studies differed. Nevertheless, common etiologies were asthma or asthma-like conditions, protracted bacterial bronchitis (PBB), and natural resolution (resolved without a specific diagnosis). Upper airway cough syndrome (UACS) or "postnasal drip" were common in only two studies, and both were based in Turkey.[22,31] Gastroesophageal reflux disease (GERD) was reported as common in two studies[5,27] that had substantial limitations in study quality. However, among the retrospective studies, GERD was common in two studies.[35,38] An etiology consistent with an infection was common in three studies.[35,36,38] Asthma (of various different definitions) was a common etiology in three of the retrospective studies.[35,37,38] It should be noted, however, that the diagnosis of asthma needs to be considered in the context of its subjective nature and the difficulty in diagnosing asthma in young children in whom objective quantification cannot be obtained. For example, in the Holinger[35] paper, "cough-variant asthma" and aberrant innominate artery were the most common diagnoses in the 0- to 18-month age group.

The studies differed substantially in quality (eg, the use of validated outcome measures of cough, a priori definitions, and follow-up of children). Hence, the findings have to be interpreted with caution. Ascribing etiologies for cough has an inherent high risk of bias related to the placebo and "period effects" (the natural resolution of cough over time[39]) that is evident in cough-related intervention studies.[33] These risks of bias can be reduced by limiting the time frame in which "response to treatment" is considered[33] when a randomized controlled trial (RCT) is not undertaken.

Despite the limitations described, common etiologies in children in the studies do not include chronic bronchitis or idiopathic cough (ie, unexplained cough), which are two conditions commonly found in adult-based cohorts.[11] Also, GERD is a commonly identified cause of chronic cough in various US and UK adult-based series[11] but not in the prospective studies in our systematic review of children (Table 1). Further, upper airway/postnasal drip and GERD are controversial causes of cough in children.[40]

TABLE 1] Prospective Studies That Have Described Various Etiologies of Chronic Cough in Children (Key Questions 1 and 2)

Study/Year	Country	Setting	Method of Assessment	Inclusion Criteria, Exclusion	No. Enrolled/ No. Completed/ Age
Asilsoy et al[22]/ 2008	Turkey	Single center, pediatric outpatients	ACCP guideline[14]	> 4 wk cough Exclusion: none reported	108/108 Mean = 8.4 y Range = 6-14 y
Chang et al[1]/ 2012	Australia	Multicenter, Respiratory outpatients	Modified ACCP[14] and TSANZ[23] guidelines	Age < 18 y cough > 4 wk duration, newly referred Exclusion: chronic respiratory illness	346/346 Mean = 4.5 y, SD, 3
Dani et al[26]/ 2002	India	Single center, pediatric outpatients	Sequential routine investigations: full blood count, erythrocyte sedimentation rate, Mantoux test, sputum, throat swab, chest radiograph Further investigations (eg, HIV, CT imaging, bronchoscopy, barium swallow) when indicated	Consecutive, immune-competent, age 1-12 y Chronic cough > 3 wk, unknown etiology Exclusion: heart disease	94 Age NR
Gedik et al[34]/ 2015	Turkey	Single center, pediatric or allergy outpatients	ACCP guideline[14]	Age < 17 y, persistent cough > 4 wk Exclusion: known chronic respiratory, neuromuscular, growth, cardiac problems; genetic syndromes; prematurity	563/563 Follow-up: NR Mean age = 5.4 y, SD, 3.8
Karabel et al[5]/ 2014	Turkey	Single center, respiratory outpatients	ACCP guideline[14]	> 4 wk cough Exclusion: neuromuscular, cardiac, syndromes, respiratory tract infection last 4 wk	270/270 Mean = 6.5 y range = 7 mo-17 y
Khoshoo et al[27]/ 2009	USA	Single center, pediatric outpatients	Chest radiograph, bronchoscopy, PFT with methacholine, sweat test, pH- or impedence-metry, skin testing, Ig levels Ohers also had: Barium meal or swallow, CT chest/sinus, laryngoscopy, Mantoux test	> 8 wk cough, born full term, neurodevelopmentally normal, no smoke exposure, no history of febrile or respiratory illness, no cardiac illness Exclusion: asthma, RAD, cystic fibrosis (unless able to do PFT/airway hyperreactivity)	40/40 Mean age = 7.8 y (range = 5-12 y)
Marchant et al[28]/ 2006	Australia	Single center, respiratory outpatients	Modified ACCP 1998[29] guideline	> 3 wk cough, age < 18 y, newly referred Exclusion: NR	108/103 Median = 2.6 y IQR = 1.2-6.9
Rehman et al[30]/ 2009	Pakistan	Single center, pediatric outpatients	Locally designed algorithm with Mantoux test	Age 6-59 mo > 4 wk cough Exclusion: use of ACE inhibitors	172/161 Summary NR
Usta et al[31]/ 2014	Turkey	Single center, pediatric allergy outpatients	British Thoracic Society guideline	Inclusion: NR Exclusion[b]	156/156 Mean = 8.4 y SD, 2.6
Yilmaz et al[32]/ 2014	Turkey	Single center, pediatric asthma, allergy outpatients	CHEST guidelines but evaluated by allergists skin prick test (house dust mites, pollen, alternaria, animal dander, latex), full blood count	Age < 18 y, chronic cough > 4 wk (nonspecific isolated dry cough) Exclusion: specific cough pointer present, wet cough, chest radiograph or PFT results abnormal, characteristic cough pattern, chronic respiratory illness, use of ICS, LTRA, ACE inhibitor	119/109 Median = 5 y IQR, 3.5-9

(Continued)

TABLE 1] *(Continued)*

Primary Outcome Used	Diagnoses Defined A Priori; Length of Follow-Up	Period Effect Considered[a]	Top 3 Most Common Diagnoses	Age or Setting Influence (or Both) Described
Cough, unspecified	Partial; Follow-up not reported	Not specified	Asthma/asthma-like n = 27 (25%) PBB = 25 (23%) UACS = 22 (20%)	No
Cough resolution by cough diary,[24,c] PC-QOL[25]	Yes; Follow-up maximum 12 mo for diagnosis and 6 mo after diagnosis	Yes, 2 wk of treatment	PBB = 142 (41%) Asthma = 55 (16%) Resolved without specific diagnosis = 48 (14%)	Common diagnoses differed in age groups and settings (rural vs cities)
Diagnosis by history and physical examination and routine investigations	NR Follow-up NR	No	Asthma = 35 (37%) Tuberculosis = 21 (22.3%) Pulmonary eosinophilia = 9 (9.5%) Sinusitis = 9 (9.5%)	No
Verbal category score	Yes Follow-up: 2 mo after cough resolution	Yes	Asthma = 140 (25%) Asthma-like = 107 (19%) PBB = 67 (12%)	Yes for age: asthma most common in all ages; second most common diagnosis: PBB in young children, psychogenic cough in older children
Not described	Partial; Follow-up: 12 mo	Not specified	Asthma = 73 (27%) Asthma-like = 42 (15.5%) GERD = 27 (10%)	No
Visual analogue scale score but success of treatment undefined Only 1 group (infection) had visual analogue scale improvement of ≥ 70%	Yes, Follow-up: none	No	GERD = 11 (27.5%) Asthma/cough variant asthma = 11 (27.5%) Allergy = 9 (22.5%)	No Note: comparison was made using mean and SD, although group size ranged from 1-11
Cough diary[24]	Yes Follow-up: maximum 12 mo for diagnosis, after diagnosis NR	Yes, 2 wk of treatment	PBB = 43 (40%) Resolved without specific diagnosis = 24 (22%) Bronchiectasis = 6 (5.6%)	No
Parents reporting—unspecified	NR Follow-up: until cough resolved (maximum 18 mo)	No	Asthma = 61 (38%) Postviral = 21 (13%) Tuberculosis = 14 (9%)	No
Cough, unspecified	Partial; Follow-up: maximum 18 mo for diagnosis, After diagnosis, NR	Not specified	Postnasal drip + asthma = 30 (19%) Postnasal drip = 29 (19%) Asthma = 19 (12%) PBB = 19 (12%)	No
Cough diary card	Yes, Follow-up: mean 21 mo (SD, 5)	No	Resolved without prescription = 23 (21%) Rest were treated with ICS for 2 wk: 24 (22%) responded, 62 (57%) partially responded	No

ACE = angiotensin-converting enzyme; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid; IQR = interquartile range; LTRA = leukotriene receptor antagonist; NR = not reported; PBB = protracted bacterial bronchitis; PC-QOL = parent cough-specific quality of life; PFT = pulmonary function test; RAD = reactive airway disease; TSANZ = Thoracic Society of Australia and New Zealand; UACS = upper airway cough syndrome. (Modified with permission from Chang et al[21] and Chang et al.[6])

[a]Period effect considered, that is, use of "time to response": the temporal relationship between use of medication and outcome was defined a priori.

[b]"Premature birth, neuromotor development retardation, developmental growth retardation, chest wall deformity, smoking habit, clubbing, cardiac disease, any known chronic disease or pulmonary disease, or both, and those who could not cooperate in pulmonary function testing."[31]

[c]Improvement of ≥ 75% or total resolution according to parental reports and cough diary data for ≥ 3 d.

TABLE 2] Retrospective Studies That Have Described Various Etiologies of Chronic Cough in Children (Key Questions 1 and 2)

Study/Year	Country	Setting	Method of Assessment	Inclusion Criteria; Exclusion	No. in Study, Age
Cash et al[38]/ 2015	USA	Single center, otolaryngological outpatients at tertiary hospital	Clinical and investigational based on clinical findings	Inclusion: chronic cough (> 4 wk) identified from medical records Exclusion: NR	58, mean age = 5.1 y (range = 2 wk-17 y)
Chan et al[37]/ 2007	Hong Kong	Single center, pediatric outpatients, secondary hospital	Clinical discretion	New referrals, > 4 wk cough Exclusion: known chronic respiratory disease	42, mean age = 5 y, SD, 2.9
Holinger[35]/ 1986	USA	Single author's practice, otolaryngological outpatients	Clinical, chest radiograph and investigational based on clinical findings	Inclusion: troublesome chronic cough (> 4 wk), age < 16 y, normal chest radiograph, referred Exclusion: NR	38, age range = 3 mo-15.75 y
Nation et al[36]/ 2014	USA	Single center Otolaryngological outpatients	Adenoidectomy, bronchoscopy, esophagoscopy + biopsy, nasal endoscopy + culture, biopsy of osteomeatalcomplex	Presenting with chronic cough (> 12 wk) with nasal congestion, rhinorrhea and unresponsive to first-line antibiotics (length + type not specified)	63 0.5-5 y, n = 18; 6-10 y, n = 9

(Continued)

Although only one study[1] specifically looked for differences in etiologies among study settings, it is clear that studies based in less affluent settings[26,30] have different common etiologies, with tuberculosis more commonly reported. In the Indian-based study,[26] pulmonary eosinophilia was also relatively common (third most common etiology), and this is likely related to GI parasites that are prevalent in such regions. A cross-sectional study based in Iran[41] that did not fulfill the inclusion criteria for our systematic review (because it focused on only one etiology) found that 25% of the 115 children with chronic cough had eosinophilia that was likely linked to *Toxocara* infection. Other parasites such as *Strongyloides* are also a common cause of systemic and pulmonary eosinophilia in settings in which parasites are endemic,[42] reinforcing the importance of the setting of the study.

The three studies (two prospective[1,34] and one retrospective[35]) that investigated the influence of age on etiologies all suggested that common diagnoses were different in younger children than in older children (Table 1). Thus, when considering further investigation of children in an attempt to determine the etiology of chronic cough (ie, bronchoscopy or blood tests), it is important to consider the age of the child as well as etiologies that are common in the local context. These data also support our previous recommendation[8] on using pediatric-based protocols.

As noted at the beginning of this paper, we chose the age cutoff of 14 years a priori for pediatric analysis of the cough data. Although the studies included in this systematic review ranged up to 18 years, it remains unclear what age threshold (12 years or 14 years) should be used to stratify adult- vs child-based protocols. In the field of cough, there are several reasons that underpin an age cutoff for children vs adults. These include the many physiological differences that influence etiological factors, outcome measures, and investigatory tests relevant to children compared with adults.[43] There are pediatric-specific, US-based guidelines for asthma,[44] GERD,[45] and interstitial lung disease (ILD),[46,47] which are all conditions associated with cough. The older version of the ILD guideline[46] does not specify the cutoff age, but the more recent version[47] specifies that the pediatric guideline extends to 18 years of age.[37] The GERD[45] guideline does not specify when adult-based protocols should be used but refers to children aged 16 years.

In the case of asthma guidelines, there are various age cutoffs used, and none of the guidelines provide evidence regarding cutoff age. The British[48] and US[44] asthma guidelines recommend three different age-specific stepwise protocols for children, with those aged > 12 years being assigned to the adult protocol. In the Australian guideline, child-specific protocols continue to be applied to adolescents (no cutoff given). Although the

TABLE 2] *(Continued)*

Primary Outcome to Define Cough	Diagnoses Defined A Priori; Follow-Up Length	Period Effect Considered[a]	Top 3 Etiology Labels Given by Study Authors	Age or Setting Influence Described (or Both)
Clinician defined	No; Follow-up: NR	No	Infection = 34% Airway hyperreactivity = 25% GERD = 24%[b]	No
Undefined parental report	No Follow-up: 4-12 mo	No	Allergic rhinitis = 13 Asthma = 12 Asthma + allergic rhinitis = 9	No
Clinician defined	No Follow-up: mean = 19.7 mo	No	Cough variant asthma n = 15 but 4 children also had airway abnormalities[a] + 1 psychogenic) Sinusitis = 6 (16%) Aberrant innominate artery = 5 Psychogenic = 5 Unknown = 5	Age influenced frequency of common diagnoses
Undefined	No Follow-up: NR	No	Maxillary antral infection = 26 (41%) Maxillary antral infection + GERD = 15 (24%) GERD = 12 (19%) All negative = 10 (16%)	Age effect: younger children more likely to have either maxillary antral infection or GERD only

See Table 1 legend for expansion of abbreviations.
[a]Subglottic stenosis, aberrant innominate artery (thus tracheomalacia).
[b]Method of diagnoses and labels given by authors are not conventional or in line with current standards. GERD diagnosed by clinical examination and laryngoscopy; infection included upper respiratory tract infection, bronchiolitis, and UACS. Airway hyperreactivity included "asthma" and "reactive airway disease" and in their chest radiographs, "small airway disease was evident."

steps recommended for adults are the same as for children as young as 5 years of age in the earlier Global Initiative for Asthma guidelines,[49] the latest version has different protocols for children aged 5 to 12 years.[50] Thus, based on this information, the upper age threshold for child-specific cough protocols should be at least 12 years. At this point, without further data we cannot validly conclude what the most valid age cutoff should be.

The studies included in our systematic review have to be interpreted in the context that most studies do have potential flaws, including not defining how cough was measured a priori or what constituted cough resolution or was considered the period effect, or both (Tables 1, 2). Many studies also lacked standardization of defining cough outcomes, an important factor for study quality.[21,43] Thus, further high-quality studies using validated tools,[51] particularly in primary care settings, are needed. This includes use of methods that take into account the period effect and use of definitions a priori for etiology and response using validated pediatric-specific cough outcome measures such as the pediatric cough-specific QoL (PC-QOL).[25,52]

Cough is a symptom that has a substantial period effect when studied[39] (ie, spontaneously improves with time) and is associated with a placebo effect as high as 80%.[53] When RCTs are not possible, strict methodological criteria (particularly for assessing response to treatment) needs to be applied. Furthermore, improvement criteria need to be defined a priori, that is, how large a change constitutes an "improvement in cough" as well as what is considered "resolution of cough." Also, a change in any subjective score needs to be large enough to be clinically relevant. Improvement (ie, reduction in cough) of $> 70\%$ measured by subjective or objective studies[54] for a defined number of days (usually 2-3 days)[28] has generally been used in pediatric studies. The importance of this lies in the fact that just by seeing a physician who takes an interest in the child's cough, the cough score and QoL can improve even before treatment.[55]

Ascribing an etiology to the cough also needs to be done a priori. Cough that improves months after an intervention may be related to the period or placebo effect, or both, rather than to the medication or intervention given. When considering the period effect, the time frame (ie, "time response") should be defined a priori and based on published RCTs and data. In most circumstances, 2 to 3 weeks is the most appropriate time frame for pediatric chronic cough studies, as noted in systematic reviews.[14]

Based on the summary of studies (Table 1) and the preceding information, and taking the findings of previous pediatric recommendations,[8,56] our recommendations were formulated. Per previous

TABLE 3] Studies That Have Described Chronic Cough and OSA in Children (Key Question 3)

Source/Year	Country	Setting	Method	Inclusion Criteria; Exclusion	No. in Study, Age	Primary Outcome to Define Cough	Diagnoses Defined A Priori; Follow-Up Length	Summary of Findings
Gurgel et al[57]/2008	USA	Otolaryngology and pediatrics, hospital	Case report	NA	2, age 2 y and 5 y	Clinician defined	NA	Children with tonsils impinging on epiglottis; both with chronic dry cough that resolved after tonsillectomy (time frame not provided)
Lewis et al[58]/2000	USA	Otolaryngology and pediatrics, hospital	Case report	NA	1, age 10 y	Clinician defined	NA	Child with 3-mo history of dry cough; 2 wk following removal of large lingual tonsils, cough abated
Poachanukoon et al[59]/2012	Thailand	Single center pediatric or allergy outpatients	Prospective cross-sectional study	Age, 1-5 y, clinical diagnosis of rhinosinusitis Exclusion: Not reported	154 Mean age = 4.9 y, SD, 3.3	Undefined	No Follow-up: Not described	Some children (undefined) with cough also had sleep apnea; no difference found between acute (10 d-4 wk) and chronic (> 4 wk)
Teoh et al[60]/2011	Australia	Cochrane Database	Systematic review	Inclusion: RCTs	NA	NA	NA	No studies found
Teng and Sullivan[61]/1997	Australia	Sleep laboratory, hospital	Case report	NA	1, age 3 y	Clinician defined	NA	Child with 2-y history of snoring and 1-y history of chronic nocturnal dry cough treated with CPAP

NA = not available; RCTs = randomized controlled trials.

recommendations,[8,56] these recommendations address children aged < 14 years but exclude premature infants and neonates. In premature infants and neonates, respiratory illnesses are much more likely to manifest as tachypnea or dyspnea or hypoxemia (or both) and rarely by chronic cough. The previous recommendations[8] included (1) using pediatric-specific cough management protocols or algorithms and (2) basing the management on the etiology of the cough. An empirical approach aimed at treating upper airway cough syndrome due to a rhinosinus condition, GERD, asthma, or a combination, should not be used unless other features consistent with these conditions are present. The findings of this systematic review consolidate previous CHEST guideline recommendations.[8]

1. Recommendations/Suggestions **For children aged ≤ 14 years, we recommend that common etiologies of chronic cough in adults are not presumed to be common causes in children** (Level 1B).

2. For children aged ≤ 14 years with chronic cough, we recommend that their age and the clinical settings (eg, country and region) are taken into consideration when evaluating and managing their chronic cough (Level 1B).

3. For children aged ≤ 14 years with chronic cough, we suggest that clinical studies aimed at evaluating cough etiologies use validated cough outcomes, a priori define response and diagnosis, take into the period effect, and undertake a period of follow-up (Ungraded consensus-based statement).

KQ 3: Summary of Evidence and Interpretation

Only five publications (Table 3,[57-61] e-Fig 2) were included in KQ3's systematic review. In this systematic review, we included case reports given the scarcity of data. Of the five studies, one was a Cochrane systematic review[60] that found no RCTs. Two papers were case reports[58,61]: one was a report on two children[57] and the remaining paper was a cross-sectional association study[59] showing that sleep apnea and cough were more common in the chronic rhinosinusitis group. Thus, there are scarce data on the relationship between chronic cough and obstructive sleep disorders in children. One study[59] of children with rhinosinusitis described cough being wet, but the rest of the studies reported that the cough was dry. Given that infection is often found in children with rhinosinusitis,[36] it is possible that the cough in these children is concurrent with PBB.

4. Recommendations/Suggestions **For children aged ≤ 14 years with chronic cough and suspected of having OSA, we suggest that they are managed in accordance with sleep guidelines** (ungraded consensus-based statement).

Areas for Further Research

To advance and improve knowledge regarding the delineation of common causes of chronic cough in children, suggested areas of research include the following:

1. Undertaking multicenter cohort studies in various clinical settings (community and hospital, rural/remote vs urban) and countries, which include children of different ages, with consideration of stratification by age. The studies should use validated cough outcomes and a priori definitions and consider the period effect.
2. Determining whether cough is related to OSA using an RCT design in which validated subjective data (including QoL and cough diaries) are supported by objective data (such as cough frequency).

Conclusions

There is moderate-quality evidence that common etiologies of chronic cough in children are different from those in adults and are dependent on age and setting. Thus, the panel recommended that for children aged ≤ 14 years (1) common etiologies of chronic cough in adults are not presumed to be common causes in children and (2) their age and the clinical settings (eg, country and region) should be taken into consideration when evaluating and managing the chronic cough. However, there were few data relating OSA to chronic cough in children. Thus, the panel suggested that these children be managed in accordance with pediatric sleep guidelines.

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Additional information: The e-Appendix and e-Figures can be found in the Supplemental Material section of the online article.

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