Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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REVIEW

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Childhood chronic cough made easy: a simplified approach for the primary care setting

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Received 21 May 2020; Accepted 19 September 2020
Available online 1 March 2021

KEYWORDS
cough;
children;
chronic cough;
cough syndromes;
diagnostic algorithm

Abstract
Cough is a defense mechanism, but when it becomes persistent and troublesome, it must be carefully assessed. Chronic cough, that is, cough persisting for more than 4 weeks, has a proven negative impact on a child's quality of life; it interferes with daily activities, sleep, and schooling and may involve frequent health care visits and long-lasting treatments. Currently, there is a plethora of algorithms in the literature aiming to assist in the assessment of chronic cough in children; however, referring to complex flowcharts may be impractical for the usually busy primary care physician. Herein, we provide a simplified tool for the assessment of children with chronic cough in the primary care setting, presenting a basic approach to the most common causes along with hints to avoid common pitfalls in everyday practice. Finally, the most common clinical scenarios are analyzed, aiming to assist primary care physicians in providing the appropriate care to these patients.

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https://doi.org/10.15586/aei.v49i2.38

Introduction

Chronic cough is a frequently encountered symptom in pediatric primary care and represents an important burden for the affected children and their families.[1] It has been estimated that the caregivers of children with persistent cough visit their family doctor five or more times before being referred to a specialized respiratory clinic.[1] In addition, chronic cough has a proven negative impact on daily activities, sleep, and schooling, thus substantially reducing the quality of life of children and their families.[2]

In adults, chronic cough is defined as cough lasting for more than 8 weeks.[3] In children, however, the definition of chronic cough varies from 3 to 12 weeks.[4–6] It has been reported that in 90% of children presenting to primary care setting with an upper respiratory tract infection, the cough resolves spontaneously within 25 days from the onset of the disease.[7,8] On the other hand, Chang et al.[9] studied 346 children with cough lasting for more than 4 weeks and found that the cough resolved spontaneously in only 13.9% of them; in the majority of cases, an underlying disorder such as protracted bacterial bronchitis (PBB), asthma, bronchiectasis, airway malacia, aspiration, and so on, could be identified.[9] Based on the above evidence, chronic cough in children is currently defined as cough lasting for more than 4 weeks.[6,10,11]

Although there is a plethora of algorithms in the literature aiming to assist in approaching the child with chronic cough,[4–6,10,11] referring to complex flowcharts may prove impractical for a usually busy primary care physician.[12] The aim of this article is to provide a simplified tool of guidance to primary care physicians treating children with chronic cough. A basic approach to the most common causes along with hints to avoid common pitfalls in everyday practice is also presented.

Dealing with the child with chronic cough

The medical approach of the child with chronic cough is classically based on history, physical examination, and appropriate first-line investigations.

History

Gathering information regarding the characteristics of chronic cough (e.g., time of onset, triggers, quality, accompanying symptoms, etc.) is the first and perhaps the most important step. Here, we present a simple mnemonic tool, the "*6 T - 6 S*" rule of thumb (Figure 1), that may help physicians to stay focused and not get lost in irrelevant or misleading information. Thus, in the case of a child with cough lasting for more than 4 weeks, the following issues should be clarified.

Time of onset

In most cases, the child's cough coincides with the start of school or nursery school attendance or with other family members' viral illness. When the cough can be dated back to early infancy, congenital malformations or inherited diseases such as tracheomalacia, cystic fibrosis (CF), and primary ciliary dyskinesia (PCD) should be excluded.[13] Protracted bacterial bronchitis often appears in infancy or early childhood, usually after an acute bronchitis that failed to resolve.[14] If the cough started after traveling to a tuberculosis (TB) endemic area or coincides with TB diagnosis in a child's close contact, investigations to exclude the disease (e.g., tuberculin skin test, interferon-gamma release assay) must be performed.[15]

Triggers and track

A history of choking in a toddler less than 3 years old should always alert the physician to the possibility of foreign body aspiration.[16,17] When the cough continues unremittent after an episode of severe respiratory tract infections, especially when other symptoms (e.g., dyspnea, exercise intolerance, wheezing, or focal crackles) co-exist, post-infectious bronchiectasis, PBB, or bronchiolitis obliterans should be considered.[16] A constant, unremitting wet cough that never stops, even during school holidays, makes the diagnosis of PBB more likely. However, when such a cough persists after

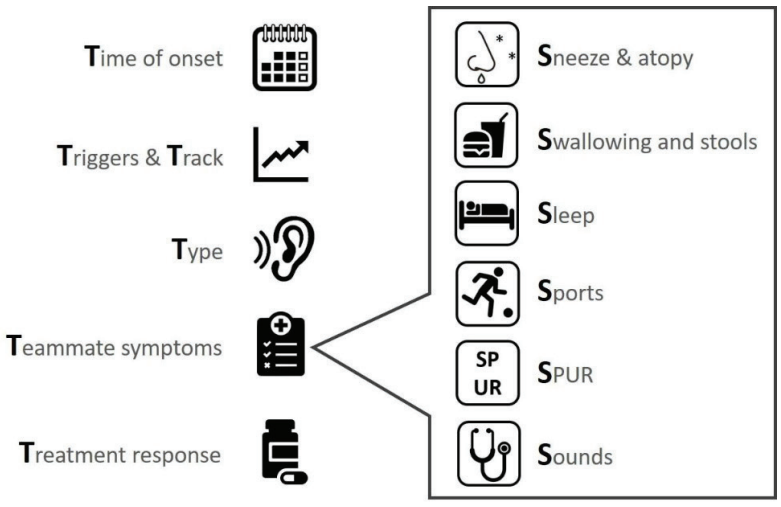

Figure 1 The "*6 T - 6 S*" rule of thumb for approaching chronic cough history.

prolonged antibiotic treatment, foreign body aspiration, bronchiectasis, or other chronic suppurative lung diseases (e.g., PCD and CF) should be considered.[18] On the other hand, a persistent cough triggered by viral infections, never accompanied by wheezing or other adventitious lung sounds, and with cough-free intervals between the episodes, probably belongs to the normal spectrum especially if it occurs in an otherwise healthy child.[19]

Type: Is the cough dry, wet, or variable?

This important information may significantly narrow down the differential diagnosis and drive the evaluation to the appropriate path (Tables 1 and 2). The physician can easily recognize the type of cough if the child coughs spontaneously or on demand during the consultation. If this is not the case, modern technology can be of help as parents may be asked to record their child's cough at home using smartphones or other electronic devices.[19,20] In any case, it is important to recognize the child with a chronic wet cough in due time, since this type of cough is usually associated with important underlying disorders.[21] Apart from being dry or wet, disease-specific characteristics can also be discerned; a paroxysmal cough with a classic inspiratory "whoop" points to the diagnosis of pertussis, a barking or brassy cough might be heard in tracheomalacia, whereas the occasional honking cough might fall within the "tic cough" frame.[19-21]

Teammates: accompanying symptoms

Chronic cough may be presenting as a sole symptom or as part of a clinical spectrum, which can be easily determined by asking the following "6 S" questions:

Sneeze and atopy

Is there a history of hay fever, eczema, or milk/food allergy? Their presence favors – but does not secure – the diagnosis of allergic asthma.[22]

Table 1 Etiology and characteristics of chronic dry cough.

Post-infectious or pertussis-like cough	• Starting as an acute illness • Paroxysmal in nature • Characteristic whoop • Post-tussive vomiting
Reactive airway disease/asthma	• History of wheeze • Shortness of breath • Personal or family history of atopy or asthma
Tic cough	• Loud honking cough • Absent at night • Absent when distracted
Tracheo-broncho malacia	• Loud barking cough • Absence of hoarseness • May become wet with viral infections
Drugs (e.g., angiotensin converting enzyme inhibitors)	• Resolves when the drug is discontinued

Table 2 Etiology and characteristics of chronic wet cough.

Persistent bacterial bronchitis	• Usually preschool child • Day-care attendance • Absence of specific cough pointers
Cystic fibrosis	• Failure to thrive • Chronic diarrhea • Family history
Primary ciliary dyskinesia	• Unexplained neonatal respiratory distress in a term baby • Early-life, year-round daily wet cough • Early-life, year-round daily rhinitis • Situs inversus totalis, heterotaxy
Recurrent small volume aspiration	• Neurodevelopmental disorders • Choking on food • Post-meal cough and/or wheeze
Immunodeficiency	• Recurrent infections
Foreign body	• History of choking
Bronchiectasis	• Wet cough not resolving after 4 weeks of antibiotics • Recurrent pneumonia • Digital clubbing • Failure to thrive

Swallowing and stools

Does the cough get worse or appear when the child is eating or drinking? Does the infant choke on milk? Does he/she get chesty post-feeding? A positive answer to these questions makes primary or secondary aspiration likely, especially if the cough is associated with a neuromuscular disorder or cerebral palsy.[23] Furthermore, poor stool quality (runny, eminently smelly, or difficult to flush away), especially if it is accompanied by other symptoms (e.g., failure to thrive, chronic or recurrent infections) makes CF or immunodeficiency a potential diagnosis.[24]

Sleep disturbance

Coughing within the first 2 h of sleep might be linked to rhinosinusitis or postnasal drip,[25] while late night coughing, especially when associated with wheezing, may be a sign of asthma.[26] However, the most important question to be answered is if the cough disappears completely as soon as the child falls asleep and likely.[27] In adolescents, a cough that appears when falling asleep after a meal might indicate gastro esophageal reflux disease.[17]

Sports

The appearance of cough when the child practices sports is a frequent condition, usually interpreted as a sign of asthma.[19] However, asthma is not the only cause of exercise-induced cough. Tracheomalacia, for example, could present as a chronic brassy cough that gets worse with exercise and may be associated with wheeze (monophonic and better heard over the trachea).[28] The persistent wet cough of PBB may also get worse during exercise.[21]

SPUR: severe-persistent-unusual-recurrent

Underlying immunodeficiency should always be excluded in a child with severe, persistent, unusual, or recurrent symptoms.[29]

Sounds

The presence of adventitious sounds that accompany the cough should always be sought in the child's history; relevant notes in health booklets or similar medical documents are particularly useful. The presence of polyphonic wheezing may be indicative of an asthma phenotype, while a monophonic and localized wheeze points to airway malacia.[30] Children with malacia may also have a history of stridor that typically worsens with feeding, crying, supine positioning, and agitation. In some cases, a "rattly" respiration is repeatedly reported.[31]

Treatment response

Different treatments, such as short-acting beta agonists (SABA), inhaled steroids (ICS), or antibiotics might have been tried in children with persistent cough. In general, failure to demonstrate an immediate response to salbutamol or an improvement of cough after a short trial of inhaled steroids, should eliminate the diagnosis of asthma or eosinophilic airways inflammation.[32] On the other hand, a chronic cough that improves on starting a course of antibiotics but relapses soon after their discontinuation, warrants further investigation for potentially serious underlying disorders.[33] Finally, patients treated with angiotensin converting enzyme (ACE) inhibitors may develop a dry, tickly, and often bothersome cough that ceases when the ACE inhibitor is discontinued.[34]

Clinical examination

The experienced physician may spot the likely diagnosis by hearing the cough (e.g., pertussis-like, barking, honking, etc.) or by inspecting the child. Children with hypotonia due to neuromuscular disorders, those with tracheostomy and some with chest wall deformities may report frequent lower respiratory tract infections or, at their very best, a chronic and unremitting wet cough.[20] The clinician should never forget to inspect the fingers. Clubbing is an ominous sign, closely related to serious lung disorders such as CF, PCD, and bronchiectasis.

The oxygen saturation of the arterial blood (SpO2) should be determined by a pulse oximeter; hypoxemia (i.e., SpO2 <92–94% at room air) must always alert the clinician.[16] The hypoxic child might suffer from severe airway disorders, an interstitial lung disease, or even a cardiovascular disorder.[35]A "runny" or chronically congested nose may be a sign of allergic rhinitis, recurrent upper respiratory tract infections or, rarely, PCD and immunodeficiency. Children with the last two pathologies might have a runny nose that has troubled them from infancy.[24,29] Any degree of respiratory distress (tachypnea, chest wall retractions, suprasternal retractions, nasal flaring), or presence of adventitious sounds on lung auscultation warrants further investigation. Polyphonic, high-pitched wheezing is indicative of asthma while low-pitched, monophonic, and localized wheeze points to obstruction, malacia, or compression of larger airways.[30] Diffuse coarse crackles indicate the presence of thin secretions within the airways (bronchi, bronchioles) such as in CF, PCD, or other suppurative bronchitis; focal coarse crackles may be indicative of bronchiectasis.[30] Diffuse fine crackles are typical for interstitial/fibrotic lung disease, while focal fine crackles may be heard in atelectasis.[30]

After examining the respiratory tract, the clinician should focus on the cardiovascular system; the presence of gallop rhythm, heart murmurs, or apex beat misplacement (e.g., dextrocardia in PCD or left shift in cardiomegaly) should be excluded. Finally, child's height and weight should be plotted on a growth chart to exclude failure to thrive. If the child falls across the centiles, more serious pathologies such as CF, PCD, and immunodeficiency should be excluded.[36]

Investigations

Arguably, in the primary care setting only a limited number of investigations can be performed. Thus, the physician must choose judiciously to avoid unnecessary tests that may eventually delay the diagnosis or lead to ineffective treatment options.

Regardless of the presence or absence of abnormal findings in history and physical examination, chest radiography (CXR), and spirometry (if available) must be considered as first-line investigations.[37]

Chest radiography

A CXR is always available even in low-income settings. If abnormal, although rarely diagnostic, it should alert the physician to a possible underlying condition that requires further investigations and/or referral to a respiratory center. Of note, the CXR should be performed at least 6 weeks from a significant lung infection to avoid false positive results.[33] The findings vary significantly, depending on the underlying cause. In children with asthma, CRX may be completely normal, while in those with severe malacia of the intrathoracic airways it may reveal bilateral hyperinflation.[37] The majority of children with pulmonary TB will show CRX changes, typically hilar and mediastinal lymphadenopathy. If the enlarged lymph node compresses the airway, hyperinflation and air-trapping or distal atelectasis may be observed.[15] In contrast, the child with PBB may have a normal or near-normal CRX with vague peribronchial infiltrates.[31,36] In children with chronic wet cough, a CRX abnormality that persists for more than 4 weeks after appropriate therapy should prompt investigations for underlying bronchiectasis.[38] Finally, the clinician must bear in mind that only 10% of foreign bodies are visible on CRX; however, the presence of "indirect" signs, such as lung asymmetry (e.g., air-trapping, emphysema), presence of peripheral infiltrates or mediastinal shift, should

raise the possibility of foreign body aspiration, especially in toddlers.[31,37]

The majority of children over 5 years of age can perform basic lung function testing if appropriately instructed.[39] Spirometry may reveal an obstructive pattern (e.g., asthma) with decreased, forced expiratory flows and volumes and reversibility to bronchodilation, thus allowing the primary care physician to plan treatment promptly.[6] In case of airway malacia, abnormalities in the expiratory or inspiratory part of the flow-volume loop may suggest collapse of intra- or extrathoracic airways, respectively.[40]

Common clinical scenarios

In everyday practice, the primary care physician who treats children with chronic cough will encounter one of the following three scenarios (Figure 2).

Scenario 1: Isolated chronic dry cough

When assessing a child with chronic dry cough and the history, clinical examination and first-line investigations are inconclusive, the physician should reassure the parents and recommend a "watchful waiting" approach; the majority of these children will be spontaneously cough-free within the next 3–4 weeks.[41] The same principle applies in the case of tic cough (previously referred to as habit cough), a bizarre and honking cough that usually follows an uneventful upper respiratory tract infection, disrupts daily life, and interferes with the child's activities, but is absent when the child is asleep or distracted.[27] However, if somatic cough disorder (previously referred to as psychogenic cough) is suspected (e.g., disproportionate and persistent thoughts about the seriousness of cough and other accompanying symptoms, high levels of anxiety, or excessive time devoted to the symptoms),[42] referral to a psychologist and/or psychiatrist is recommended.[27,42]

An exception to the "watchful waiting" approach is the child with a history of choking, even when the clinical examination and the investigations are normal. These patients may initially present with a persistent dry cough that eventually becomes wet. Thus, a history of choking should prompt the physician to immediately refer the child to a respiratory center with bronchoscopy facilities.[20] The "watchful waiting" approach may also be bypassed in the case of atopic children, especially if they have experienced similar episodes of persistent cough in the past. In this case, a 4- to 8-week treatment with an adequate dose of inhaled corticosteroid (ICS) followed by cessation and reassessment, is recommended.[22] The resolution of cough shortly after the initiation of ICS does not necessarily mean the patient has asthma; as already mentioned, the majority of these children would be spontaneously cough-free within the next weeks.[41] However, the diagnosis of asthma should be seriously considered if the cough recurs after the discontinuation of ICS.[22]

If an isolated chronic dry cough does not resolve after 4 weeks of watchful waiting or ICS administration, referral to a tertiary center for specific investigations and management is warranted.[37]

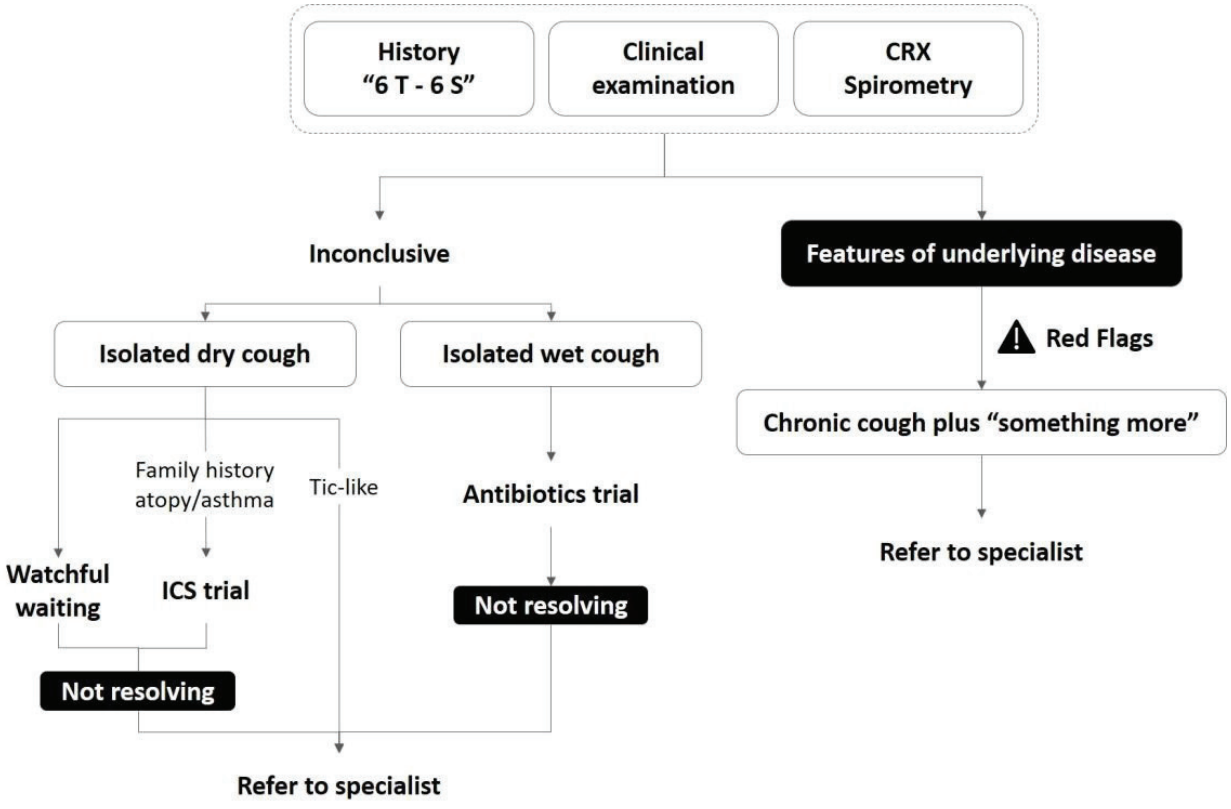

Figure 2 The simplified approach of chronic cough in children.

Scenario 2: Isolated chronic wet cough

Wet cough is indicative of the presence of secretions within the airways; an isolated chronic cough usually has an infectious etiology.[33] In developed countries, up to 40% of children referred to specialized centers with chronic wet cough are diagnosed with PBB.[36] PBB is actually an umbrella term covering three different endotypes: PBB-clinical, PBB-extended, and PBB-recurrent.[43] The definition of PBB-clinical is based on three diagnostic criteria:[36] (a) wet cough for more than 4 weeks; (b) absence of symptoms or signs of other causes; (c) cough resolution following 2 weeks of appropriate antibiotic treatment. Obviously, the diagnosis cannot be made until after the cough resolution following the 2-week course of antibiotics.[36]

Although different regimens have been proposed, amoxicillin-clavulanate is the most recommended.[44–46] The duration of treatment varies substantially[44]; however, most specialists suggest to begin with a 2-week course and extend it to 4 weeks if the cough does not resolve.[6,13,36] If the wet cough requires 4 weeks of antibiotics to clear, then the diagnosis of PBB-extended should be considered. This endotype usually points towards an underlying tracheo-bronchomalacia, and the child should be investigated accordingly.[44] Finally, a small proportion of children will present recurrent (>3 per year) episodes of PBB (PBB-recurrent). Children with this endotype are likely to have underlying bronchiectasis and should be referred to a respiratory center for specialist assessment.[47]

Scenario 3: Chronic cough plus "something more"

The last scenario involves children with chronic cough and suspicious history, abnormal clinical examination, or abnormal CXR and/or spirometry. A summary of these "red flags" is given in Table 3; their presence points towards an underlying pathology,[9] thus it would be prudent to refer these children to a specialized respiratory center for further assessment.[6,10,37]

Children with chronic cough are commonly encountered by primary care physicians worldwide. Cough is a defense mechanism, but when it becomes persistent and troublesome, it should be carefully assessed. In such cases, its precise characteristics must be determined from the patient's history and a thorough examination along with appropriate first-line investigations must be performed. In the primary-care setting, the most common scenarios involving children with chronic cough include the isolated dry cough, the isolated wet cough, and the chronic cough accompanied by alarming symptoms and signs. Primary care physicians must be familiar with easy-to-remember management algorithms to be able to promptly provide the appropriate care for these patients.

Table 3 Alarming clinical signs ("red flags") and possible diagnoses.

Cough dated since early infancy	Congenital lung anomalies, CF, PCD
Failure to thrive	CF, immunodeficiency, cardiac disorders
Digital clubbing	Suppurative lung disease, cardiac disorders
Presence of heart murmur or gallop rhythm	Cardiac disorders
Low oxygen saturation	Parenchymal lung disease, cardiac disorders
Recurrent infections	Immunodeficiencies
Feeding problems or postprandial cough	Aspiration lung disease
Hypotonia, neuromuscular disorders	Aspiration lung disease
Hemoptysis	Suppurative bronchitis (e.g., CF), bronchiectasis, foreign body, TB
Exercise-induced dyspnea	Asthma, cardiac disorders
Recurrent pneumonias	Congenital lung anomalies, CF, PCD, foreign body, immunodeficiency, aspiration

CF: cystic fibrosis; PCD: primary ciliary dyskinesia; TB: tuberculosis.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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