

# Chronic Cough and Gastroesophageal Reflux in Children



## CHEST Guideline and Expert Panel Report

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**BACKGROUND:** Whether gastroesophageal reflux (GER) or GER disease (GERD) causes chronic cough in children is controversial. Using the Population, Intervention, Comparison, Outcome (PICO) format, we undertook four systematic reviews. For children with chronic cough (> 4-weeks duration) and without underlying lung disease: (1) who do not have gastrointestinal GER symptoms, should empirical treatment for GERD be used? (2) with gastrointestinal GER symptoms, does treatment for GERD resolve the cough? (3) with or without gastrointestinal GER symptoms, what GER-based therapies should be used and for how long? (4) if GERD is suspected as the cause, what investigations and diagnostic criteria best determine GERD as the cause of the cough?

**METHODS:** We used the CHEST Expert Cough Panel's protocol and American College of Chest Physicians (CHEST) methodological guidelines and GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. Delphi methodology was used to obtain consensus.

**RESULTS:** Few randomized controlled trials addressed the first two questions and none addressed the other two. The single meta-analysis (two randomized controlled trials) showed no significant difference between the groups (any intervention for GERD vs placebo for cough resolution; OR, 1.14; 95% CI, 0.45-2.93;  $P = .78$ ). Proton pump inhibitors (vs placebo) caused increased serious adverse events. Qualitative data from existing CHEST cough systematic reviews were consistent with two international GERD guidelines.

**CONCLUSIONS:** The panelists endorsed that: (1) treatment(s) for GERD should not be used when there are no clinical features of GERD; and (2) pediatric GERD guidelines should be used to guide treatment and investigations. CHEST 2019; 156(1):131-140

**KEY WORDS:** children; cough; evidence-based medicine; gastroesophageal reflux

**ABBREVIATIONS:** ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease; KQ = Key Question; NASPGHAN = North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; NICE = National Institute for Health and Care Excellence; pH-MII = multichannel intraluminal impedance with pH monitoring; PICO = Population, Intervention, Comparison, Outcome; PPI = proton pump inhibitor; RCT = randomized controlled trial

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## Summary of Recommendations/Suggestions

1. For children aged  $\leq 14$ -years with chronic cough ( $> 4$  weeks duration) without an underlying lung disease, we recommend that treatment(s) for GERD should NOT be used when there are no clinical features of gastroesophageal reflux such as recurrent regurgitation, dystonic neck posturing in infants, or heartburn/epigastric pain in older children. (Grade 1B)
2. For children aged  $\leq 14$ -years with chronic cough ( $> 4$  weeks duration) without an underlying lung disease but who have symptoms and signs or tests consistent with gastroesophageal pathological reflux, we recommend that they be treated for GERD in accordance to evidence-based GERD-specific guidelines.<sup>1,2</sup> (Grade 1B)
3. For children aged  $\leq 14$ -years with chronic cough ( $> 4$  weeks duration) without an underlying lung disease but who have symptoms and signs or tests consistent with gastroesophageal pathological reflux, we recommend that acid suppressive therapy should not be used solely for their chronic cough. (Grade 1C)
4. For children with chronic cough ( $> 4$  weeks duration) who do not have an underlying lung disease but with gastrointestinal GER symptoms, we suggest that they be treated for GERD in accordance to evidence-based GERD-specific guidelines<sup>1,2</sup> for 4-8 weeks and their response reevaluated. (Ungraded Consensus-based Statement)

*Remark:* The agent used for the “trial of treatment” approach is dependent on the child’s age, feeding

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regimen, and symptoms.<sup>1,2</sup> PPIs and H<sub>2</sub> receptor antagonists should not be used for longer than 4 to 8 weeks without further evaluation.

5. For children with chronic cough ( $> 4$  weeks duration) and without an underlying disease, if GERD is suspected as the cause based on GER symptoms, we suggest following the GERD guidelines for investigating children suspected for GERD. (Ungraded Consensus-based Statement)

*Remark:* The workup suggested by the GERD guidelines<sup>1,2</sup> is largely dependent on the child’s age and constellation of symptoms. In most situations, endoscopy is suggested before pHmetry or pH-MII.<sup>1,2</sup>

## Introduction

Chronic cough ( $> 4$  weeks duration<sup>3</sup>) in children, a common presenting symptom to pulmonologists and allergists, is associated with burden (eg, recurrent doctor visits and use of medications) and impaired quality of life to the child and their parents.<sup>4,5</sup> Among the many possible etiologies of pediatric chronic cough, gastroesophageal reflux disease (GERD) has been postulated.<sup>6</sup> While GERD is commonly reported to be associated with chronic cough in adults,<sup>7</sup> it has not been commonly identified as the cause of pediatric cough.<sup>6</sup> Indeed, proving causality is difficult<sup>8,9</sup> for several reasons that include the absence of a gold standard diagnostic tool for the diagnosis of GERD in infants and children.<sup>1</sup> Also, there are a wide array of possible interventions for GERD, and some of these may result in more potential harm than benefit (eg, surgery<sup>10</sup> and proton pump inhibitors [PPIs]<sup>11,12</sup>). For this update to the 2006 CHEST Pediatric Cough guideline on this topic, we restricted our data to systematic reviews and randomized controlled trials (RCTs).

Using the Population, Intervention, Comparison, Outcome (PICO) framework, we performed systematic reviews to address key questions (KQs) relating to chronic cough and GERD in children. Here, we present the systematic reviews for the KQs, summary of the evidence, and the formulated recommendations/suggestions based upon these findings utilizing CHEST’s cough guidelines methods and framework.<sup>13</sup> The four KQs addressed were:

KQ1: In children with chronic cough ( $> 4$  weeks duration) who do not have gastrointestinal GER symptoms or an underlying chronic lung disease, should empirical treatment for GERD be used?

KQ2: In children with chronic cough ( $> 4$  weeks duration) and with gastrointestinal GER symptoms

but without an underlying chronic lung disease, does treatment for GERD resolve the cough?

KQ3: In children with chronic cough (> 4 weeks duration) who do not have an underlying lung disease, with or without gastrointestinal GER symptoms, what GER-based therapies should be used and for how long?

KQ4: In children with chronic cough (> 4 weeks duration) without an underlying disease, if GERD is suspected as the cause, what investigations and diagnostic criteria best determines GERD as the cause of the cough?

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## Materials and Methods

We undertook the systematic reviews based on the protocol<sup>13</sup> established by selected members of the CHEST Expert Cough Panel. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting. The KQs were framed by this paper's main authors. The planned systematic review for each of the four KQs was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (e-Appendix 1).

### Study Identification and Eligibility Criteria

Searches for the systematic reviews were externally undertaken by a librarian (Nancy Harger, MLS) from the University of Massachusetts Medical School, using a combined search strategy for all KQs (e-Appendix 1). We included only studies published or available in English. Duplicates found between Scopus and PubMed searches were identified and removed by the librarian before sending the abstracts to the two authors (A. B. C. and J. J. O.) who reviewed the abstracts independently.

### Data Extraction and Quality Assessment

The two reviewers fully agreed on which full-text articles to retrieve to assess for potentially eligible studies. It was planned that disagreements that could not be resolved by consensus would be adjudicated by a third reviewer (R. S. I.). We excluded studies and Cochrane reviews that were included in guidelines published since 2015. Risk of bias assessments for RCTs were independently undertaken by two reviewers. Other data were extracted by a single author (A. B. C.) and checked by a second (J. J. O.), as previously done.<sup>6,14</sup>

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## Results

The search results and PRISMA diagrams (e-Figs 1-4) for all KQs are presented in the supplemental file. Of note, both the GER-specific guidelines included in this analysis<sup>1,2</sup> examined and evaluated evidence relating to the treatment and investigations possibly associated with extra-esophageal diseases such as cough.

### Summary of Evidence and Interpretation (KQ1)

Four systematic reviews<sup>1-3,8</sup> were included in KQ1 and the pertinent data summarized in Table 1. Our search did not identify any other studies postpublication of these reviews that fulfilled our inclusion criteria. Three papers<sup>1,2,8</sup> were GERD-specific and one addressed the general management of chronic cough.<sup>3</sup> One review<sup>8</sup> did not provide the level of evidence or PRISMA diagram, while the other three<sup>1-3</sup> were guidelines with their findings fully depicted. Two of these guidelines<sup>1,2</sup> were

### Recommendation/Suggestion Framework

We used standard methods<sup>13</sup> utilized in the CHEST guidelines. Briefly, results from the systematic reviews addressing the KQs were used to support the evidence-graded recommendations or suggestions using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. The strength of recommendation is determined based on the quality of evidence, balance of benefits and harms, patients' values and preferences, and availability of resources. "Suggestions" are formulated instead of recommendations when there is insufficient evidence. The GRADE framework separates the process of rating the quality of evidence from that of determining the strength of recommendation and includes consumer or patient input as part of the Delphi approach. During the Delphi approach, those with a "conflict of interest" are requested not to vote. Because none of the panelists had a conflict of interest, none was excluded from voting. "A structured consensus-based Delphi approach was used to provide expert advice on guidance statements. In this regard, for a recommendation or suggestion to be approved by the Expert Cough Panel, 75% of the eligible Panel members had to vote and 80% of those voting had to strongly agree or agree with the statement. Quality assessment also included grading the strength of recommendations based on consideration of the balance of benefits to harms, patient values and preferences, and the quality of the evidence supporting the recommendation. Harms incorporated risks and burdens to the patients that can include convenience or lack of convenience, difficulty of administration, and invasiveness."<sup>13</sup> The Delphi panel included patient representation.

GER-specific and based on systematic reviews undertaken in the United States and Europe<sup>1</sup> and the United Kingdom.<sup>2</sup> The former,<sup>1</sup> published in 2018, was led by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), and the latter<sup>2</sup> was led by the National Institute for Health and Care Excellence (NICE).

The summary findings for all four included papers were the same. One paper<sup>8</sup> reiterated findings of the 2008 British Thoracic Society cough guideline<sup>15</sup> (Table 1), while all three guidelines<sup>1-3</sup> were consistent in the recommendation of not treating GER in children who have chronic cough without any gastrointestinal GER symptoms (recurrent regurgitation, dystonic neck posturing/back arching in

**TABLE 1 ] Summary of Data of the Included Publications Relevant to Key Question 1: For Children With Chronic Cough (> 4 Weeks Duration) Who Do Not Have Gastrointestinal GER Symptoms or an Underlying Chronic Lung Disease, Should Empirical Treatment for GERD Be Used?**

Paper and Year	Evidence Level	Key Relevant Recommendation	Comment
CHEST guidelines 2017 <sup>3</sup>	Cohort studies and one RCT	For children aged ≤ 14-years with chronic cough, we recommend basing the management on the etiology of the cough. An empirical approach aimed at treating upper airway cough syndrome due to a rhinosinus condition, GERD and/or asthma should not be used unless other features consistent with these conditions are present. Strong recommendation	Systematic review focused on children with chronic cough and was not specific for GER
de Benedictis and Bush, 2018 <sup>8</sup>	Not stated	"In otherwise well children with non-specific cough, empirical GER therapy is unlikely to be beneficial and is generally not recommended" <sup>8</sup>	PRISMA data not shown
NASPGHAN and ESPGHAN guideline, 2018 <sup>1</sup>	Expert opinion	"Based on expert opinion, the working group suggests not to use H <sub>2</sub> receptor antagonists or PPIs in patients with extraesophageal symptoms (ie, cough, wheezing, asthma), except in the presence of typical GERD symptoms and/or diagnostic testing suggestive of GERD." Weak recommendation	GER-specific systematic review and guideline
NICE guideline, 2015 <sup>2</sup>	"Based on high, moderate, and low quality evidence from observational studies" <sup>25</sup>	"Do not routinely investigate or treat for GER if an infant or child without overt regurgitation presents with chronic cough" <sup>2</sup>	GRADE profile of the studies shown in Table 18 of the paper

ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NASPGHAN = North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; NICE = National Institute for Health and Care Excellence; PPI = proton pump inhibitor; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

infants, or heartburn, chest, or epigastric pain in older children<sup>1</sup>). The "red flag" symptoms of GER that necessitate referral to a gastrointestinal specialist service are growth failure associated with overt regurgitation, hematemesis, melena, dysphagia, feeding aversion with regurgitation, dystonic neck posturing, unexplained distress in children with communication difficulties, and unexplained iron-deficiency anemia.<sup>2</sup>

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

#### Summary of Evidence and Interpretation (KQ2-4)

For KQ2, we identified two papers<sup>16,17</sup> that were not referenced in any of the systematic reviews<sup>1-3,8</sup> used

for KQ1. One<sup>16</sup> was an RCT, and the second<sup>17</sup> was a systematic review (Table 2). We excluded the Cochrane review<sup>18</sup> on pharmacological treatment for GERD as it was included in one of the guidelines<sup>19</sup> and did not examine cough as a separate outcome.

A causal link between GER and cough and its response to treatment for GER is complex and difficult to prove.<sup>8,9</sup> Only one small RCT<sup>16</sup> specifically addressed this question (Table 2). However, several other RCTs included cough as part of a symptom complex of GERD that were included in the Cochrane review<sup>20</sup> that specifically evaluated GER treatment for prolonged nonspecific cough. We used data from the Cochrane review<sup>20</sup> for the quantitative analyses, but only data from two studies (one using PPI<sup>21</sup> and the other using thickened feed<sup>22</sup>) could possibly be combined for any cough outcome measure. However, as there was statistical heterogeneity ( $I^2 > 50\%$ <sup>13</sup>), we did not combine the data. We contacted the primary author of the RCT,<sup>16</sup> but he was unable to provide additional data.

**TABLE 2 ] Summary of Data of the Included Publications Relevant to Key Question 2: For Children With Chronic Cough (> 4 Weeks Duration) and With Gastrointestinal GER Symptoms But Without an Underlying Chronic Lung Disease, Does Treatment for GERD Resolve the Cough?**

Paper and Year	Evidence Level for Finding/ Recommendation	Key Relevant Finding(S) or Recommendation	Comment
<b>RCTs with data specific for chronic cough (risk of bias assessment in Table 5)</b>			
Adamko et al, 2012 <sup>16</sup>	Single-center RCT with 4 arms (placebo/placebo, omeprazole/placebo, bethanacol/placebo, omeprazole/bethanacol)	Median values of coughing spells/day were provided in very small groups (n range from 3 to 6 per group), and thus data could not be included in meta-analysis. The only group where a significant difference in this outcome was found was the omeprazole/bethanacol group, comparing symptoms after a month of medications to respective baseline values. No between-group comparisons undertaken	25 enrolled, 19 completed RCT. Limited validity
Chao and Vandenplas, 2007 <sup>22</sup>	Single-center, double-blind RCT comparing a commercial cornstarched milk AR formula to a regular 1.25% strength formula in infants with frequent regurgitation/vomiting	Cornstarch-thickened formula feeding decreased the frequency of regurgitation/vomiting with accelerated gastric emptying compared with 1.25% strength formula. Cough resolved in all 5 infants on AR formula and 2 of the 4 infants on 1.25% strength formula (after 8 weeks)	Only 9 of the 81 infants had cough, but data were provided for the 9 infants
Orenstein et al, <sup>21</sup> 2009	Multicenter double-blind RCT (lansoprazole vs placebo) involving 162 infants with persisting symptoms attributed to GERD	"No difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants age 1 to 12 months. Serious adverse events, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo" <sup>21</sup>	Data specific to cough were obtained from Prof Orenstein when the Cochrane review <sup>20</sup> was undertaken
<b>Qualitative data from systematic reviews</b>			
CHEST guidelines, 2017 <sup>3</sup>	Cohort studies and one RCT on generic chronic cough management	For children aged $\leq$ 14-years with chronic cough, we recommend basing the management or testing algorithm on cough characteristics and the associated clinical history. No specific recommendation for children with cough and GERD but it is implied that GERD on its own should be treated	Systematic review focused on children with chronic cough and not specific for GER
de Benedictis and Bush, 2018 <sup>8</sup>	Not stated	"Anti-GER medications should not be routinely used for treatment of poorly controlled asthma, chronic cough and laryngitis. If these medications are used, and there is no response, rather than escalating therapy uncritically, a second specialist opinion is recommended" <sup>8</sup>	PRISMA data not shown
Mattos et al, 2017 <sup>17</sup>	Systematic review that included 23 RCTs focused on the use H <sub>2</sub> receptor antagonists and/or PPIs in children with GER	"Ten studies failed to demonstrate significant benefits of proton pump inhibitors or histamine H2 receptor antagonists for the treatment of unspecific manifestations attributed to gastroesophageal reflux in infants. Conclusion: Proton pump inhibitors or histamine H2 receptor antagonists may be used to treat children with gastroesophageal reflux disease, but not to treat asthma or unspecific symptoms"	

(Continued)



**TABLE 2 ] (Continued)**

Paper and Year	Evidence Level for Finding/ Recommendation	Key Relevant Finding(S) or Recommendation	Comment
NASPGHAN and ESPGHAN guideline, 2018 <sup>1</sup>	Not applicable	No specific recommendation for children with cough and GERD but it is implied that GERD on its own should be treated	GER-specific systematic review and guideline
NICE guideline, 2015 <sup>2</sup>	Not applicable	No specific recommendation for children with cough and GERD but it is implied that GERD on its own should be treated	GER-specific systematic review and guideline

AR = anti-reflux. See Table 1 legend for expansion of other abbreviations.

Quantitative summary data for the effect of GER therapies on cough could only be obtained from two studies, one study on PPI<sup>21</sup> and the second<sup>22</sup> involving a commercial milk formula. In the PPI study,<sup>21</sup> the number of children with chronic cough after 4 weeks of lansoprazole compared with placebo were not significantly different between groups (OR, 1.61; 95% CI, 0.57, 4.55, favoring placebo). However, serious adverse events (particularly lower respiratory tract infections) were significantly higher in the PPI-treated group compared with controls (OR, 6.56; 95% CI, 1.18,

26.25)<sup>21</sup> (e-Fig 5). This is consistent with reviews on serious adverse events related to prolonged PPI use.<sup>23</sup>

It thus remains unclear whether treatments for GERD resolve chronic cough in children. The qualitative data summary (Table 2) depict consistency among all the guidelines. Possible treatment adverse events need to be balanced with possible efficacy, and there is increasing evidence of the overuse<sup>11</sup> and adverse events related to PPI use, such as increased risk of infections, vitamin B<sub>12</sub> deficiency, and bone fractures.<sup>11</sup>

**TABLE 3 ] Summary of Data of the Included Publications Relevant to Key Question 3: For Children With Chronic Cough (> 4 Weeks Duration) Who Do Not Have an Underlying Lung Disease, With or Without Gastrointestinal GER Symptoms, What GER-Based Therapies Should Be Used and for How Long? (If We Find No to Q1, Q2 Should Be Omitted)**

Paper and Year	Evidence Level	Key Relevant Recommendation	Comment
de Benedictis and Bush, 2018 <sup>8</sup>	Not stated	“Children with chronic cough and typical symptoms of GERD should undergo medical treatment—dietary, lifestyle modifications and acid suppression therapy. Here, we suggest that a three-stage therapeutic trial should be completed before diagnosing reflux-related cough: (1) clear-cut response to a 4 to 8-week treatment with PPI; (2) relapse on stopping medication; (3) new response to recommencing medication, with weaning down therapy as appropriate to the child’s symptoms” <sup>8</sup>	PRISMA data not shown
NASPGHAN and ESPGHAN guideline, 2018 <sup>1</sup>	Expert opinion	No specific recommendation for children with cough and GERD but it is implied that GERD on its own should be treated. In the treatment of GERD: “Based on expert opinion, the working group recommends evaluation of treatment efficacy and exclusion of alternative causes of symptoms in infants and children not responding to 4 to 8 weeks of optimal medical therapy for GERD.” <sup>1</sup> Strong recommendation	GER-specific systematic review and guideline
NICE guideline, 2015 <sup>2</sup>	Experience and opinion of the group	No specific recommendation for children with cough and GERD but it is implied that GERD on its own should be treated. For GERD treatment, “Assess the response to a 4 week trial of the PPIs or H <sub>2</sub> receptor antagonist and consider referral to a specialist for possible endoscopy if the symptoms do not resolve or recur after stopping the treatment” <sup>2</sup>	GER-specific systematic review and guideline

See Table 1 legend for expansion of abbreviations.

**Recommendation 2: For children aged ≤ 14-years with chronic cough (> 4 weeks duration) without an underlying lung disease but who have symptoms and signs or tests consistent with gastroesophageal pathological reflux, we recommend that they be treated for GERD in accordance to evidence-based GERD-specific guidelines.<sup>1,2</sup> (Grade 1B)**

**Recommendation 3: For children aged ≤ 14-years with chronic cough (> 4 weeks duration) without an underlying lung disease but who have symptoms and signs or tests consistent with gastroesophageal pathological reflux, we recommend that acid suppressive therapy should not be used solely for their chronic cough. (Grade 1C)**

As the summary data for KQ2 did not provide any data specific for cough with GERD, KQ3 cannot be directly answered. Table 3 summarizes the qualitative data from GERD-specific systematic reviews for treating GERD. There were no data that addressed

whether any of the many possible interventions for cough associated with GERD were superior to another. Treatments recommended for GERD are age and symptom dependent. For formula-fed infants, treatment options include reducing feed volumes (with increasing frequency), use of feed thickeners (eg, rice or cornstarch, locust or carob bean gum)<sup>1,2</sup> for 1 to 2 weeks<sup>2</sup> or hydrolyzed milk-formula for 2 to 4 weeks.<sup>1</sup> In breast-fed babies, alginates may be tried.<sup>2</sup> Pharmacological therapy include PPIs or H<sub>2</sub> receptor antagonists, but these should not be used for longer than 4 weeks<sup>2</sup> to 8 weeks<sup>1</sup> when evaluating for treatment efficacy.

**Suggestion 4: For children with chronic cough (> 4 weeks duration) who do not have an underlying lung disease but with gastrointestinal GER symptoms, we suggest that they be treated for GERD in accordance to evidence-based GERD-specific guidelines<sup>1,2</sup> for 4-8 weeks and their response reevaluated. (Ungraded Consensus-based Statement)**

**TABLE 4 ] Summary of Data of the Included Publications Relevant to Key Question 4: For Children With Chronic Cough (> 4 Weeks Duration) Without an Underlying Disease, if GERD Is Suspected as the Cause, What Investigations and Diagnostic Criteria Best Determines GERD as the Cause of the Cough?**

Paper and Year	Evidence Level	Key Relevant Recommendation	Comment
de Benedictis and Bush, 2018 <sup>8</sup>	Not stated	"MII-pH monitoring should be reserved for those with refractory symptoms and those considered for anti-reflux surgery" <sup>8</sup>	PRISMA data not shown
NASPGHAN and ESPGHAN guideline, 2018 <sup>1</sup>	Expert opinion	No specific recommendation for cough and GERD but it is implied that an algorithm is used for "persistent symptoms" whereby an endoscopy is undertaken first followed by pH-metry or pH-MII. It was recommended that "Based on expert opinion, the working group suggests to consider to use pH-MII testing only to (1) Correlate persistent troublesome symptoms with acid and non-acid gastroesophageal reflux events, (2) Clarify the role of acid and non-acid reflux in the etiology of esophagitis and other signs and symptoms suggestive for GERD, (3) Determine the efficacy of acid suppression therapy or (4) Differentiate NERD, hypersensitive esophagus and functional heartburn in patients with normal endoscopy" <sup>1</sup>	GER-specific systematic review and guideline
NICE guideline, 2015 <sup>2</sup>	"Based on high, moderate, and low quality evidence from observational studies" and expert opinion <sup>25</sup>	No specific recommendation for cough and GERD. The guideline stated: "Consider performing an oesophageal pH study (or combined oesophageal pH and impedance monitoring if available) in infants, children and young people with: suspected recurrent aspiration pneumonia, unexplained apnoeas, unexplained non-epileptic seizure-like events, unexplained upper airway inflammation, dental erosion associated with a neurodisability, frequent otitis media, a possible need for fundoplication or a suspected diagnosis of Sandifer's syndrome." <sup>2</sup> Cough was not listed as one of the conditions	GER-specific systematic review and guideline

NERD = nonerosive reflux disease; pH-MII = multichannel intraluminal impedance with pH monitoring. See Table 1 legend for expansion of other abbreviations.

**TABLE 5 ] Risk of Bias Assessment of RCTs Included in Our Systematic Review**

Paper	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Adamko et al, 2012 <sup>16</sup> (for non-open-label part)	Low	Low	Unclear	Low	High	High	High • Analyses • RCT ended prematurely
Chao and Vandenplas, 2007 <sup>22</sup>	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Orenstein et al, <sup>21</sup> 2009	Low	Low	Low	Low	Low	Low	Low

See Table 1 legend for expansion of abbreviation.

*Remark:* The agent used for the “trial of treatment” approach is dependent on the child’s age, feeding regimen, and symptoms.<sup>1,2</sup> PPIs and H<sub>2</sub> receptor antagonists should not be used for longer than 4 to 8 weeks without further evaluation.

The various objective methods to diagnose GERD include endoscopy, pHmetry (known in some centers as pH monitoring), manometry, and combined esophageal multichannel intraluminal impedance with pH monitoring (pH-MII).<sup>1</sup> Various symptom association scales have been used (symptom index, symptom sensitivity index, and symptom association probability) to study the association between cough and GER.<sup>1</sup> However, these scales have limitations as they are dependent on symptom reporting (which may be inaccurate,<sup>24</sup> especially in young children), the assumed time range associated with the symptom, and the limited capture or download rate of 0.25 Hz (ie, data points recorded once every 4 s after the glottic closure phase of cough, whereby the greatest intrathoracic pressure generated lasts 0.2 s in commercial pHmetry).<sup>9</sup> Currently, most studies involving “symptom association scores” use a time range of 2 min before/after the “event,” but this time range has not been systematically studied for cough with reflux events.

We did not find any RCTs that addressed KQ4 and only qualitative data from GERD-specific systematic reviews<sup>1,2,8</sup> could be included, as summarized in Table 4.

**Suggestion 5: For children with chronic cough (> 4 weeks duration) and without an underlying disease, if GERD is suspected as the cause based on GER symptoms, we suggest following the GERD guidelines for investigating children suspected for GERD.** (Ungraded Consensus-based Statement)

*Remark:* The workup suggested by GERD guidelines<sup>1,2</sup> is largely dependent on the child’s age and constellation of symptoms. In most situations, endoscopy is suggested before pHmetry or pH-MII.<sup>1,2</sup>

### Summary

Given the controversies relating chronic cough to GERD, we limited our review to systematic reviews and RCTs. This CHEST cough guideline relating to cough and GERD in children found a paucity of high-level evidence in this field. Nevertheless, the data used that were predominantly based on pediatric GER-specific evidenced-based guidelines from NICE<sup>2</sup> (its recommendations and level of evidence summarized in another paper<sup>25</sup>) and NASPGHAN/ESPGHAN<sup>1</sup> showed



consistency of recommendations with existing CHEST chronic cough findings<sup>26</sup> and guidelines<sup>3,6</sup> relating to common KQs (KQ1-2). Where there was insufficient high-level evidence, both of the GER-specific guidelines<sup>1,2</sup> were also consistent in their approach and for these KQs (KQ3-4), “consensus-based suggestions” were framed.

## Areas for Further Research

To advance and improve knowledge regarding the possible relationship between chronic cough and GERD in children, we suggest several areas of research.

1. RCTs that specifically target children with cough and GERD. RCTs should include various interventions (eg, motility agents, diet, PPIs) that may be efficacious for chronic cough associated with GERD combined with various diagnostic tests (eg, pHmetry, pH-MII) and differentiate acid from nonacid GERD. The RCTs should use validated cough outcomes and *a-priori* definitions.
2. The optimal duration of various interventions to treat cough associated with GERD in infants (aged < 12-months) and children should be delineated.
3. How best to define clinically important reflux-cough or cough-reflux episodes (eg, relating the cough episode with the time [eg, 30, 60, 120 s] of the GER event [acid or nonacid reflux]) and its severity (duration of event, recovery, depth of pH change) should be systematically and objectively evaluated.
4. The phenotypes of GER and its relation (if any) to cough in children should be determined.

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

## References

1. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66(3):516-554.
2. NICE guideline. Gastro-oesophageal reflux disease in children and young people: diagnosis and management. <https://www.nice.org.uk/guidance/ng1>. Accessed August 19, 2018.
3. Chang AB, Oppenheimer JJ, Weinberger MM, et al. Use of management pathways or algorithms in children with chronic cough: CHEST Guideline and Expert Panel Report. *Chest.* 2017;151(4):884-890.
4. Chang AB, Robertson CF, van Asperen PP, et al. A multi-centre study on chronic cough in children: burden and etiologies based on a standardized management pathway. *Chest.* 2012;142(4):943-950.
5. Marchant JM, Newcombe PA, Juniper EF, et al. What is the burden of chronic cough for families? *Chest.* 2008;134(2):303-309.
6. Chang AB, Oppenheimer JJ, Weinberger MM, et al. Etiologies of chronic cough in pediatric cohorts: CHEST Guideline and Expert Panel Report. *Chest.* 2017;152(3):607-617.
7. Kahrilas PJ, Altman KW, Chang AB, et al. Chronic cough due to gastroesophageal reflux in adults: CHEST Guideline and Expert Panel Report. *Chest.* 2016;150(6):1341-1360.
8. de Benedictis FM, Bush A. Respiratory manifestations of gastro-oesophageal reflux in children. *Arch Dis Child.* 2018;103(3):292-296.
9. Chang AB, Connor FL, Petsky HL, et al. An objective study of acid reflux and cough in children using an ambulatory pHmetry-cough logger. *Arch Dis Child.* 2011;96(5):468-472.
10. Madiwale MV, Sahai S. Nissen fundoplication: a review of complications for the pediatrician. *Clin Pediatr (Phila).* 2015;54(2):105-109.
11. DeBruyne P, Ito S. Toxicity of long-term use of proton pump inhibitors in children. *Arch Dis Child.* 2018;103(1):78-82.
12. Gyawali CP. Proton pump inhibitors in gastroesophageal reflux disease: friend or foe. *Curr Gastroenterol Rep.* 2017;19(9):46.
13. Lewis SZ, Diekemper RL, French CT, et al. Methodologies for the development of the management of cough: CHEST Guideline and Expert Panel Report. *Chest.* 2014;146(5):1395-1402.
14. Chang AB, Oppenheimer JJ, Weinberger MM, et al. Children with chronic wet or productive cough—treatment and investigations: a systematic review. *Chest.* 2016;149(1):120-142.
15. Shields MD, Bush A, Everard ML, et al. British Thoracic Society guidelines recommendations for the assessment and management of cough in children. *Thorax.* 2008;63(suppl 3):iii1-iii15.
16. Adamko DJ, Majaesic CM, Skappak C, et al. A pilot trial on the treatment of gastroesophageal reflux-related cough in infants. *Transl Pediatr.* 2012;1(1):23-34.
17. Mattos AZ, Marchese GM, Fonseca BB, et al. Antisecretory treatment for pediatric gastroesophageal reflux disease. *Arq Gastroenterol.* 2017;54(4):271-280.
18. Tighe M, Afzal NA, Bevan A, et al. Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database Syst Rev.* 2014;(11):CD008550.
19. Crengle S, Robinson E, Ameratunga S, et al. Ethnic discrimination prevalence and associations with health outcomes: data from a nationally representative cross-sectional survey of secondary school students in New Zealand. *BMC Public Health.* 2012;12:45.
20. Chang AB, Lasserson T, Gaffney J, et al. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev.* 2011;(1):CD004823.
21. Orenstein SR, Hassall E, Furmaga-Jablonska W, et al. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr.* 2009;154(4):514-520.
22. Chao HC, Vandenplas Y. Comparison of the effect of a cornstarch thickened formula and strengthened regular formula on regurgitation, gastric emptying and weight gain in infantile regurgitation. *Dis Esophagus.* 2007;20(2):155-160.
23. De BP, Ito S. Toxicity of long-term use of proton pump inhibitors in children. *Arch Dis Child.* 2018;103(1):78-82.
24. Rosen R, Amirault J, Giligan E, et al. Intraesophageal pressure recording improves the detection of cough during multichannel intraluminal impedance testing in children. *J Pediatr Gastroenterol Nutr.* 2014;58(1):22-26.
25. Davies I, Burman-Roy S, Murphy MS. Gastro-oesophageal reflux disease in children: NICE guidance. *BMJ.* 2015;350:g7703.
26. Chang AB, Oppenheimer JJ, Weinberger MM, et al. Use of management pathways or algorithms in children with chronic cough: systematic reviews. *Chest.* 2016;149(1):106-119.