



# Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,  
Alergología y Asma Pediátrica

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REVIEW

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## Chronic cough in childhood: A systematic review for practical guidance by the Italian Society of Pediatric Allergy and Immunology

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Received 4 August 2020; Accepted 15 November 2020

Available online 1 March 2021

### KEYWORDS

adolescents;  
algorithm;  
children;  
chronic cough;  
diagnosis;  
dry cough;  
wet cough

### Abstract

The current systematic review presented and discussed the most recent studies on pediatric chronic cough. In addition, the Italian Society of Pediatric Allergy and Immunology elaborated a comprehensive algorithm to guide the primary care approach to a pediatric patient with chronic cough.

Several algorithms on chronic cough management have been adopted and validated in clinical practice; however, unlike the latter, we developed an algorithm focused on pediatric age, from birth until adulthood. Based on our findings, children and adolescents with chronic cough without cough pointers can be safely managed, initially using the watchful waiting approach

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<https://doi.org/10.15586/aei.v49i2.44>

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and, successively, starting empirical treatment based on cough characteristics. Unlike other algorithms that suggest laboratory and instrumental investigations as a first step, this review highlighted the importance of a “wait and see” approach, consisting of parental reassurance and close clinical observation, also due to inter-professional collaboration and communication between general practitioners and specialists that guarantee better patient management, appropriate prescription behavior, and improved patient outcome. Moreover, the neonatal screening program provided by the Italian National Health System, which intercepts several diseases precociously, allowing to treat them in a very early stage, helps and supports a “wait and see” approach.

Conversely, in the presence of cough pointers or persistence of cough, the patient should be tested and treated by the specialist. Further investigations and treatments will be based on cough etiology, aiming to intercept the underlying disease, prevent potentially irreversible tissue damage, and improve the general health of patients affected by chronic cough, as well as the quality of life of patients and their family.

Further high-quality randomized controlled trials are needed to validate this algorithm’s performance in real clinical practice.

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## Overview

Cough is defined as “a forced expulsive maneuver, usually against a closed glottis, and is associated with a characteristic sound.” Cough is a protective physiological reflex deputed to clear secretion from the airways or remove inhaled material. As a physiological reflex, healthy children usually cough on average 11 times (range 1-34) daily. On the other hand, cough may also be the key symptom of diseases affecting the upper or lower respiratory airways, requiring prompt diagnosis and treatment. Cough may be pragmatically classified, considering its duration and characteristics. Conventionally, acute cough lasts less than 4 weeks, whereas chronic cough lasts more than 4 weeks. Cough may be wet, such as productive (associated with secretion), or dry, such as irritative. The current review aims to present and discuss recent evidence on chronic cough. This document, provided by the Italian Society of Pediatric Allergy and Immunology (SIAIP), proposes a practical algorithm to manage and improve clinical outcomes of children and adolescents with a chronic cough in clinical practice.

## Pathophysiological mechanisms

Cough is a multifaceted neuromuscular phenomenon characterized by three dynamic steps: a deep inspiration, an exaggerated expiratory effort against the closed glottis, and the opening of the glottis, closure of the nasopharynx, and forced and exaggerate airflow emission through the mouth.<sup>1</sup> These events are orchestrated by the sequential activation and coordination of an afferent circuit, a central processing pathway, and an efferent arm.<sup>2</sup>

Cough receptors are generally in the larynx, trachea, bronchi, and pleura, and also the nose and paranasal sinuses, in the auditory canal, pericardium, esophagus, and stomach. Stimulation of these receptors may also elicit the cough. For example, the ear-cough reflex (Arnold’s reflex) is known.<sup>2</sup> The application of an endogenous and/or

exogenous stimulus on cough receptors, localized to vagal afferent nerve terminations in the airway’s mucosa, activates a complex neuronal response, which, via the release of numerous mediators, induces the cough neural circuits. From multiple peripheral and central sites, the afferent signal is transported to trigger both on-site and distal responses, thus activating the bronchopulmonary sensory nerve as well as peripheral and central sites in the brainstem. Herein, the afferent reflex is modulated, and an efferent response is generated to induce a neuromuscular effect involving laryngeal abductor and adductor muscle, diaphragm, muscles of the chest wall, and cervical and abdominal muscles.<sup>3</sup>

Coughing is a protective reflex that removes foreign bodies entered into airways or enhances airway clearance, acting as an innate, built-in defense mechanism.<sup>4</sup>

However, when it occurs chronically, cough becomes a disruptive health problem for the child/adolescent affected. Chronic cough, defined as a daily cough lasting for >4 weeks,<sup>5</sup> represents a common pediatric health problem, with a prevalence of 35% in school-age children.<sup>6</sup> Chronic cough may require multiple physician visits and hospitalization, with substantial implications for the child and patient’s family and a relevant burden for healthcare. Accordingly, appropriate diagnostic management has long been recognized as imperative to achieve the correct diagnosis promptly and guarantee the best possible therapy. Although cough is commonly considered to originate from the respiratory system, several extrapulmonary or systemic diseases can cause a chronic cough. This event is frequently observed in children with a nonspecific chronic cough in which, due to the lack of corresponding clinical symptoms, the risk of misdiagnosis and/or underdiagnosis is high. It reflects the importance of both a careful and a multidisciplinary assessment of the affected child/adolescent.

Herein, we performed an updated systematic review regarding the management of chronic cough in children and adolescents; a diagnostic and therapeutic algorithm of a chronic cough has also been developed to offer a practical guide for the pediatrician.

## Methodology

### Study design

A systematic review was performed according to the Cochrane handbook guidelines.<sup>7</sup> The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement has been used for reporting of the systematic review, filling a 27-item checklist and a flow diagram (Figure 1).<sup>8</sup>

### Search strategy

A literature search was performed covering papers published from January 1, 2008 to July 31, 2019; the PubMed and Excerpta Medica Database (EMBASE) databases were systematically searched. In PubMed, the following search strategy was used: “cough” [MeSH] AND “chronic” [All Fields] AND “infant” [MeSH] OR “child” [MeSH] OR “adolescent” [MeSH] OR “children” [MeSH].

In EMBASE, the following search strategy was used: “cough”:ab,ti AND “chronic”:ab,ti AND “infant”/de OR “child”/de OR “adolescent”/de OR “children”.

An additional research was conducted on the Cochrane Database of Systematic Reviews, and the references of relevant articles were further cross-checked.

### Inclusion criteria

Studies were considered eligible if they showed the following characteristics: pediatric population (aged <18 years), papers published in English, year of publication (from 2008 to 2019), study design consisting of prospective or retrospective observational studies, and randomized controlled trial (RCT).

### Exclusion criteria

Studies related to the adult population, non-pertinent articles, duplicates, letters, commentaries, case series including

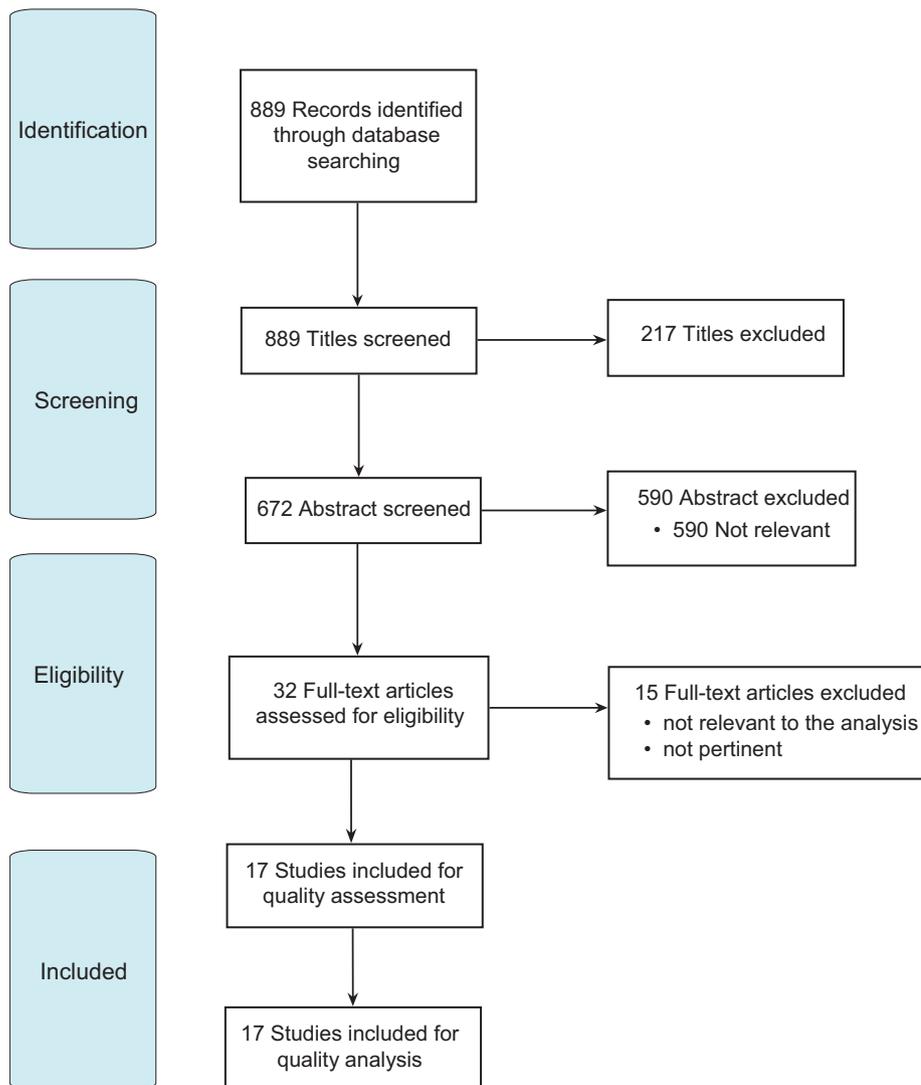


Figure 1 Flow chart of study selection.

< 10 children, reviews, guidelines, and articles not written in the English language were excluded from the analysis.

### Studies selection

Studies focusing on the definition of the disease, clinical presentation, and laboratory and instrumental investigations on children with chronic cough were selected.

Titles and abstracts of studies identified during the initial search were screened for inclusion, and papers focusing on chronic cough were included in this review. After that, the full text of all included papers was analyzed for further evaluation. The references of relevant articles were also crosschecked.

### Data extraction

Data were independently extracted by two authors (SM and EC), and any disagreements or conflicts were discussed with other authors.

The following data were extracted for each study: authors, year of publication, the title of the study, location, the number of subjects included, the age of children, study type, number and type of included studies, aims/outcomes, results, and comments/limitations of the study.

The study characteristics are summarized in [Table 1](#).

## Results

### Literature findings

The initial search identified 889 records (306 from the PubMed database and 583 from the EMBASE database) of which 104 were duplicates. One additional record was identified using the Cochrane Database of Systematic Reviews. Thirty-two studies met the inclusion criteria after abstracts and titles were evaluated. Fifteen of these studies were excluded because data were not pertinent or not relevant ([Table 2](#)); 17 studies (2 systematic reviews, 4 retrospective observational studies, 10 prospective analyses and 1 clinical trial) were judged eligible and included in the final analysis. The search results and the selection process are shown in [Figure 1](#).

### Study characteristics

This systematic review included 17 studies. Overall, 7337 children aged 24 months to 18 years presenting with chronic cough were included in the review. The study settings included emergency departments, pediatric departments, or outpatient clinics and services.

### Definition

The definition of chronic cough is nonunanimous. Most of the studies defined chronic cough as a cough longer than 4 weeks.<sup>9-25</sup> One study defined chronic cough as lasting

more than three consecutive weeks.<sup>24</sup> Two studies defined chronic cough as a cough of >8 weeks duration.<sup>5,21</sup> Another study, by the age, defined chronic cough as a cough lasting >4 weeks in children <15 years and >8 weeks for adolescents ≥15 years.<sup>18</sup> Only one study did not make the chronic cough definition explicit.<sup>17</sup> More recently, according to the latest CHEST Expert Cough Panel guidelines, chronic cough has been defined as the presence of daily cough for more than 4 weeks for children aged ≤14 years.<sup>26</sup>

### Clinical history and symptoms

Chronic cough may be the expression of several diseases. Thus, the ability of the clinician to interpret the clinical history correctly, the type of cough, and the presence of other symptoms is crucial to establishing an accurate differential diagnosis.

Although none of the included studies was explicitly focused on clinical history and presentation of chronic cough in children,<sup>9,24</sup> it has been noted that positive personal and family history of atopy and a previous history of chronic cough were commonly detected in children affected by chronic cough.<sup>11,16,18-20</sup> Passive tobacco exposure was commonly reported in patients with chronic cough.<sup>11,16,18,20</sup>

At the time of presentation, the average cough duration differed widely among studies, ranging from <7 days to 30.6 weeks.<sup>11,22,24</sup>

Running nose and nasal congestion, dry throat with foreign body sensation, and repeated clearing of the throat often accompanied chronic wet cough that aggravates when the posture is changed or in the early morning.<sup>15</sup> It can signify an underlying illness, such as aspiration lung disease, cystic fibrosis, or noncystic fibrosis bronchiectasis.<sup>9</sup>

Children with dry cough are more commonly aggravating or onset at night and/or early morning. Dry cough is associated with a high rate of spontaneous resolution without any therapeutic intervention.<sup>13</sup>

Symptoms of post-tussive emesis, purulent nasal discharge, and postnasal drip showed a predictive value for a positive sinus X-ray ( $p < 0.001$ ). Worsening cough at night and with exercise did not correlate with sinusitis underlying chronic cough<sup>19</sup>; conversely, these symptoms appeared suggestive, more commonly, of asthma and, less frequently, of gastroesophageal reflux disease (GERD).<sup>21</sup>

### Etiology of chronic cough

The etiology of chronic cough is broad and differs significantly in clinical settings. Airway hyperreactivity, GERD, and infectious diseases were reported as the most common causes underlying a positive history for chronic cough in adults.<sup>11</sup>

By stratifying the pediatric population by age, a significant difference in the etiology of chronic cough appeared per the age range.<sup>12,15,18,20</sup>

In the infant population (5 months-1 year of age), the sequence of the common causes of nonspecific chronic cough was upper airway cough syndrome (33.3%), cough

Table 1 Characteristics of the included studies.

N.	Authors [Ref.]	Year	Title	Country	N. pts	Age	Type of study	N. and type of included studies	Aims/Outcomes	Results	Comments (Limitations of the study)
1	Chang AB et al. <sup>9</sup>	2016	Children with chronic wet or productive cough-treatment and investigations: A systematic review	Australia	2,144	10 months to 8.4 years (age range)	Systematic review	1 RCT, 11 prospective and 5 retrospective studies	1. How effective are antibiotics in improving the resolution of cough? If so, what antibiotic should be used, and for how long? 2. When should they be referred for further investigations?	1. Not pertinent with our research 2. Investigations should be undertaken when specific cough pointers (e.g., cough with feeding and digital clubbing) are present and when the wet cough does not resolve within a specific time frame (4 weeks to >6 months) following the use of antibiotics	There is high-quality evidence that when specific cough pointers are present in children with a wet cough, further investigations should be conducted. When the wet cough does not improve by 4 weeks of antibiotic treatment, there is moderate evidence that these children should be referred to a major center for further investigations to determine whether an underlying lung disease is present.
2	Asilsoy S et al. <sup>10</sup>	2015	Seroprevalence of <i>Chlamydia pneumoniae</i> and <i>Mycoplasma pneumoniae</i> in children with chronic cough	Turkey	41	8.00 ± 1.96 (mean, SD)	Prospective study	NA	To evaluate <i>M. pneumoniae</i> and <i>C. pneumoniae</i> serology and diagnosis and treatment in children with chronic cough	<i>M. pneumoniae</i> IgM positivity was found in 17.07% (7/41), <i>C. pneumoniae</i> IgM positivity in 2.85% (1/35), <i>M. pneumoniae</i> IgM and/or IgG positivity in 41.46% (17/41), and <i>C. pneumoniae</i> IgM and/or IgG positivity in 25.7% (9/35) of patients	1. The authors analyzed one serum sample 2. The study did not include a control group
3	Cash H et al. <sup>11</sup>	2015	Chronic cough in children	USA	58	Mean 5.1 years (range, 2 weeks to 17 years)	Retrospective analysis	NA	1. Response to treatment 2. Diagnostic workup	1. Not pertinent 2. a. Otolaryngologist consult, b. Chest radiography (it was more likely to be ordered odds ratio [OR], 16.4; 95% CI, 1.91-140.8; P = 0.002) pulmonary consult	1. Retrospective review 2. It is subject to bias from data and findings as reported in medical records

(continue)

Table 1 Continued.

N.	Authors [Ref.]	Year	Title	Country	N. pts	Age	Type of study	N. and type of included studies	Aims/Outcomes	Results	Comments (Limitations of the study)
4	Chang AB et al. <sup>12</sup>	2012	A multicenter study on chronic cough in children: Burden and etiologies based on a standardized management pathway	Australia	346	4.5 years (mean age)	Prospective study	NA	<ol style="list-style-type: none"> <li>To evaluate the burden and etiologies using a standard management pathway in various settings</li> <li>To determine the influence of age and setting on disease burden and etiologies and etiology on disease burden</li> </ol>	<p>17.6% of children had a serious underlying diagnosis (bronchiectasis, aspiration, and cystic fibrosis). PBB was more likely found in the younger children (&lt;2 years of age); no significant difference among age range was reported for diagnosis of asthma, bronchiectasis, cough resolved without a specific diagnosis, and tracheomalacia. Moreover, 61/346 children (17.6%) reported more than one diagnosis: tracheomalacia was with PBB (n = 27), asthma with PBB (n = 13), and mycoplasma pneumoniae infection (n = 2), PBB with asthma (n = 8) and aspiration lung disease (n = 4), upper airways syndrome with asthma (n = 2) and PBB (n = 2), aspiration lung disease with bronchiectasis (n = 1), and gastroesophageal reflux disease (GERD) with PBB (n = 2)</p>	<p>Comments:</p> <ol style="list-style-type: none"> <li>The frequency of etiologies of chronic cough is dependent on the clinical setting and age has less influence</li> </ol> <p>Limitations:</p> <ol style="list-style-type: none"> <li>Lack of an objective measurement of cough</li> </ol>

5	Chang AB et al. <sup>13</sup>	2015	Children with chronic cough: when is watchful waiting appropriate? Development of likelihood ratios for assessing children with chronic cough	Australia	326	<18 years	Retrospective analysis	NA	<p>1. To determine how well cough pointers differentiate specific cough from nonspecific cough</p> <p>2. Describe the clinical profile of children whose cough resolved without medications (spontaneous resolution)</p>	<p>1. significant ORs (95% CI) were found for:</p> <p>a. Wet cough: 73.7 (10-544.2)</p> <p>b. Wheeze or reversible airway obstruction 21.2 (1.3-349.8)</p> <p>c. Chest radiograph abnormality: 20.3 (1.2-335.4)</p> <p>d. For protracted bacterial bronchitis (PBB); asthma and bronchiectasis, the specificity of all pointers was high (&gt;98%), but sensitivity was generally low other than wet cough for PBB and dry cough for asthma</p> <p>2. Only two children in the spontaneously resolved group had a specific cough pointer, whereas at least one cough pointer was present in all children in the specific cough all-cause group.</p> <p>Although the absence of other individual cough pointers did not change the pretest probability very much (negative LRs close to 1), the absence of all the pointers had a negative LR of 0 (95% CI: 0-0.03).</p>	<p>1. The definition of the duration of chronic cough is controversial (&gt;4 weeks vs. &gt;8 weeks).</p> <p>2. The guidelines that use the shorter time frame do not advocate the use of medications for all children at that time point, assuming cough resolves spontaneously.</p> <p>3. The comparative control group used for this study was non-homogeneous, and the LR values may change.</p> <p>4. The data set used for this study was based mainly on a hospital cohort of young children, and thus the LRs calculated may change in primary care settings and older children.</p>
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Table 1 Continued.

N.	Authors [Ref.]	Year	Title	Country	N. pts	Age	Type of study	N. and type of included studies	Aims/Outcomes	Results	Comments (Limitations of the study)
6	Chang AB et al. <sup>14</sup>	2016	Use of management pathways or algorithms in children with chronic cough: Systematic reviews	Australia	NA	≤14 years old	SR	RCT: 3 Cohort: 13	To evaluate the use of management pathways or algorithms in children with chronic cough: 1. Do cough management protocols (or algorithms) improve clinical outcomes? 2. Should the cough management or testing algorithm differ depending on the duration and/or severity? 3. Should the cough management or testing algorithm differ depending on the associated characteristics of the cough and clinical history?	<p>The presence of any one of the specific cough pointers was a highly sensitive measure (sensitivity: 100%).</p> <p>The absence of all cough pointers ruled out the possibility of specific cough with a negative predictive value of 100% (one-sided 97.5% CI: 91-100%)</p> <p>1. The first use of the cough algorithm improved QoL significantly and had a higher proportion of children who were cough-free and a shorter duration of cough. All of the cohort studies reported high success in achieving a diagnosis irrespective of the algorithm used.</p> <p>2. No studies for Q2</p> <p>3. Yes, it differs by clinical history and cough characteristics</p>	<p>1. Few RCTs for Q1 and Q3, and no studies for Q2</p> <p>2. Different algorithms were evaluated and compared</p>

7	Chen X et al. <sup>15</sup>	2018	Etiology of non-specific chronic cough in children of 5 years and younger	China	85	3.8±1.1 years (mean age, SD)	Retrospective study	NA	To improve the diagnostic and treatment levels of pediatricians for non-specific chronic cough in young children	The etiology distribution of chronic cough was as follows: 27 cases had variant asthma (31.8%), 32 cases had upper airway cough syndrome (37.6%), 16 cases had a cough after infection (18.8%), 3 cases had gastroesophageal reflux cough (3.5%), 2 cases had an allergic cough (2.4%), and 5 cases had unknown causes of cough (5.9%).	The primary composition ratio of the etiology of chronic cough in children of 5 years old and below is as follows: upper airway cough syndrome, cough variant asthma, and post-infection cough.
8	Gedik AH et al. <sup>16</sup>	2015	Evaluation of 563 children with chronic cough accompanied by a new clinical algorithm	Turkey	563	5.4±3.8 years (mean age, SD)	Prospective study	NA	To analyze the etiological factors of chronic cough in the pediatric population, according to the age group.	The most common final diagnosis from all the participants was as follows: asthma (24.9%), asthma-like symptoms (19%), protracted bacterial bronchitis (PBB) (11.9%), and upper airway cough syndrome (9.1%). The psychogenic cough was the second most common diagnosis in the subjects over 6 years of age.	Different age groups in children may have a different order of frequencies
9	Hare KM et al. <sup>17</sup>	2018	Do combined upper airway cultures identify lower airway infections in children with chronic cough?	Australia	309	2.3 years (median age)	Prospective study	NA	To compare respiratory bacterial pathogens cultured from nasopharyngeal and	<i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , and <i>Moraxella catarrhalis</i> were more prevalent in nasopharyngeal than in oropharyngeal	Neither nasopharyngeal nor oropharyngeal swabs alone or in combination reliably predicted lower airway infection in children with chronic wetcough.

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Table 1 Continued.

N.	Authors [Ref.]	Year	Title	Country	N. pts	Age	Type of study	N. and type of included studies	Aims/Outcomes	Results	Comments (Limitations of the study)
10	Ilarslan NEC et al. <sup>18</sup>	2018	Evaluation of children with chronic cough including obstructive sleep apnea: A single-center experience	Turkey	237	5 (0.28-13.95) years (median age)	Prospective study	NA	oropharyngeal swabs with BAL cultures as the "gold standard" to diagnose lower airway infection in children with a chronic wet cough.	swabs (37%, 34%, and 23% vs. 21%, 6.2%, and 3.2%, respectively). PPV and NPV for lower airway infection by any of these three pathogens were 63% (95% confidence interval [95% CI]: 55, 70) and 85% (95% CI: 78, 91) for nasopharyngeal swabs, 65% (95% CI: 54, 75) and 66% (95% CI: 59, 72) for oropharyngeal swabs, and 61% (95% CI: 54, 68) and 88% (95% CI: 81, 93) for both swabs, respectively. In children older than 2 years of age, asthma appeared the most common cause of chronic cough, followed by PBB, GERD, OSAS, and pneumonia. In the younger children (<2 years of age), PBB is more likely found, followed by asthma, GERD, and pneumonia.	Limitations: 1. The authors enrolled children with comorbidities 2. The follow-up period was short.
11	Wilson NW et al. <sup>19</sup>	2012	Sinusitis and chronic cough in children	Nevada	86	5.6 years (mean age)	Retrospective study	NA	1. To examine the frequency of an abnormal sinus X-ray in children with a chronic cough of more than 4 weeks duration	1. Sinus abnormalities were detected by X-ray and associated with prolonged cough in 65% of children	Comments: 1. The Water's view sinus film is a clinically useful screening tool for clinicians in the workup of chronic cough

12	Karabel M et al. <sup>20</sup>	2013	The evaluation of children with prolonged cough accompanied by American College of Chest Physicians guidelines	Turkey	270	6.5 ± 2.3 years (mean age, SD)	Prospective study	NA	<p>2. To compare the interpretation of the sinus film between allergy/pulmonary clinicians and radiologists</p> <p>3. To correlate symptoms with X-ray results</p> <p>To analyze etiological factors of chronic cough</p> <p>The most common etiologic factors were asthma (27%), asthma-like syndrome (15.5%), and GERD (10%).</p> <p>When the diagnosis of chronic cough in children is made by using the standard approach for adult patient care, there is a high probability of making the wrong diagnosis as well as the use of unnecessary drugs and parental concerns</p>
13	Khoshoo V et al. <sup>21</sup>	2009	Associated factors in children with chronic cough	New Orleans	40	7.8 years (mean age)	Prospective study	NA	<p>To analyze etiological factors of chronic cough</p> <p>The most common etiologic factors were gastroesophageal reflux disease (27.5%), allergy (22.5%), asthma (12.5%), infection (5%), aspiration (2.5%), and multiple etiologies (20%).</p> <p>Reflux, allergy, and asthma accounted for &gt;80% of the likely etiologic factors of chronic cough in children and responded to appropriate treatment</p>
14	O'Grady KF et al. <sup>22</sup>	2017	Chronic cough post-acute respiratory illness in children: A cohort study	Australia	2586	2.3 years (median age)	Prospective study	NA	<p>1. To identify the prevalence of chronic cough following acute respiratory illness</p> <p>Most children (n = 627, 74.8%) had a cough duration of &lt;7 days at enrolment. At day 28, 171/839 (20.4%, 95% CI: 17.7 to 23.1) children presenting to</p> <p>The limitations of the study included a large proportion of children who were screened but not enrolled and/or the likely high number of children presenting to</p>

(continue)

Table 1 Continued.

N.	Authors [Ref.]	Year	Title	Country	N. pts	Age	Type of study	N. and type of included studies	Aims/Outcomes	Results	Comments (Limitations of the study)
15	Usta G et al. <sup>23</sup>	2013	The assessment and management of chronic cough in children according to the British Thoracic Society guidelines: Descriptive, prospective, clinical trial	Turkey	156	8.42 ± 2.6 years (mean, SD)	Prospective study	NA	2. To determine the diagnostic outcomes of children with chronic cough	had persistent cough irrespective of cough duration at enrolment. The cough was wet in 59/171 (34.5%), dry in 45/171 (26.4%) and variable in 28/171 (16.1%). Of these 117 children, 117 (68.4%) were reviewed by a pediatric pulmonologist. A new and serious chronic lung disease was diagnosed in 36/117 (30.8%) children; 55/117 (47.0%) were diagnosed with PBB	ED outside of research nurse hours who were not screened. It places constraints on the generalizability of the study.
								To evaluate the assessment and management of chronic cough in children	19.2% (n = 30) were diagnosed with postnasal drip syndrome plus asthma, 18.6% (n = 29) with postnasal drip syndrome, 12.2% (n = 19) with asthma, 12.2% (n = 19) with protracted bacterial bronchitis, 11.5% (n = 18) with nonspecific isolated cough, 9.6% (n = 15) with cough variant asthma, 5.7% (n = 9) with psychogenic cough, and 3.2% (n = 5) with gastroesophageal reflux disease	Comments: Postnasal drip syndrome and asthma were the most common cause of chronic cough Limitations: The authors did not perform a 24-h pH-monitoring study, which is the gold standard for the diagnosis of GERD.	

16	Yildiz Y et al. <sup>24</sup>	2016	Evaluation of fractionated nitric oxide in chronic cough patients	Turkey	90	10.8 ± 3.6 years (mean, SD)	Prospective study	NA	To investigate FeNO measurement as a noninvasive technique that can assist the clinician with diagnosis in patients presenting with chronic cough	FeNO measurement exhibited 78% sensitivity, 92% specificity, 82% PPV, and 91% NPV in the diagnosis of asthma in patients with chronic cough.	FeNO measurement can be used as a quick and reliable diagnostic method in patients presenting with chronic cough due to its high positive predictive value.
17	Zgherea D et al. <sup>25</sup>	2012	Bronchoscopic findings in children with a chronic wet cough	USA	109	0-3 years of age	Retrospective study	NA	To determine the frequency of bacterial bronchitis in children with chronic wet cough and to analyze their bronchoscopic findings	Of 109 children, 33 (30.3%) had laryngomalacia and/or tracheomalacia. The bronchoscopy showed purulent bronchitis in 56% (110) cases and non-purulent bronchitis in 44% (87). The bronchoalveolar lavage bacterial cultures were positive in 46% (91) of the children and showed nontypable <i>Haemophilus influenzae</i> (49%), <i>Streptococcus pneumoniae</i> (20%), <i>Moraxella catarrhalis</i> (17%), <i>Staphylococcus aureus</i> (12%), and <i>Klebsiella pneumoniae</i> in 1 patient.	Children who present with chronic wet cough are often found to have evidence of purulent bronchitis on bronchoscopy

Ref., reference; SD, standard deviation; NA, not applicable; RCT, randomized controlled trial; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; SR, systematic review; OSA, obstructive sleep apnea.

**Table 2** List of excluded studies and reasons for exclusion.

N.	Authors	Year	Title	Reasons for exclusion
1	Xepapadaki P et al.	2010	Impulse oscillometry testing in chronic cough in children.	Focused on impulse oscillometry testing
2	Anne S et al.	2016	What are management options for chronic cough in children?	Review
3	Chang AB et al.	2017	Management of children with chronic wet cough and protracted bacterial bronchitis: CHEST guideline and expert panel report	Guidelines
4	Greifer M et al.	2015	Pediatric patients with chronic cough and recurrent croup: the case for a multidisciplinary approach.	It is not possible to extract data only on chronic cough
5	Petrinin Y et al.	2018	Pediatric chronic cough characteristics and etiology - A retrospective tertiary clinic cohort study	Abstract Meeting
6	Willis C et al.	2010	Multicentre RCT using a standardized management algorithm for the treatment of chronic cough in children	Abstract Meeting
7	Schmit KM et al.	2013	Evaluating cough assessment tools: A systematic review	It is not possible to extract data only on chronic cough.
8	Chang AB et al.	2006	Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines.	Guidelines
9	Zgherea D et al.	2012	Bronchoscopic findings in children with a chronic wet cough	Focused on protracted bacterial bronchitis
10	Zhou J et al.	2018	Values of fractional exhaled nitric oxide for cough-variant asthma in children with chronic cough	Focused on the diagnosis of cough-variant asthma in children with chronic cough
11	Chang AB et al.	2013	A cough algorithm for chronic cough in children: A multicenter, randomized controlled study	Algorithm
12	Fracchia MS et al.	2019	The diagnostic role of triple endoscopy in pediatric patients with chronic cough	It is not possible to extract data only on the pediatric population
13	Hare KM et al.	2015	Respiratory bacterial culture from two sequential bronchoalveolar lavages of the same lobe in children with chronic cough	Not pertinent
14	McCallum GB et al.	2014	Clinical pathways for chronic cough in children	Review
15	Yilmaz O et al.	2014	Children with a chronic nonspecific isolated cough	Focused on treatment

N: number.

variant asthma (25.9%), post-infectious cough (22.2%), GERD (3.7%), and allergic cough (3.7%).<sup>15</sup>

In children younger than 2 years of age, protracted bacterial bronchitis (PBB) was more likely found (30.8%), followed by asthma (27%), asthma-like syndrome (15.5%), GERD (10%), and pneumonia (7.6%).<sup>12,18,20</sup>

In children of 5 years old and below, the main etiologies of chronic cough were as follows: asthma (31.8%), upper airway cough syndrome (37.6%), cough after infection (18.8%), GERD (3.5%), allergic cough (2.4%), and unknown causes of cough (5.9%).<sup>15,16</sup>

In the pediatric population aged 5-16 years, GERD, allergy, asthma, infections, and aspiration accounted for >80% of the likely etiologic factors of chronic cough.<sup>21,23</sup> The

psychogenic cough was also a common cause of chronic cough in children over 6 years of age (Table 3).<sup>16,23</sup>

By the characteristics of the cough, it has been reported that asthma, rhinosinusitis, and GERD were the most frequent causes of chronic specific cough, with an incidence of 69.82%, 4.6%, and 8.3%, respectively.<sup>16</sup> The remaining 21% of patients showed noncystic fibrosis bronchiectasis, cystic fibrosis, bronchiolitis obliterans, tuberculosis, pneumonia, foreign body aspiration, hemosiderosis, and ganglioneuromas.<sup>16</sup> PBB was the second most common cause of chronic wet cough, with bacterial culture positive for *Hemophilus influenzae* (43.2%), *Streptococcus pneumoniae* (23.9%), *Moraxella catarrhalis* (23.9%), *Streptococcus pyogenes* (6%), and *Staphylococcus aureus* (3%).<sup>16</sup>

**Table 3** The most common causes of chronic cough in the pediatric population by age.

Population	Causes
Infants (5 months to 1 year of age)	Airway cough syndrome (33.3%) Cough-variant asthma (25.9%) Post-infection cough (22.2%) GERD (3.7%) Allergic cough (3.7%)
Children (1-2 years of age)	Protracted bacterial bronchitis (30.8%) Asthma (27%) Asthma-like syndrome (15.5%) GERD (10%) Pneumonia (7.6%)
Children (2-5 years of age)	Asthma (31.8%) Upper airway cough syndrome (37.6%) Cough after infection (18.8%) GERD (3.5%) Allergic cough (2.4%) Unknown causes of cough (5.9%)
Children (5-16 years of age)	>80%: GERD Allergy Asthma Infections Psychogenic cough

GERD, gastroesophageal reflux disease.

Patients with a dry cough showed croup, tracheo-bronchomalacia, psychogenic cough, vascular, and airway abnormalities as the most frequent etiologies.<sup>16</sup> *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were the most common post-infectious causes in patients with chronic dry cough on normal pulmonary function tests (PFTs) and chest X-rays.<sup>10</sup>

Moreover, two or more associated causative factors were frequently identified in children with a chronic cough in some studies.<sup>12,21</sup> Specifically, Chang et al. found that 17.6% of children had more than one diagnosis: tracheomalacia was with PBB (n = 27), asthma with PBB (n = 13), and *M. pneumoniae* infection (n = 2), PBB with asthma (n = 8) and aspiration lung disease (n = 4), upper airways syndrome with asthma (n = 2) and PBB (n = 2), an aspiration lung disease with bronchiectasis (n = 1), and GERD with PBB (n = 2).<sup>12</sup>

### Laboratory and instrumental findings

Currently, the clinical history and cough characteristics have been adopted as criteria to determine the diagnostic workup of chronic cough.

In their prospective study, Chang et al.<sup>13</sup> enrolled 326 children newly referred for chronic cough and evaluated data on specific cough pointers (Boxes 1 and 2). They showed that the presence of a specific cough pointer indicating a cause of chronic cough had a sensitivity of 1.0 (95% confidence interval [CI]: 0.98-1.0), specificity of 0.95 (95%

**Box 1** List of systemic and pulmonary cough pointers.

Systemic* cough pointers	Pulmonary* cough pointers
Cardiac abnormalities	Chest pain
Digital clubbing	Daily moist or productive cough
Failure to thrive	Hemoptysis
Medications or drugs associated with chronic cough	Abnormal cough characteristics and/or auscultatory findings
Neurodevelopmental abnormality	Recurrent pneumonia
Fever	Hypoxia/cyanosis
Immunodeficiency	History of the previous lung disease or predisposing causes
Feeding difficulties	Exertional dyspnea or dyspnea at rest or tachypnea
History of contacts	Chest wall deformity
	Chest radiograph or pulmonary function test Abnormalities

CI: 0.82-0.99), positive predictive value (PV) of 0.99 (95% CI: 0.97-1.0), negative PV of 1.0 (95% CI: 0.89-1.0), positive likelihood ratio (LR) of 20 (95% CI: 5.18-77.21), and negative LR of 0 (95% CI: 0-0.03).<sup>13</sup> Thus, those authors concluded that children with chronic cough without any cough pointers could be safely managed using the watchful waiting approach, while, in the presence of any cough pointers, children would benefit from further investigations, with an odds ratio (OR) of 5.28 (95% CI: 1.23-22.73).<sup>13</sup>

When specific cough pointers (systemic and/or pulmonary cough pointers (Boxes 1 and 2) are present (high-quality evidence) and/or cough does not resolve within a specific time frame (ranging from 1 to >6 months) following the use of antibiotics (moderate-quality evidence), investigations should be undertaken to determine if an underlying lung disease or other diseases are present.<sup>9</sup>

In this regard, the most frequently performed investigations were fiberoptic bronchoscopy (FB) with bronchoalveolar lavage (BAL) and chest computed tomography (CT) scans or assessment of immunity; however, the chest radiograph remains the first line of instrumental investigation to perform in children with chronic cough. The FB was reporting up to 74% airway abnormalities,<sup>9</sup> purulent bronchitis in 56% of cases, and laryngomalacia and/or tracheomalacia in 30.3% of cases.<sup>25</sup> BAL, considered as the "gold standard" to identify lower airway infections, was used to detecting *Haemophilus influenzae* (49%), *S. pneumoniae* (20%), *M. catarrhalis* (17%), and *S. aureus* (12%) as the most common bacteria.<sup>25</sup> Chest CT scans were also reported as positive, and poor radiologic outcomes and structural airway abnormalities were more frequently occurring with longer cough duration.<sup>9</sup>

A retrospective analysis, enrolling 58 pediatric patients younger than 18 years, revealed that flexible laryngoscopy, chest radiograph, and CT scan of the sinuses were also commonly performed in patients with chronic cough. Flexible laryngoscopy appeared useful both in the diagnosis

**Box 2** Cough pointers and related underlying diseases.

Cough pointers	Underlying disease
Wheezing episodes	Asthma
Atopy	
Dyspnea on exertion	
Allergic salute	Allergic rhinitis
Clearing throat	Postnasal drip
Wet/productive cough	Cystic fibrosis
Persistent/recurrent endobronchial infections	Primary ciliary dyskinesia
	Protracted bacterial bronchitis
Choking with food	Recurrent aspiration
Penetration syndrome	Foreign body inhalation
Brassy or barking cough	Tracheo/bronchomalacia, airways compression
“Bizarre” cough	Psychogenic cough
Dry cough, breathless, restrictive spirometry	Interstitial lung disease
Progressive cough, weight loss, fevers	Exertional dyspnea or dyspnea at rest or tachypnea
History of contacts	Tuberculosis
Hemoptysis	Interstitial lung disease
	Bronchiectasis
	Chronic lung disease
Chest deformity	
Auscultatory findings	
Symptoms worsening after feeding or when lying down	GERD
Digital clubbing	Systemic immunodeficiency
Neonatal onset	Congenital abnormalities
Positive history for prematurity and neonatal respiratory intensive care	Bronchopulmonary dysplasia
Cough productive of casts	Plastic bronchitis or asthma
Chronic wet cough in mornings only	Suppurative lung disease

GERD, gastroesophageal reflux disease.

of upper respiratory tract affections and GERD.<sup>19</sup> A chest radiograph was ordered for patients for whom the treatment failed, resulting in positive in most cases.<sup>19</sup> OR for abnormal chest radiograph findings appeared significant for the diagnosis of PBB and pneumonia, showing a sensitivity of 0.20 (95% CI: 0.16-0.26), specificity of 1.0 (95% CI: 0.89-1.00), positive PV of 1.00 (95% CI: 0.92-1.0), negative PV of 0.15 (95% CI: 0.11-0.2), positive LR infinity, and negative LR of 0.8 (95% CI: 0.75-0.85) for the specific cough all-causes.<sup>13</sup> CT scan of the sinuses was positive in patients with chronic nasal symptoms and chronic cough; X-ray of the sinuses was able to detect sinus abnormalities in more than half of the cases.<sup>19</sup>

Although spirometry (pre- and post- $\beta_2$ -agonists) is commonly performed in daily practice, literature data are lacking regarding its use in the pediatric population with chronic cough.<sup>9-12,14-23</sup> Nevertheless, in their multicenter study, the authors revealed that spirometry showed a sensitivity of 0.03 (95% CI: 0.01-0.06), specificity of 1.0 (95% CI: 0.89-1.00), positive PV of 1.00 (95% CI: 0.60-1.0), negative PV of 0.13 (95% CI: 0.09-0.17), positive LR infinity, and negative LR of 0.97 (95% CI: 0.95-0.95) for the specific cough all-causes.<sup>13</sup>

Finally, only one of the studies included in our systematic review investigated the diagnostic role of fractional

exhaled nitric oxide (FeNO) in 90 children, aged 6-17 years, with chronic cough.<sup>24</sup> By assuming 24 part per billion (ppb) and above values for FeNO positivity, Yildiz et al. revealed that FeNO showed a sensitivity of 0.78, a specificity of 0.92, a positive PV of 0.81, and a negative PV of 0.91, supporting its use as a quick and reliable diagnostic method in patients with chronic cough.<sup>24</sup>

## Discussion

Chronic cough, defined as the presence of daily cough for more than 4 weeks in duration, is hugely complicated to evaluate, and very often, the underlying disease remains not diagnosed, misdiagnosed, and/or inappropriately treated. After conducting an updated systematic review about the management of chronic cough in children and adolescents, the SIAIP proposed a diagnostic algorithm to offer a practical guide for the pediatrician to improve management and clinical outcomes (Figure 2).

The initial assessment of chronic cough includes a detailed history and physical examination. First, obtaining a comprehensive clinical history allows the pediatrician to understand whether the patient is affected by a chronic

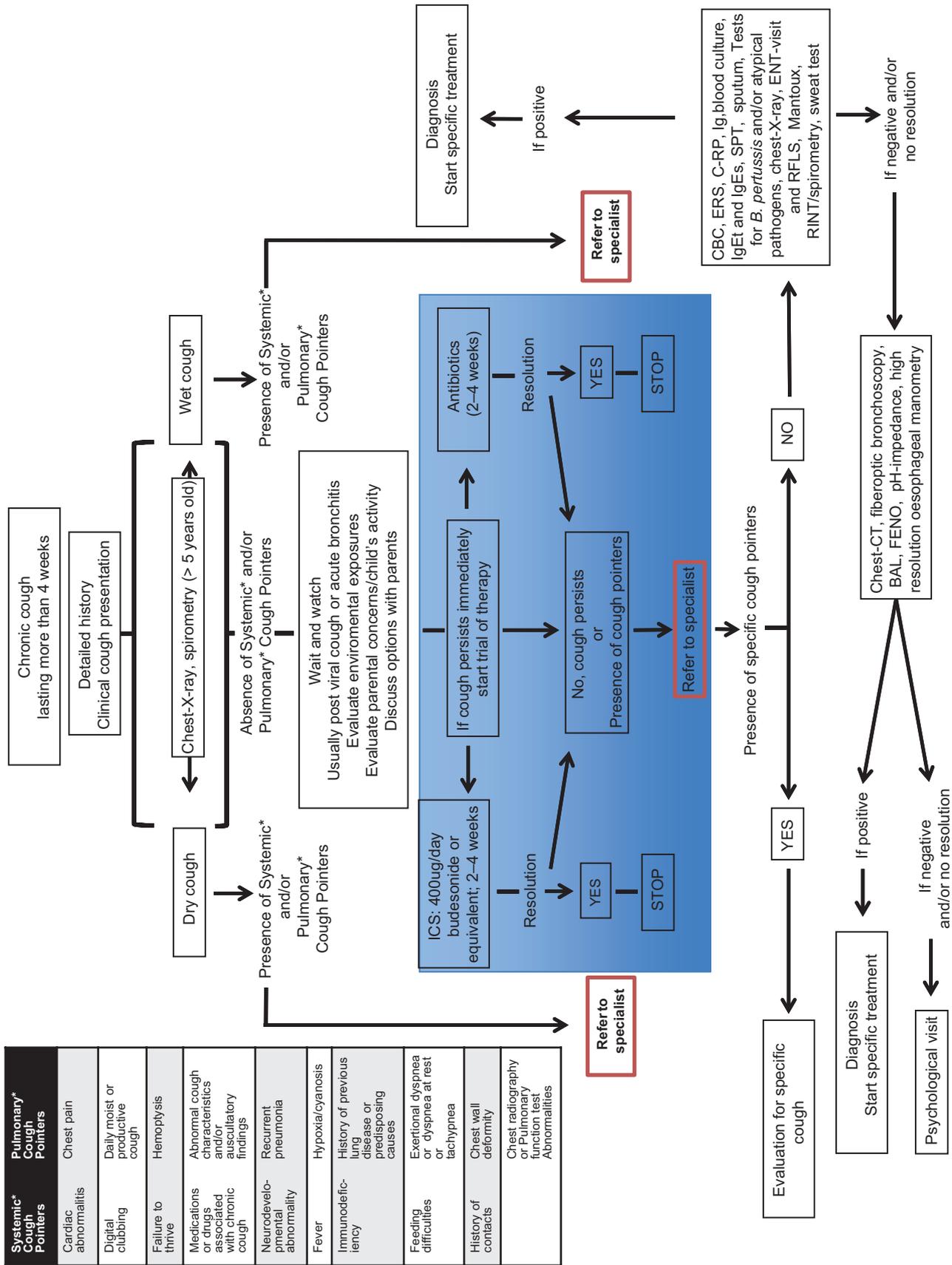


Figure 2 Flow chart of chronic cough assessment for children.

cough. The definition of chronic cough is nebulous, and it varies widely among the studies.<sup>9,24</sup> In this study, we adopted a period longer than 4 weeks as a cutoff period to define the cough as chronic. This prolonged observation period allows observing a spontaneous cough resolution for 20% of otherwise healthy children, according to the postinfectious etiology in many children with chronic cough.<sup>5,12</sup> Furthermore, during childhood, numerous anatomical and physiological maturation processes in the respiratory tract, nervous system, and immune response naturally occur and positively contribute to spontaneous cough resolution.<sup>27,28</sup>

A detailed clinical history also permits to guide the workup for a specific diagnosis by the age of the child, the age at symptom onset, and the presence or absence of systemic and/or pulmonary “red flags” (Boxes 1 and 2). If the cough starts early after birth, spontaneously or acquired after prior intubation, trauma, infection, or inflammation, genetic disorders (cystic fibrosis, primary ciliary dyskinesia [Box 3]<sup>29</sup>); immunodeficiencies; congenital anomalies (pulmonary, cardiac, and vascular abnormalities); pulmonary disorders (tracheobronchomalacia and surfactant dysfunction); and neuromuscular diseases must be clinically suspected.<sup>6</sup> A sudden onset, a history of choking, followed by prolonged cough in a healthy child between 0 and 3 years of age, may suggest foreign body aspiration.<sup>6,30</sup> Due to the enhanced responsiveness of the cough receptors, prolonged ciliary repair, and increased mucus secretion following infections, 28-57% of preschool children with a previous positive history of pneumonia suffer from post-infectious cough, which is generally self-limited.<sup>31-35</sup> The history of post-tussive vomiting and nausea, paroxysmal cough, and/or inspiratory whoop suggests that chronic cough can be caused by *Bordetella pertussis*.<sup>32</sup> The “allergic salute” and the “throat-clearing” type of cough can suggest the presence of postnasal drip, although the evidence of a relationship between postnasal drip and irritation of the larynx is lacking.<sup>36</sup>

Attention must be paid to the occurrence of symptoms of a dry, noisy, and barking cough occurring only during the night, which in many cases suggests a functional breathing

disorder (somatic or tic cough). Although some guidelines suggest that the presence or absence of nighttime cough with barking or honking characteristics should not be used to diagnose or exclude a dysfunctional cough syndrome, undoubtedly, the sudden occurrence of cough symptoms in an adolescent exclusively during the night remains suggestive of somatic or tic cough.<sup>37</sup>

Exposure to pollution, allergen, and smoke may be a reason for chronic cough.<sup>6</sup> The presence of comorbidities and the use of drugs must also be investigated; interstitial lung diseases can occur in patients who experience autoimmune or neoplastic diseases and/or undergo cytotoxic drugs or radiation treatment.<sup>5</sup> Finally, the impact of cough on patients' quality of life should also be recorded by administering validated questionnaires (e.g., Parent Cough-Specific QOL Questionnaire [PC-QOL], generic child: Pediatric QOL Inventory 4.0 [PedsQL], parent QOL questionnaires [SF-12], visual analog score [VAS], and verbal category descriptive [VCD] score), which might be helpful to stage cough and report changes in clinical symptoms.<sup>34</sup>

Differentiating between a dry and wet cough may detect the presence or absence of cough pointers (Boxes 1 and 2) that would point to an underlying disease. At this point, a chest radiograph and, when age-appropriate, spirometry should be undertaken in the first-line assessment of children with chronic cough, since the presence of abnormalities implies the presence of disease.<sup>26</sup>

In the absence of cough pointers, a short-term of high-dose (400 µg/d) inhaled corticosteroids (ICS), budesonide or beclomethasone, trial (2-4 weeks) in children with a chronic dry cough could provide a modest but significant benefit in cough symptoms.<sup>6,35</sup> Among the guidelines on chronic cough, a defined period of ICS trial is not provided, ranging from at least 2 to 12 weeks.<sup>5,6,35</sup> Probably, the authors aimed to differentiate the responders to a 2-week trial from the non-responders, requiring a more extended treatment period and eventually developing asthma.<sup>5,6,35,36</sup> Specifically, if asthma therapy is warranted, the use of a 400 µg/d equivalent dose of budesonide (or beclomethasone) up to 2 weeks has been suggested, and a clinical reassessment after 2-3 weeks is also recommended. Cough

**Box 3** Seven-point questionnaire-based prediction tool (Primary Ciliary Dyskinesia Rule: PICADAR) to predict the likelihood of primary ciliary dyskinesia (PCD).<sup>29</sup>

PICADAR	
Does the patient have a daily wet cough that started in early childhood?	Yes - complete PICADAR No - STOP. PICADAR is not designed for patients without a wet cough
Was the patient born pre-term or full-term?	Term 2
Did the patient experience chest symptoms in the neonatal period (e.g., tachypnoea, cough, and pneumonia)?	Yes 2
Was the patient admitted to a neonatal unit?	Yes 2
Does the patient have a situs abnormality (situs viscerum inversus or heterotaxy)?	Yes 4
Does the patient have a congenital heart defect?	Yes 2
Does the patient have persistent perennial rhinitis?	Yes 1
Does the patient experience chronic ear or hearing symptoms (e.g., glue ear, serous otitis media, hearing loss, ear perforation)?	Yes 1
<b>Total score =</b>	

that is unresponsive to ICS treatment should not be treated with increased doses of ICSs. On the other hand, the resolution of cough with ICS therapy does not necessarily support a diagnosis of asthma, as an asthma-like transient clinical syndrome may occur post-upper respiratory tract infections (URTIs); thus, the patient should be reevaluated after treatment is stopped.<sup>26,38</sup>

A 2-4-week course of appropriate oral antibiotic guarantees a high response rate (>75%) in the resolution of chronic wet cough.<sup>6,39</sup> The efficacy of antibiotics in chronic wet cough treatment was assessed by three RCTs, showing a clear benefit.<sup>9</sup> However, in their systematic review, Chang et al.<sup>39</sup> found lower-level evidence about the type and duration of antibiotics required. Amoxicillin-clavulanate appeared the most commonly used antibiotic, followed by clarithromycin, erythromycin, and cefaclor. Macrolide antibiotics are generally administered in children with pertussis.<sup>36</sup> Other antibiotics were rarely used in chronic cough treatment.<sup>40</sup> The duration of treatment ranged from 1 to 8 weeks: a 2-week course was sufficient, but when a chronic wet cough persists after 2 weeks of antibiotic treatment, an additional treatment of 2 weeks is suggested, especially if a PBB is suspected (Box 4).<sup>26</sup> If a PBB diagnosis is confirmed, the patient should undergo bronchoalveolar lavage or sputum to differentiate “PBB without lower airway bacteria confirmation” from “PBB with lower airway bacteria confirmation,” requiring a specific therapeutic regimen.<sup>26</sup> Children not reporting clinical improvement after 4 weeks of antibiotic treatment showed an increased risk of CT scan-diagnosed bronchiectasis that can occur with several chronic lung diseases, such as cystic fibrosis, primary ciliary dyskinesia, and also with PBB (adjusted OR: 5.9 [95% CI: 1.2-28.5]).<sup>9,41</sup> Therefore, further investigations such as chest CT and flexible bronchoscopy should be performed to assess for an underlying disease.<sup>42</sup>

In the presence of cough pointers or persistence of cough, a referral from a primary care physician to a specialist is suggested. If systemic or pulmonary cough pointers are detected (Boxes 1 and 2), further diagnostic and therapeutic management will be guided by the clinical features and etiologic hypothesis. If no specific pointers are reported, we suggest that further investigations need to be undertaken and targeted toward the patient.

**Box 4** Diagnostic criteria for the clinical diagnosis of protracted bacterial bronchitis (PBB).\*

Diagnostic criteria

1. Presence of continuous chronic (>4 weeks' duration) wet or productive cough
2. Absence of symptoms or signs (i.e., specific cough pointers) suggestive of other causes of wet or productive cough
3. Cough resolved following a 2-4-week course of an appropriate oral antibiotic

\*All three of the above-reported criteria must be fulfilled.<sup>36</sup>

Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein, and first-step immunity evaluation (immunoglobulin [Ig]A, IgM, and IgG) should be performed for cases with the most likely causes of chronic cough.<sup>38</sup> Viruses such as *Cytomegalovirus*, *Respiratory Syncytial Virus*, and *Adenovirus*, or atypical microorganisms, including *M. pneumoniae*, *C. pneumoniae*, *B. pertussis* or *Parapertussis* can result in chronic cough. Accordingly, blood culture, serology, or polymerase chain reaction on nasopharyngeal secretions and sputum should be attempted in case of suspected infectious causes. In settings with high tuberculosis exposure or abnormal X-ray findings, appropriate tests for *Mycobacterium tuberculosis* infection are required.<sup>39,40</sup>

As conflicting findings about the relationship between chronic cough and atopy are reported, in the absence of symptoms and signs of allergy, testing for sensitization, such as skin prick test, total, and specific IgE, should not be performed.<sup>5,6</sup> It has been reported that all these tests are unlikely to predict the patient's response to treatment, and cough sensitivity in atopic children is not elevated.<sup>26</sup>

Children with a chronic wet cough should also be investigated to document the underlying causes such as cystic fibrosis.<sup>5</sup>

In patients with chronic cough reporting recurrent symptoms suggestive of sinus and nasal inflammation, an otorhinolaryngological visit, nasal endoscopy, and sinus CT scan may be performed.<sup>39,40</sup> On the one hand, nasal discharge and chronic cough are symptoms commonly reported in a child affected by chronic sinusitis, while, on the other hand, the evidence does not support the cause-effect relationship and reveal discordance between clinical symptoms and diagnostic tests and, consequently, the non-appropriateness of treatment options.<sup>5,42,43</sup>

Airways resistance determined by the interrupter technique and spirometry pre- and post- $\beta_2$ -agonists test is useful in detecting isolated cough associated with airway hyperresponsiveness and asthma.<sup>6</sup>

A child with a chronic cough should undergo a chest radiograph. However, in the presence of chronic cough refractory to treatment in a child without a precise diagnosis, despite a normal chest X-ray, a chest CT scan should be attempted to evaluate small airway structural integrity and document lung diseases not visible on chest radiograph and, potentially, requiring FB.<sup>5,6</sup> Other indications for FB in children affected by chronic cough are localized radiology changes, suspicion of inhaled foreign body, aspiration lung disease, or the need to perform clearance, lavage, and microbiological investigations.<sup>5</sup> Purulent bronchitis, laryngomalacia, and tracheomalacia are frequently detected in children with a chronic wet cough by performing FB.<sup>25</sup> Although BAL findings are widely reported and interpreted by the study authors as being consistent with infections, only a few studies have performed quantitative bacteriologic testing. Among these, prospective and retrospective studies have found clinically significant levels of both respiratory bacteria density (>10<sup>4</sup> colony forming units/mL) and neutrophils assessing a persistent airways infection in children with chronic wet cough.<sup>9,40,44</sup>

The clinical usefulness of FeNO measurement in aiding diagnosis in patients with chronic cough has not yet been systematically evaluated, due to its high positive predictive

value. However, we suggest that FeNO can be used as the second level of investigation in patients presenting with chronic cough-variant asthma.<sup>6,45,46</sup>

Despite claims to the contrary, gastroesophageal reflux appears to be a less frequent and doubtful cause of chronic cough in the pediatric population.<sup>5</sup> Although there is a high incidence of esophageal dysmotility in patients with chronic cough, it is more likely that reflux is the effect and not the cause of chronic cough.<sup>5</sup> For children with a chronic cough in the absence of underlying lung disease, the treatment for GERD is not suggested when clinical features of GER, such as recurrent regurgitation, dystonic neck posturing in infants, or heartburn/epigastric pain in older children, are absent. The patient should be treated following evidence-based GERD-specific guidelines<sup>47</sup>; if an acid-suppressive therapy is required, it should be administered for 4-8 weeks and, after treatment suspension, a clinical reassessment is recommended.<sup>26</sup> Esophageal impedance 24-hour pH monitoring is the most sensitive tool for assessing all types of gastroesophageal reflux; in children aged less than 2 years, cough episodes were frequently preceded by weak acid reflux.<sup>48</sup> Other diagnoses (Box 5) require further

**Box 5** Symptoms that may be associated with gastroesophageal reflux disease (GERD) and ‘Red Flag’ symptoms are suggestive of disorders other than GERD in infants and children 0-18 years old.<sup>47</sup>

Symptoms associated with GERD	Red Flags symptoms
<p><b>General:</b></p> <ol style="list-style-type: none"> <li>1. Irritability</li> <li>2. Failure to thrive</li> <li>3. Feeding refusal</li> <li>4. Dystonic neck posturing</li> </ol>	<p><b>General:</b></p> <ol style="list-style-type: none"> <li>1. Weight loss</li> <li>2. Lethargy</li> <li>3. Fever</li> <li>4. Excessive irritability/pain</li> <li>5. Dysuria</li> <li>6. Onset of regurgitation/vomiting &gt;6 months or increasing/persisting &gt;12-18 months of age</li> </ol>
<p><b>Gastrointestinal:</b></p> <ol style="list-style-type: none"> <li>1. Recurrent regurgitation with/without vomiting in the older child</li> <li>2. Heartburn/chest pain</li> <li>3. Epigastric pain</li> <li>4. Hematemesis</li> <li>5. Dysphagia/odynophagia</li> </ol>	<p><b>Neurological:</b></p> <ol style="list-style-type: none"> <li>1. Bulging fontanel/rapidly increasing head circumference</li> <li>2. Seizures</li> <li>3. Macro/microcephaly</li> </ol>
<p><b>Airway:</b></p> <ol style="list-style-type: none"> <li>1. Wheezing</li> <li>2. Stridor</li> <li>3. Cough</li> <li>4. Hoarseness</li> </ol>	<p><b>Gastrointestinal:</b></p> <ol style="list-style-type: none"> <li>1. Persistent forceful vomiting</li> <li>2. Nocturnal vomiting</li> <li>3. Bilious vomiting</li> <li>4. Hematemesis</li> <li>5. Chronic diarrhea</li> <li>6. Rectal bleeding</li> <li>7. Abdominal distension</li> </ol>

investigations such as laboratory tests, contrast imaging, upper gastrointestinal endoscopy, and high-resolution esophageal manometry, depending on presenting symptoms.<sup>5,47,48</sup> Recently, a multidisciplinary “triple” endoscopy has been proposed as a useful investigative tool for patients with recalcitrant aero-digestive complaints like chronic cough.<sup>49</sup> In their retrospective study, the authors reported that a rigid upper airway evaluation, a flexible bronchoscopy, bronchoalveolar lavage, and an endoscopy with biopsies performed by a gastroenterologist could provide more than one diagnosis, usually missed by one single procedure.<sup>49</sup>

Finally, if an extensive evaluation fails to clarify the etiology of chronic cough, somatic cough disorder such as habit cough, tic cough, and a psychogenic cough must be hypothesized, and counseling or referral to a psychologist/psychiatrist has been suggested in the diagnostic management.<sup>5,6</sup> Although the habit cough is featured by a repetitive cough with barking or honking characteristics, and absence of symptom once asleep, these characteristics should be not used as a marker of habit cough. Similar to tics, suppressibility, distractibility, suggestibility, variability, and the presence of a premonitory sensation should be taken into consideration. Moreover, by the DSM-5 classification of diseases, the authors suggest substituting the diagnostic term “tic cough” with “habit cough” and “somatic cough” with “psychogenic cough”.<sup>26</sup>

## Limitation of the study

We developed this systematic review using a rigorous research method. However, we cannot exclude that some studies have not been included in the present manuscript.

## Conclusions

In summary, we elaborated a comprehensive algorithm to guide a primary care approach to pediatric patients with chronic cough.

Several algorithms for the management of chronic cough have been adopted and validated in clinical practice<sup>5,6,16,20,35</sup>; however, unlike the latter, we developed an algorithm focused on the pediatric age, and, also, in accordance with the Italian National Health System, which always follows the child from birth to all life-long. Based on our findings, children with chronic cough without cough pointers can be safely managed, initially, using the watchful waiting approach and, successively, starting empirical treatment based on cough characteristics. Unlike other algorithms that suggest laboratory and instrumental investigations as a first step,<sup>5,6,16,20,35</sup> we highlighted the importance of a “wait and see” approach, consisting of parental reassurance and close clinical observation, also due to interprofessional collaboration and communication between general practitioners and specialists that guarantee better patient management, appropriate prescription behavior, and improved patient outcome. Moreover, the neonatal screening program, provided by the Italian National Health System, which intercepts several diseases precociously allowing to treat

them in a very early stage, helps and supports a “wait and see” approach.

Conversely, in the presence of cough pointers or persistence of cough, the patient should be tested and treated by a specialist. Further investigations and treatments will be based on cough etiology, aiming to intercept the underlying disease, prevent potentially irreversible tissue damage, improve the general health of patients affected by chronic cough, as well as the quality of life of patients and its family.

Further high-quality RCTs are needed to validate this algorithm's performance in real-life clinical practice.

## Declarations

**Ethical Approval and Consent to participate:** not applicable

**Consent for publication:** not applicable

**Availability of supporting data:** not applicable.

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** The publication of this article has been supported by the Italian Society of Pediatric Allergy and Immunology.

**Authors' contributions:** This study was a collaboration between all authors.

**Acknowledgments:** not applicable.

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