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## Yardstick for Managing Cough, Part 1 In adults and adolescent patients older than 14 years of age

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1 INTRODUCTION:

2 This manuscript, part 2 in this yardstick series on chronic cough, will serve as a  
3 review and expert opinion on the diagnosis and management of chronic cough in the pediatric  
4 population (<14 years of age). For a review of diagnosis and management of cough in the  
5 adult population, we refer the reader to Part 1 of this series.<sup>1</sup> This manuscript will focus on  
6 chronic cough (lasting >4 weeks) in the pediatric population, and will not address acute and  
7 subacute cough which, unlike the chronic cough, have no randomized controlled trials (RCTs)  
8 to assess diagnostic validity. Clinicians need to be cognizant that the vast majority of the  
9 causes of pediatric acute coughs are benign (i.e., resolve spontaneously). However, cough is  
10 bothersome to both parents and the children and may represent the first presentation of an  
11 underlying lung disease that may progress to chronic cough in a subset of children.<sup>2,3</sup> Thus,  
12 all children with chronic cough require careful evaluation. In fact, studies based out of  
13 specialist children's hospitals suggest that up to 30.8% of children presenting with acute  
14 cough may progress to chronic cough.<sup>2,4</sup> This percentage, however, will likely be  
15 substantially lower for pediatric patients presenting to primary care with acute or subacute  
16 cough.

17

18 BACKGROUND:

19 Definition

20 Pediatric chronic cough is defined as a daily cough lasting >4 weeks. Reasons for this  
21 are based on the natural history of viral-related cough (which usually resolves within 4 weeks)  
22 and to ensure that a serious underlying condition is not missed.<sup>5,6</sup> A multicenter study that  
23 used a cough algorithm found a serious potentially progressive underlying respiratory illness  
24 (e.g., bronchiectasis, aspiration lung disease or cystic fibrosis) in 18% of 346 children who  
25 presented to pediatric pulmonologists with chronic cough.<sup>7</sup> Similarly, published studies that

26 systematically assessed outcomes of individual children at a children’s specialist hospital who  
 27 had new onset cough that persisted for >4 weeks found a new and serious chronic lung  
 28 disease (e.g. chronic pneumonia, bronchiectasis) in up to 30.8% children.<sup>2,3</sup>

29 For cough management purposes, the age cut-off used in children is usually 14 years  
 30 (i.e., before post-pubertal age.) which is suggested for many reasons, including maturational  
 31 changes in lung anatomy, different age-related exposures (e.g., school or daycare exposures to  
 32 viruses), and different medication related exposures.<sup>5</sup>

34 **ETIOLOGIES AND DIAGNOSIS**

35 To help identify the etiology of chronic cough in the pediatric population, clinicians  
 36 should use a thorough history and physical examination that will aid in identifying  
 37 diagnostic clues or pointers (signs, symptoms,  
 38 comorbidities, test results). Once the diagnostic pointers (summarized  
 39 in Table 1) are identified (if present), then the clinician can utilize well-characterized and  
 40 evaluated cough algorithms (Figures 1 and 2) to aid in coming to a diagnosis.<sup>4,5</sup> Utilization  
 41 of these cough algorithms to identify and manage pediatric chronic cough has been shown to  
 42 be effective in improving clinical outcomes in various settings (community primary care and  
 43 specialties) utilizing observational studies and RCTs<sup>8 9 4</sup>

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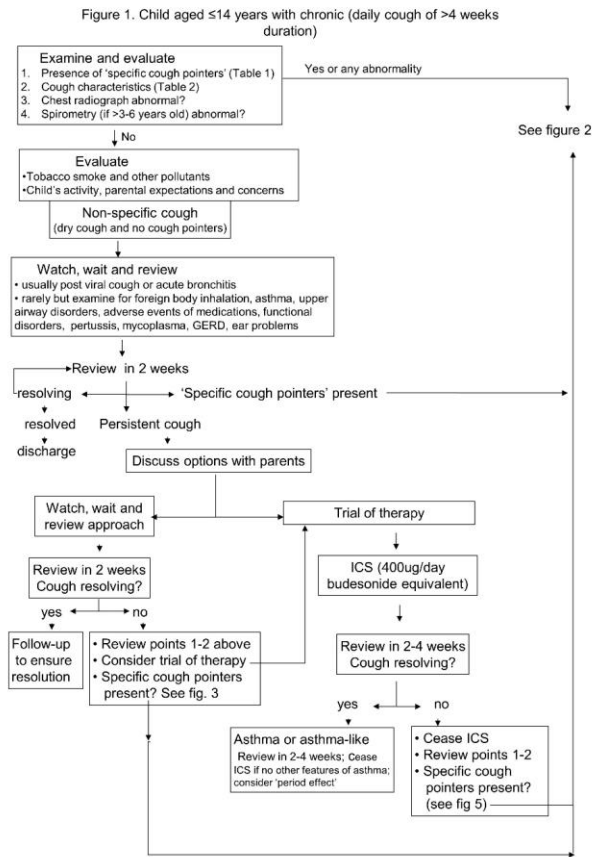
45 **Table 1: Diagnostic pointers to presence of specific cough\*** [adapted with permission from Chest  
 46 2020;158:303-29]

<i>Abnormality</i>	<i>Examples of etiology</i>
<b>Comorbidities</b>	
<b>Cardiac abnormalities</b>	Associated airway abnormalities, cardiac failure, arrhythmia
<b>COVID-19</b>	Possible long COVID syndrome
<b>Feeding difficulties</b>	Any serious systemic including pulmonary illness, aspiration
<b>Growth failure</b>	Any serious systemic including pulmonary illness such as cystic fibrosis
<b>Immuno deficiency</b>	Infectious etiologies, bronchiectasis
<b>Other significant illness eg. History of oncological disorders, autoimmune disease</b>	Increased risk of infections and other pulmonary complications eg. Bronchiolitis obliterans, interstitial lung disease

<b>Neurodevelopmental abnormality</b>	Aspiration lung disease
<b>Previous history of chronic lung or esophageal disease (e.g. neonatal lung disease, esophageal atresia)</b>	Multiple causes e.g. second H-fistula, bronchiectasis, aspiration, asthma
<b>Recurrent pneumonia</b>	Immunodeficiency, atypical infections, suppurative lung disease, congenital lung abnormalities, trachea-esophageal H fistulas
<i>Exam Findings</i>	
<b>Creptitations</b>	any airway lesions (from secretions) or parenchyma disease such as interstitial disease
<b>Chest wall deformity</b>	Any pulmonary airway or parenchyma disease
<b>Digital clubbing</b>	Suppurative lung disease
<b>Wheeze – monophonic</b>	Large airway obstruction (e.g. from foreign body aspiration, malacia and/or stenosis, vascular rings, lymphadenopathy, and mediastinal tumors. Tuberculosis should be considered in selected settings e.g. high prevalence or HIV
<b>Wheeze – polyphonic</b>	Asthma, bronchiolitis obliterans, bronchiolitis
<i>Symptoms</i>	
<b>Chest pain</b>	Arrhythmia, cardiac causes, asthma
<b>Choking history (any)</b>	Foreign body inhalation
<b>Daily wet/productive cough</b>	Protracted bacterial bronchitis, suppurative lung disease, recurrent aspiration, atypical infections, tuberculosis, diffuse panbronchiolitis
<b>Dyspnea or tachypnea</b>	Any pulmonary airway or parenchyma disease
<b>Exertional dyspnea</b>	Any airway or parenchymal disease
<b>Facial pain/purulent nasal discharge</b>	Chronic sinusitis (protracted bacterial bronchitis), primary ciliary dyskinesia
<b>Hoarse voice/stridor</b>	Laryngeal cleft/problems, airway abnormalities
<b>Hemoptysis</b>	Suppurative lung disease, vascular abnormalities
<b>Hypoxia/cyanosis</b>	Any airway or parenchyma disease, cardiac disease
<b>Neonatal-onset symptoms</b>	Usually reflects inheritable cause eg. Primary ciliary dyskinesia
<i>Tests</i>	
<b>Chest radiograph (other than peribronchial changes) or spirometry abnormality</b>	Any cardio-pulmonary disease and changes are dependent on cause e.g with RML syndrome, atelectasis or consolidation in right middle lobe or left lingula

47 \*As the causes of chronic cough encompass the entire spectrum of pediatric pulmonology and extra-  
48 pulmonary diseases, this list outlines the more common symptoms and signs and is not exhaustive  
49

50 ~~Once the diagnostic pointers are identified (if present) then the clinician can utilize~~  
51 ~~well characterized and evaluated cough algorithms (Figures 1 and 2) to aid in coming to a~~  
52 ~~diagnosis.<sup>10</sup> Utilization of these cough algorithms to identify and manage pediatric chronic~~  
53 ~~cough has been shown to be effective in improving clinical outcomes in various settings~~  
54 ~~(community primary care and specialties) utilizing observational studies and RCTs.<sup>8,9,11</sup>~~  
55



56

57 **Figure 1: Approach to a child aged  $\leq 14$ -years with chronic cough**

58 The algorithm should be read with the accompanying text. \*Spirometry can usually be reliably performed in  
 59 children aged  $> 6$ -years and in some children  $> 3$ -years if trained pediatric personnel are present. [reproduced  
 60 with permission from Chest 2020;158:303-29]

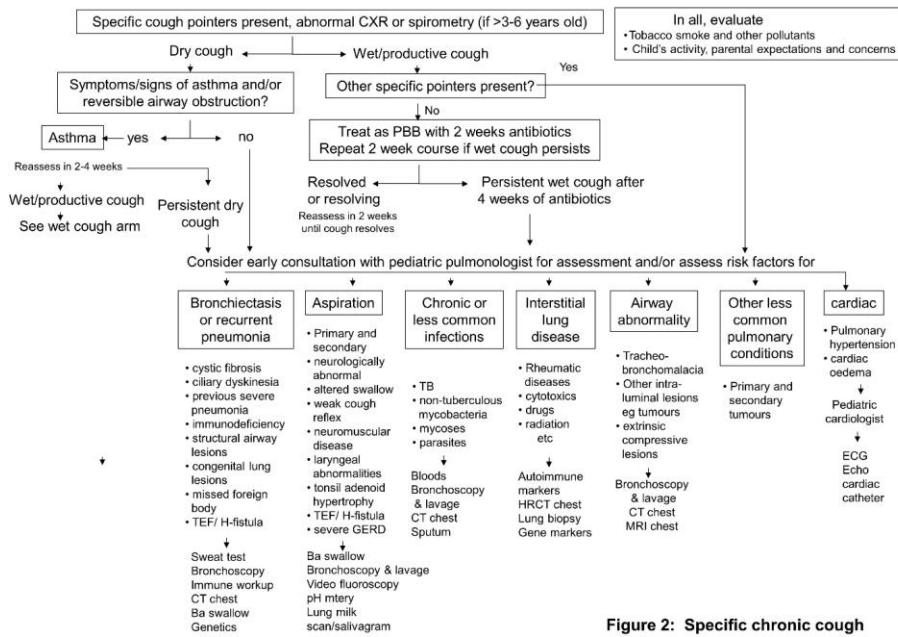


Figure 2: Specific chronic cough

61

62 **Figure 2: Approach to a child aged ≤14-years with chronic specific cough (i.e., cough associated with other**  
 63 **features suggestive of an underlying pulmonary and/or systemic abnormality).**  
 64 \*Children aged >14-years should be managed as outlined in adult guidelines but there is no good evidence where  
 65 the age cut-off should be. [reproduced with permission from Chest 2020;158:303-29] PBB is defined as the  
 66 presence of chronic wet cough in absence of other cough pointers and the resolution of the cough with 2-4 weeks  
 67 of appropriate oral antibiotics.  
 68

69

70 In addition to the diagnostic clues in table 1, the algorithm utilizes the nature of the cough  
 71 construct to aid in diagnosis, utilizing non-specific cough and specific cough as described [in](#)  
 72 [detail](#) below. [In brief, non-specific cough refers to cough refers to dry, chronic cough with no](#)  
 73 [identifiable pointers \(Table 1\) that likely resolves spontaneously while specific cough](#)

74 is chronic cough that is not likely to resolve on its own and has a likely specific etiology that  
75 must be addressed to address the cough.

#### 76 Non-specific Cough

77 When a dry, chronic cough is present AND in conjunction with a thorough history,  
78 examination, chest radiography and spirometry that do not reveal any specific cough pointers,  
79 it is highly likely that the cough will resolve spontaneously (termed non-specific cough). In  
80 the pediatric patient, this is most commonly due to effects from a prior viral illness, and it is  
81 appropriate to solely monitor and not actively treat the cough. However, attention should be  
82 made with respect to the impact of the cough on quality of life and environmental exposures  
83 (e.g. tobacco smoke) and the parents should be told to notify the clinician if the character of  
84 the cough changes or the child develops new symptoms that would warrant re-evaluation, as  
85 non-specific cough may evolve.

86 Even in the absence of specific diagnostic pointers, there are some etiologies of non-  
87 specific cough beyond post-viral cough that should be considered. The more common causes  
88 are detailed below.

#### 89 *Asthma*

90 Chronic cough can be a presenting symptom in children with asthma. Classical asthma  
91 symptoms of polyphonic wheeze and/or dyspnea that responds to  $\beta_2$  agonist is part of specific  
92 cough (Table 1) but when these symptoms are absent, i.e. isolated chronic dry cough (i.e. in  
93 the absence of other suggestive symptoms or signs) is rarely due to asthma.<sup>12,13</sup> Symptoms  
94 and signs suggestive of asthma include exertional dyspnea, bilateral recurrent wheeze,  
95 personal or family history of atopy (e.g., eczema). Spirometry demonstrating a reversible  
96 obstructive pattern and chest radiograph that shows bilateral hyperinflation, would support the  
97 diagnosis of asthma in a child with a chronic cough. When asthma is unequivocally diagnosed  
98 in line with asthma guidelines, they should be treated in accordance with asthma guidelines.

99 When symptoms other than cough are absent, the term ‘cough-variant asthma’ is sometimes  
100 used but ‘cough-dominant asthma’ is arguably a better term as asthma is often over-diagnosed  
101 in children with chronic cough.<sup>12, 14</sup>

102 Diagnostic steps beyond spirometry and chest radiograph could include tests of airway  
103 hyper-responsiveness (> 10% fall in FEV<sub>1</sub> with challenge test) and bronchodilator  
104 responsiveness (FEV<sub>1</sub> increase ≥12% following 400µg of inhaled β<sub>2</sub> agonist).<sup>15</sup> In addition,  
105 the recent European Respiratory Society guideline for diagnosing asthma in children aged 5-  
106 12 years recommends measuring exhaled nitric oxide (FeNO) as part of the diagnostic work-  
107 up, with values >25 parts per billion as supportive of the diagnosis.<sup>15</sup> However, this remains  
108 controversial as it is not a recommendation in other guidelines and the precise cut-off is  
109 debatable.<sup>16</sup>

110 Even in situations of normal spirometry and chest radiograph, where further testing is  
111 not completed, a trial of asthma therapies may be considered in some children. If a trial of  
112 asthma medications is warranted, bronchodilators and low-dose inhaled corticosteroids (ICS)  
113 are recommended for a defined period (usually two to four weeks) before re-evaluation for  
114 response [for the cough](#). A short-term higher ICS dose is suggested to prove/disprove the  
115 diagnosis with an adequate trial. It must be remembered that cough therapies demonstrate a  
116 significant placebo effect and non-specific cough will spontaneously resolve; thus, these  
117 asthma medications should only be continued if a definitive diagnosis is made. Failure to  
118 respond to the medication trial makes the diagnosis unlikely.

119 <sup>17</sup>Readers are referred to the pediatric asthma yardstick for further elucidation of this issue.<sup>18</sup>

120 <sup>17</sup>Readers are referred to the pediatric asthma  
121 yardstick for further elucidation of this issue.<sup>18</sup>

122 *Gastro-esophageal reflux disease (GERD)*



123 Although GERD is an important and common cause of chronic cough in adults, it is an  
124 uncommon cause, as opposed to an association, in children less than 15 years of age, except  
125 when aspiration is present.<sup>19,20</sup> One systematic review found that GERD was found as a cause  
126 in only two of ten prospective pediatric chronic cough studies.<sup>19</sup> Furthermore it also difficult  
127 to prove GERD as the cause of chronic cough in children;<sup>19,21</sup> in fact, 84% of coughs (as  
128 measured by a cough meter) were not temporally associated with a reflux event when  
129 measured concurrently with an esophageal pH monitoring device.<sup>22</sup>

130 Based on the above, a recent CHEST expert panel report recommended against  
131 treating children for chronic cough with anti-GERD therapy when no GI symptoms of GERD  
132 are present.<sup>20</sup> Evidence-based GERD-specific guidelines should be followed if GERD  
133 symptoms are present, which includes a trial of medications that is age-dependent and no  
134 longer than 4-8 weeks duration.<sup>23</sup>

#### 135 *Upper airway cough syndrome (UACS) and rhinosinusitis*

136 While UACS or postnasal drip is thought to be a common cause of adult chronic  
137 cough, it remains a controversial cause in children. The most recent rhinitis guideline  
138 considers cough as one of the symptoms of rhinitis although the evidence is weak and  
139 considered a co-morbidity.<sup>24</sup> Intranasal corticosteroids (INCS) and intranasal anti-histamines  
140 are considered the appropriate first-line therapies for allergic  
141 and non-allergic rhinitis.<sup>24</sup>

142 It is possible, but remains unproven, that the cough associated with chronic  
143 rhinosinusitis is related to protracted bacterial bronchitis (PBB), and emerging clinical entity  
144 discussed in detail below. This concept is akin to the unified airways hypothesis with  
145 neutrophilic airway inflammation from nose to bronchus. The  
146 recommended treatment for acute bacterial rhinosinusitis in children includes antibiotics  
147 (amoxicillin<sup>25</sup> or amoxicillin-clavulanate<sup>26</sup> for 7-10 and 20<sup>26</sup> days respectively, not dissimilar

148 to PBB), and the common bacterial pathogens in sinusitis are identical to those in PBB.<sup>27, 28</sup>

149 However, it remains to be determined whether the relationship between nasal secretions and  
150 cough is linked by a common etiology (infection and/or inflammation causing both) or due to  
151 clearing of secretions reaching the larynx.

#### 152 *Infections: pertussis and mycoplasma*

153 It is always important to consider pertussis, which can present as non-specific cough,  
154 without the typical paroxysmal whoop, particularly in low income countries (which account  
155 for 95% of pertussis).<sup>29</sup> Classic pertussis has 3 stages: catarrhal, paroxysmal and convalescent  
156 but vaccination modifies the classical disease.<sup>30</sup> In one prospective study, 20% of children  
157 with chronic cough had evidence of recent pertussis infection, most of whom have been  
158 immunized, necessitating considering this disease even in those immunized<sup>31</sup> for public health  
159 reasons. We suggest that clinicians consider that the cough could be caused by pertussis if  
160 there is paroxysmal cough, post tussive vomiting, and inspiratory whooping in the acute phase  
161 of the illness or if there is history of contact.<sup>30</sup>

162 A retrospective study identified that the median duration of cough in children with  
163 positive mycoplasma serology was 39 days (95% CI 24-54).<sup>32</sup> Thus, mycoplasma is another  
164 possible cause of non-specific chronic cough in children. Unlike pertussis with public health  
165 consequences and the likelihood that antibiotics will be effective in the treatment of  
166 mycoplasma infection without pneumonia is debatable, identification of non-acute  
167 mycoplasma infection is less important as the effectiveness of antibiotics for this illness is  
168 controversial and one might suggest that this is not consistent with good antibiotic  
169 stewardship.<sup>33</sup>

170 Thus, even in cases where pertussis or mycoplasma are the cause of chronic cough,  
171 once the patient is at the chronic stage, there is little utility in treating with antibiotics.

#### 172 *Post-COVID syndrome*

173 Although post COVID syndromes are rarer in children compared to adults,<sup>34</sup> chronic  
174 cough has been described as part of post-COVID syndrome (including long COVID) (5.4% of  
175 the 129 children who had COVID pre availability of vaccines<sup>35</sup>). However, in a meta-analysis,  
176 the pooled risk difference in post-COVID cases compared to controls demonstrated no  
177 significant difference between groups.<sup>36</sup> The authors also emphasized the importance of  
178 having a control group in studies involving children.<sup>36</sup>

179 *Tic cough (previously referred to as habit cough) or somatic cough disorder (previously*  
180 *referred to as psychogenic cough or dysfunctional respiratory symptoms)*

181 Tic cough can be brassy or barking like<sup>37</sup> but this cough characteristic can also signify  
182 tracheomalacia.<sup>38</sup> Tic cough is usually single repetitive cough and suppressible [and often](#)  
183 [absent when asleep](#) but no feature is fully diagnostic.<sup>39</sup> In contrast, cough related to  
184 tracheomalacia is not single/repetitive but occurs in bouts and present nocturnally and often  
185 wet.<sup>40</sup> Medications should be avoided, as treatment strategies can be relatively simple with the  
186 'art of suggestion'.<sup>41</sup> Tic cough should not be confused with cough hypersensitivity and a  
187 suggested step-by-step approach to management has been described elsewhere.<sup>42</sup> [In children,](#)  
188 [cough hypersensitivity as a diagnosis \(unlike adults\) is not appropriate for many reasons that](#)  
189 [is beyond the scope of this document. For further reading about the cough hypersensitivity](#)  
190 [syndrome, readers are referred to Part 1 of the cough yardstick on adults and adolescents.](#)<sup>1</sup>

191 *Non-pulmonary causes*

192 Non-pulmonary causes of pediatric chronic cough include otogenic causes (Arnold's  
193 ear-cough reflex due to a foreign body irritating the external auditory canal), medications, and  
194 sleep disorders. These are rare causes in cohort studies that have evaluated the underlying  
195 etiology of chronic cough in the pediatric population.<sup>19</sup>

196 Medications can rarely be the cause of pediatric chronic cough. Examples include  
197 ACEI,<sup>43</sup> asthma medications immediately after inhalation,<sup>44</sup> psychostimulant medications

198 (e.g. dextroamphetamine resulting in new onset tics),<sup>45</sup> and etanercept<sup>46</sup> It has also been  
199 reported as a complication of chronic vagus nerve stimulation,<sup>47</sup> a procedure rarely  
200 undertaken in children. However, the reported prevalence of ACEI-induced cough is low in  
201 children (~2%);<sup>48</sup> and the cough resolves within days (3-7 days) after withdrawing the  
202 medication,<sup>43, 49</sup> and may not recur if the medication is reinitiated.<sup>43</sup>

203 Although sleep disorders (e.g., obstructive sleep apnea) as a cause of chronic cough is  
204 still controversial in children, its presence should be evaluated and managed accordingly.<sup>5</sup>

#### 205 *Treatment of non-specific cough*

206 As stated above, non-specific cough is typically self-limiting and can be managed with  
207 observation alone. If an etiology such as those listed above is uncovered, then treatment of  
208 that underlying condition is warranted.

209 Using non-specific therapies to target cough (e.g., cough suppressants, anti-  
210 histamines, opioids), however, is not recommended. For example, the efficacy of anti-  
211 histamines in relieving cough in children is minimal, if at all, except when used to treat  
212 environmental (respiratory) allergies, and this is not recommended for empiric treatment of  
213 chronic cough in children.<sup>50</sup> As noted in a Cochrane review,<sup>51</sup> two therapeutic studies  
214 described no significant difference between the antihistamine and control groups with both  
215 achieving significant improvement.

216 Regarding other OTC cough medications, one systematic review<sup>52</sup> concluded that  
217 (other than honey) they have little, if any, benefit. Importantly many OTC preparations  
218 contain antihistamines and dextromethorphan that have been associated with adverse events.  
219 The use of OTC medications has to be balanced with adverse events, which includes reported  
220 death from toxicity in young children.<sup>53, 54</sup> In fact, in 2018, the FDA altered the labeling for  
221 prescription opioid cough and cold medicines to limit their use to adults  $\geq 18$ -years.<sup>55</sup>

222 Although still used widely, there is a decreasing trend in US in the use of OTC medications  
223 for cough, excluding anti-histamines that have actually increased.<sup>56</sup>

#### 224 Specific Chronic Cough

225 In specific cough (vs non-specific cough), there is an identifiable underlying  
226 abnormality or cause and the cough may be dry or wet/mixed with the presence of other  
227 symptoms. Cough “pointers” (Table 1) can be used to identify a likely underlying cause for  
228 the cough, with each pointer having different specificity and sensitivity and associated  
229 likelihood ratios,<sup>57</sup> and will invariably be setting-dependent. Importantly, an absence of all of  
230 these “pointers” makes a specific cough very unlikely with a strongly negative likelihood  
231 ratio of 0 (95% CI 0, 0.03).<sup>57</sup>

232 As the specific cough etiologies cover the entirety of pediatric respiratory illnesses, it  
233 is not possible to list all the etiologies. Table 1 lists several cough pointers and their  
234 associated etiologies. The more common causes are briefly listed below.

#### 235 *Protracted Bacterial Bronchitis (PBB)*

236 PBB is the most common etiology of chronic cough in some settings<sup>19</sup> and may be an  
237 underestimated cause of chronic cough in other settings.<sup>58</sup> PBB is now an internationally  
238 recognized diagnostic entity.<sup>17, 27, 59</sup> Its diagnosis requires 3 criteria: (a) presence of chronic  
239 wet/productive cough (>4-wks), (b) cough resolution with 2-4 weeks of appropriate oral  
240 antibiotics,<sup>60</sup> and (c) absence of other causes of chronic wet cough.<sup>17, 60</sup> However, chronic wet  
241 cough is the key presenting symptom in other conditions, such as bronchiectasis.<sup>27</sup> Both PBB  
242 and bronchiectasis have some shared pathology such as lower airway bacterial infection with  
243 inflammation.<sup>60</sup> They are on a continuum with shared and graded clinical and pathobiological  
244 features (e.g., airway gene expression profiles<sup>61</sup> and phagocytic dysfunction<sup>60</sup>).

245 Children with PBB are typically young (median age 1.8-4.8 years) but it also can  
246 occur in older children (>12 years).<sup>60</sup> They may have or examination may reveal a “rattle” on

247 chest auscultation, thought to be secretions moving in the large airways. Children with PBB  
248 are otherwise healthy with normal growth and development with a chest radiograph that is  
249 normal or shows non-specific changes of peribronchial thickening. Their spirometry values  
250 are normal.<sup>60</sup> Compared to controls, their exposure to tobacco is not elevated. Also, atopic  
251 features, clinical history (such as eczema, rhinitis), elevated total IgE, positive test for specific  
252 serum IgE or positive skin prick test for aeroallergens, are similar in children with PBB and  
253 control groups.<sup>14</sup> Risk factors for developing PBB following an acute respiratory infection are  
254 young age (<12-months: adjusted relative risk [aRR]=4.31, 95% CI 1.42-13.10; 12-<24  
255 months: aRR=2.00, 95% CI 1.35-2.96), childcare attendance (aRR=2.32, 95% CI 1.48-3.63),  
256 and prior history of chronic cough (aRR=2.63, 95% CI 1.72-4.01).<sup>62</sup>

257 Treatment is 2 to 4 weeks of amoxicillin-clavulanate<sup>17, 63</sup> [\(that treats the most common](#)  
258 [bacteria found in PBB i.e. \*Haemophilus influenzae\*, especially non-typable \*H. influenzae\*,](#)  
259 [Streptococcus pneumoniae and Moraxella catarrhalis\).](#) A recent RCT finding that there  
260 was no difference in cough resolution between children with chronic wet cough randomized  
261 to 2 or 4 weeks of antibiotics.<sup>64</sup> While those who received 4 weeks had a longer cough-free  
262 period,<sup>64</sup> there is currently insufficient data to recommend a 4 week course in all children  
263 suspected of having PBB. Trimethoprim-sulfamethoxazole is an alternative when  
264 [penicillin](#) allergy is present. [Although we are aware that azithromycin has been used,](#)  
265 [there is currently no published data on its efficacy for PBB.](#)

266 As children with PBB may later develop bronchiectasis, we suggest that parents  
267 should be counselled regarding this potential sequela. In children with PBB who had flexible  
268 bronchoscopy undertaken, those with lower airway *H. influenzae* and recurrent PBB (>3  
269 episodes/year) were at risk of having bronchiectasis in the next 2 years.<sup>65</sup> By 5 years, these  
270 independent risk factors were confirmed but a new finding of asthma was also described.<sup>66</sup>

271 *Bronchiectasis*

272 Pediatric bronchiectasis was previously defined by imaging alone and considered  
273 irreversible, but in the current era it is now defined as the presence of a clinical syndrome  
274 (chronic or recurrent wet/productive cough, with or without other features such as growth  
275 failure, exertional dyspnea, feeding difficulties, coarse crackles on chest auscultation or  
276 digital clubbing ) with evidence of radiological abnormal airway dilatation (broncho-arterial  
277 ratio (BAR) of >0.8) on chest CT scan.<sup>27, 67</sup> The hallmark is abnormal increased BAR given  
278 the appearance of a signet-ring appearance, but other radiological features (e.g. bronchial wall  
279 thickening and failure of bronchial structure to taper toward lung periphery) may also be  
280 present.<sup>27</sup>

281 Bronchiectasis is a heterogenous disease and has varying etiologies from various  
282 insults, including: cystic fibrosis, post-infectious (tuberculosis, adenovirus, severe  
283 pneumonia), post-transplant, immunodeficiency, primary ciliary dyskinesia, aspiration lung  
284 disease and foreign body inhalation.<sup>27, 68</sup> Having a high level of suspicion, leading to early  
285 diagnosis and optimal management is important in children as it leads to better outcomes,  
286 including radiological abnormality improvement or even reversal.<sup>27, 67</sup> Currently, there is still  
287 a lack of awareness in the general community and increasing it is a priority expressed by  
288 parents of children with bronchiectasis.<sup>69</sup>

289 All children with, or suspected of having bronchiectasis should be evaluated with at  
290 least a computed tomography (CT) chest scan with high resolution and obtaining an airway  
291 specimen, and a panel of tests as a minimum.<sup>27, 67</sup> This panel of tests include a sweat test and  
292 basic immunology to evaluate for the presence of cystic fibrosis and common primary  
293 immunodeficiencies.<sup>27, 67</sup> Other tests (eg those specific for PCD and genetic tests) are based  
294 on the clinical setting and clinical features may also be required and readers are referred to  
295 bronchiectasis guidelines.<sup>27, 67</sup> Thus, they should be referred to a specialty center, under the  
296 care of a multi-disciplinary team.<sup>27, 67</sup>

297 *Chronic Lung Infections*

298 Infections such as tuberculosis, hydatid disease, non-tuberculosis mycobacteria and  
299 parasitic infections should be a consideration in endemic areas. For example, a Hungarian  
300 study reported toxocariasis associated with chronic cough in childhood in 32% of the 425  
301 children evaluated.<sup>70</sup> Readers are referred to the CHEST guideline on chronic cough related to  
302 tuberculosis.<sup>71</sup>

303 *Immunodeficiency*

304 Likewise, children with immunodeficiency (primary or secondary) should also be  
305 evaluated in accordance with local protocols as most of these children will need further  
306 targeted evaluation (such as chest CT scan and flexible bronchoscopy). These children require  
307 specialist review and details are beyond the purview of this yardstick.

308 *Right Middle Lobe Syndrome*

309 Right middle lobe (RML) syndrome (recurrent or chronic collapse of the middle lobe  
310 of the right lung or lingula) may or may not be of infective origin but can present with chronic  
311 cough. Children with RML syndrome should always be carefully evaluated for tuberculosis,  
312 asthma and the majority require a flexible bronchoscopy to ensure it is not related to an  
313 obstructive lesion.<sup>72</sup> It is easily diagnosed on a chest radiograph. Like bronchiectasis, early  
314 diagnosis of the underlying cause and timely management is important for better long-term  
315 outcomes.

316 *Anatomical Airway Abnormalities*

317 In the evaluation of a child with chronic cough, tracheo-bronchomalacia should  
318 always be considered. Children with major anatomical airway lesions such as tracheo-  
319 bronchomalacia are at risk of frequent and prolonged cough,<sup>73</sup> as well as PBB and  
320 bronchiectasis.<sup>74</sup> A prospective study found 68% of children with PBB had tracheo-



321 bronchomalacia.<sup>14</sup> However, this was no higher than that in the control group (53%) that  
322 consisted of children undergoing bronchoscopy for reasons other than chronic cough.<sup>14</sup>

323 It is highly unlikely that the tracheo-bronchomalacia itself causes the cough but rather  
324 that the cough is a consequence. Airway malacia impedes clearance of secretions<sup>75</sup> and it is  
325 plausible that the prolonged cough in these children relates to a bronchitic process distal to the  
326 lesion. A prospective study<sup>73</sup> of children with malacia found increased likelihood of  
327 respiratory illness frequency, severity, significant cough and a tendency for delayed recovery  
328 but neither the site nor severity of malacia had an effect on respiratory illness. Systematic  
329 reviews<sup>17,40</sup> of available studies show that the relationship between airway lesions and cough  
330 is not straightforward.

331 When tracheomalacia is present, the cough is typically brassy or barking.<sup>38</sup> While  
332 there are different modalities to diagnose tracheo-bronchomalacia,<sup>40</sup> the most commonly used  
333 is flexible bronchoscopy that also allows obtaining broncho-alveolar lavage for assessment of  
334 lower airway infection. Management of children with tracheo-bronchomalacia is  
335 individualized, based on the child's clinical history.<sup>40</sup>

#### 336 *Aspiration lung disease*

337 Recurrent small volume aspiration is a potential cause of chronic cough and should be  
338 considered particularly in children with neurological, neuromuscular and developmental  
339 disorders.<sup>76</sup> Typically, there is a history of coughing with feedings but silent aspiration occurs  
340 in up to 28% of children with severe neurological dysfunction.<sup>76</sup> Thus, absence of coughing  
341 with feeding does not imply aspiration is not the cause of the chronic cough in a child with  
342 neurodevelopmental disorders.

343 Aspiration may also be secondary to gastroesophageal reflux, tracheoesophageal  
344 fistula or laryngeal cleft. Evaluation for primary aspiration requires swallow assessment such  
345 as video fluoroscopy/ modified barium swallow. Sometimes, other modalities such as

346 bronchoscopy with broncho-alveolar lavage and assessment of esophageal function may also  
347 be required. Management of aspiration is highly individualized and should be undertaken by a  
348 multi-disciplinary team that includes speech pathologists.

349 *Inhaled airway foreign body*

350 All children with chronic cough should be assessed for possible retained airway  
351 foreign body. While more common in young children (aged <5 years), it also occurs in older  
352 children.<sup>77</sup> By the time chronic cough develops post inhalation of a foreign body, the cough is  
353 typically wet, but may occasionally be dry, especially at initial presentation. A history of  
354 onset of cough following a choking episode should be sought. Chest examination may  
355 demonstrate signs of asymmetrical breath sounds and focal sounds, most commonly a  
356 monophonic and unilateral low-pitched wheeze. Chest radiograph may show unilateral lung  
357 hyperinflation consistent with bronchial obstruction, which becomes more apparent on an  
358 expiratory film and occasionally the foreign body itself may be seen on the plain film.  
359 However, a normal chest exam or chest radiograph do not exclude the presence of an inhaled  
360 foreign body. Immediate referral to specialist care for bronchoscopy is warranted if there is a  
361 suggestive history, as longer retention of a foreign body is associated with poorer outcomes.<sup>78</sup>

362 *Cardiac causes*

363 While heart failure in adults may present with cough, this is rarely the presenting  
364 symptom in children. Children with congenital heart disease have a higher risk of respiratory  
365 tract infections and primary ciliary dyskinesia, but cough in these conditions is usually wet.

366 **CONCLUSIONS:**

367 While chronic cough in children is often benign and self-limiting, in some cases it can  
368 represent a serious underlying condition. Utilizing established and validated protocols as well  
369 as specific pointers (clues in history, findings on exam) can aid the clinician in identifying  
370 causes when present and improve outcomes.

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