should not be considered a substitute for clinical judgment or as a protocol applicable to all patients.

This set of guidelines differs from the 2009 guidelines in several ways: (1) it focuses on reducing acid suppression whenever possible with short empiric trials of 4 to 8 weeks recommended for GERD symptoms; (2) it shifts away from attributing respiratory and laryngeal symptoms to GER; (3) it adds an algorithm for typical symptoms to incorporate reflux testing to further characterize patients to differentiate patients with reflux based diagnoses versus functional diagnoses; and (4) it adds a recommendation for change of formula to a protein hydrolysate or amino acid based formula before acid suppression in infants.

METHODS

This project started in March 2015 with a literature search for international guidelines concerning pediatric GERD. This search identified 2 guidelines; that is, the 2009 guidelines of the NASPGHAN/ESPGHAN and the more recent 2015 National Institute for Health and Care Excellence (NICE) guideline (1,3). Two reviewers (M.T. and M.S.) independently appraised guideline quality using the 23-item AGREE-II instrument, which rates reporting of the guidance development across 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence (available online through: *http://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf* (4). Total scores were calculated as standardized averages by domain. In conclusion, the NASPGHAN/ESPGHAN 2009 guidelines were considered of poor overall quality, lacking of appropriate guideline development methodology (ie, due to no clear description of aims and purpose of guideline, target population(s) and outcome measures; lack of reproducibility and complexity of data representation). The 2015 NICE guidelines were considered to overall be of high quality.

The working group agreed that many statements and recommendations of the 2009 guidelines are largely still applicable, despite its limitations in methodology. It was therefore decided to use relevant and applicable information from the 2009 guidelines in the development of this present document. The updating process was then performed by using the approach of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) from October 1, 2008 onward (the end of the 2009 guideline's literature search) (5).

Using this approach, the project started by formulating 8 clinical questions. Questions were chosen first to update the topics already addressed by the 2009 ESPGHAN/NASPGHAN GERD guidelines. Second, additional (sub)questions were determined by consensus agreement on current gaps in knowledge on diagnosis and management of pediatric GERD. After the questions were formulated, the guidelines committee was subdivided into groups that dealt with each question separately. Questions 1, 2, and 8 were answered based on expert opinions and earlier published guidelines and literature relevant to the research question (1,3). Questions 3, 4, 5, 6, and 7 were answered using the results of systematic literature searches. Two algorithms, 1 for infants and 1 for children, for the diagnostic and therapeutic work-up for GERD were developed (Algorithm 1 and 2, respectively).

Overview of the Clinical Research Questions

Question 1:	What is the definition of GER/GERD in infants and children 0–18 years?
Question 2:	What are the ''red flag'' findings and diagnostic clues to distinguish infants and children with GERD (or conditions other than GERD), from GER?
Question 3:	What diagnostic interventions have additional value to history taking and physical examination in infants and children with suspected GERD?
Question 4:	What non-pharmacologic treatment options are effective and safe for the reduction of signs and symptoms of GERD?
Question 5:	What are effective and safe pharmacologic treatment options for the reduction of signs and symptoms of GERD
Question 6:	Which infants and children would benefit from surgical treatment such as fundoplication and what are the efficacies of other surgical therapies for GERD?
Question 7:	What is the prognosis of GERD in infants and children and what are prognostic factors?
Question 8:	What is the appropriate evaluation of infants and children 0–18 years with GERD refractory to non-pharmacological and pharmacological treatment?

H2 = histamine receptor H2; pH-MII = pH multichannel intraluminal impedance; PPI = proton pump inhibitor.

Literature search:

Systematic literature searches were performed by a clinical librarian. The Embase, MEDLINE, PubMed and the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Clinical Trials databases were searched from October 1, 2008 or from inception for those aspects not addressed in the 2009 guideline, to June 1, 2015. Searches were also conducted from inception in case of large inconsistency in findings in comparison to findings of the 2009 guidelines.

Inclusion criteria were as follows (all inclusion criteria relevant to the research question to be met):

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M.L., PhD, is aguideline methodologist. A.S., MD, is an expert in pediatric motility disorders and gastroesophageal reflux disease. N.T., MD, is an expert in pediatric motility disorders. N.T., MD, is an expert in pediatric motility disorders. M.T., MD, PhD, is an expert in gastroesophageal reflux disease.

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1. Study population consisting of children aged 0 to 18 years with GER(D). The key words to describe GERD were ''Gastroesophageal Reflux'' and its abbreviations, ''gastric acid reflux'' and ''esophagitis'', taking into account differences in British and American spelling. Additionally, a clear definition of GER(D) had to be provided by the authors.
2. To evaluate the value of tests in diagnosing GERD (question 2), the following inclusion criteria were used: systematic reviews and original studies related to the diagnostic accuracy of the specific tests. The reference standard for GERD had to be defined by the authors in terms of findings at history and physical exam.
3. In studies evaluating the effect of treatments or interventions for GERD (questions 4, 5, 6) the following inclusion criteria were used: systematic reviews of randomized controlled trials (RCT) and/or RCTs containing at least 10 individuals per arm.
4. In studies evaluating the outcome of GERD (question 7), the following inclusion criteria were used: systematic reviews of prospective or retrospective controlled studies, one of the aims of the study was to evaluate the prognosis and clinical course of GERD expressed as duration or recurrence of GERD and determinants that influence prognosis, baseline measurement of at least one of the outcomes of the research population should be provided and a follow-up of at least 8 weeks was required.

Additional strategies to identify studies involved searching the reference lists of review articles. No language restriction was applied. In addition, all guideline members were asked to search the literature with respect to their assigned topics in order to possibly uncover further studies that may have been missed by the former search.

Special Considerations and Limitations

Because GERD was defined as the presence of bothersome symptoms related to the passage of gastric contents from the stomach into the esophagus and the included studies needed to use symptom resolution as an outcome as part of one of the predefined outcome measures, no extraesophageal studies met the inclusion criteria using the GRADE methodology. However, because extraesophageal symptoms are a primary reason for referral to pediatric gastroenterologists, whenever possible a narrative review of the literature was included on this topic to provide clinical guidance for the diagnosis and management of these patients.

Selection of Outcome Measures

The GRADE approach was used to identify outcome measures for the research questions (5). A draft version was circulated by M.T. and M.S., and every workgroup member was allowed to add outcomes. Group members were asked to rate relative importance of the outcomes on a 9-point scale: limited (1–3), important but not critical (4–6), or critical (7–9) for decision making. The workgroup members were also asked to discuss personal experience and to discuss outcome measures of interest with their patients in daily practice. Finally 8 outcome measures were selected: esophagitis (endoscopic/histologic), complications of GERD (Barrett metaplasia, esophageal stenosis, and others as specified by authors), GERD related signs and symptoms (assessed by the I-GERQ-R instrument (6)), quality of life (both parent and patient reported when applicable), crying and distress (parent reported), visible vomiting and/or regurgitation (both parent and patient reported when applicable), heartburn (both parent and patient reported when applicable), and side effects of treatment. All outcome measures were considered of critical importance based on the mean scores of the guidelines group members.

Levels and Quality of Evidence, Grade of Recommendations

Levels of evidence and quality of evidence were assessed using the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS; diagnostic questions) and the GRADE system (Cochrane Risk of Bias Tool; therapeutic questions) and are summarized in the appendices (7). The items in the QUADAS tool include patient spectrum, reference standard, disease progression bias, verification bias, review bias, clinical review bias, incorporation bias, test execution, study withdrawals, and indeterminate results. The QUADAS tool is presented together with recommendations for scoring each of the items included. To assess risk of bias of studies evaluating the outcome of GERD the Quality in Prognostic Studies (QUIPS) tool was used by 2 reviewers (MT and ML) (7–9). The QUIPS tool assesses risk of bias in 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and presentation. Ratings of the quality of evidence for each statement are based on the grading of the literature. For the diagnostic and prognostic questions, for which the GRADE approach is still in development, conclusions were formulated taking into account overall risk of bias. The results of the risk of bias and quality of the evidence assessment are summarized in Appendices C and D.

Therapeutic Questions (Question 4 and 5)

Using the GRADE system, the quality of evidence for therapeutic interventions was graded as follows:

- High: Further research is unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Very low: Any estimate of effect is uncertain.

Strength of recommendations was defined as follows:

Strong: when the desirable effects of an intervention clearly outweigh the undesirable effects, or they clearly do not. Strong recommendations are formulated as ''the working group recommends (. . .).''
Weak: when the tradeoffs are less certain (either because of the low quality of evidence or because the evidence suggests that desirable and undesirable effects are closely balanced). Weak recommendations are formulated as ''the working group suggests (. . .).''

A summary of the definitions and recommendations is provided at the end of this document.

Non-therapeutic Questions (Question 3)

Because of a lack of a validated method for determining the strength of the recommendation for questions other than therapy, we elected to classify recommendations based on the quality of

available evidence including the methodology and outcomes assessed. We categorized the evidence as:

Strong: if there were adequately powered, prospective studies supporting the conclusions.
Moderate: if there were large retrospective studies or small prospective studies supporting the evidence.
Weak: if there were only retrospective studies or expert opinion supporting the results.

Consensus Meeting and Voting

A 3-day consensus meeting was held in April 2016 (Keflavik, Iceland) in order to achieve consensus on and formulate all recommendations. Each subgroup presented the recommendations during these consensus meetings, wherein these were discussed and modified according to the comments of the attendees. Committee members with conflict of interest with a specific topic excused themselves from the discussion of that topic.

Consensus was formally achieved through nominal group technique, a structured quantitative method. The group anonymously voted on each recommendation. A 9-point scale was used (1 = strongly disagree to 9 = fully agree), and votes are reported for each recommendation. Consensus was reached if >75% of the working group members voted >6. The consensus was reached for all of the questions. The final draft of the guidelines was sent to all of the committee members for approval in November 2016 (Figs. 1–5).

QUESTION 1: WHAT IS THE DEFINITION OF PEDIATRIC GASTROESOPHAGEAL REFLUX DISEASE?

A definition of gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) specific to the pediatric population was developed in 2009 as an international consensus document, based on evidence reviewed from pediatric studies (10). This document was developed in recognition of the special clinical and scientific needs of the pediatric population, not fully addressed by the Montreal consensus document on the adult definition and classification of GERD) (11). Both documents define GER as the passage of gastri contents into the esophagus with or without regurgitation and/or vomiting. GER is considered

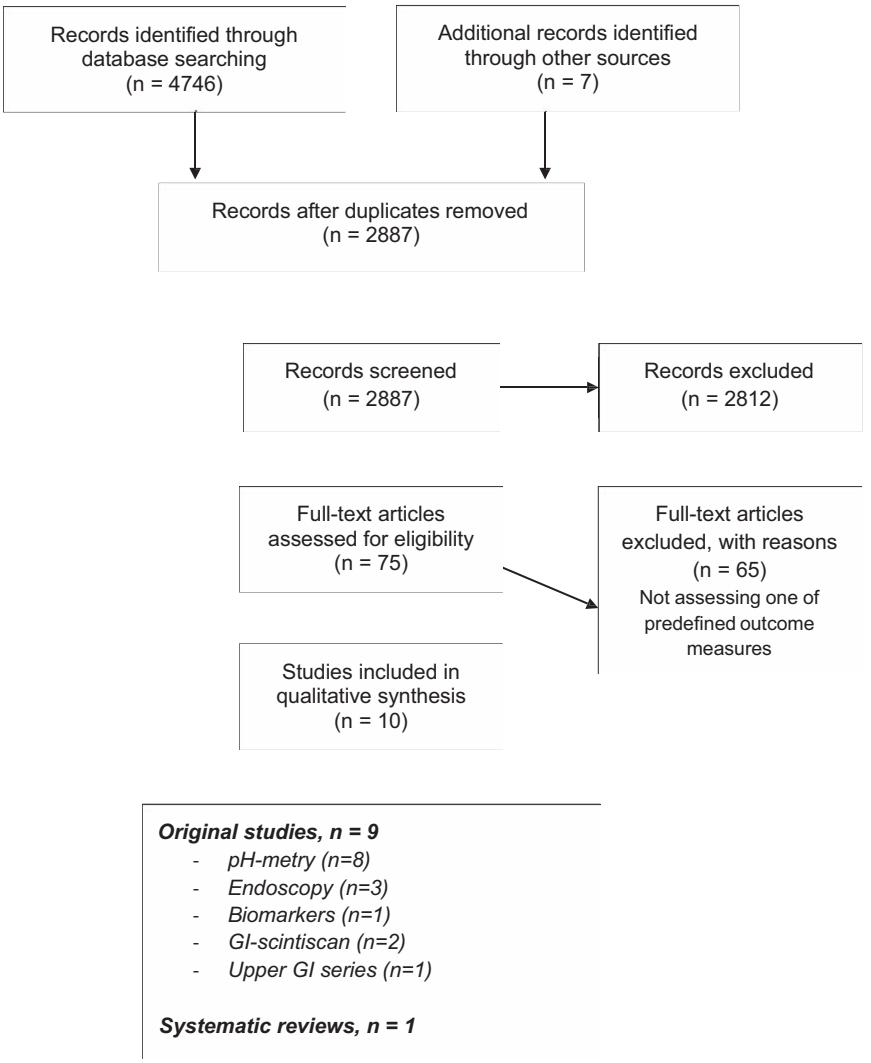


FIGURE 1. Flow-chart to identify articles related to diagnostic testing.

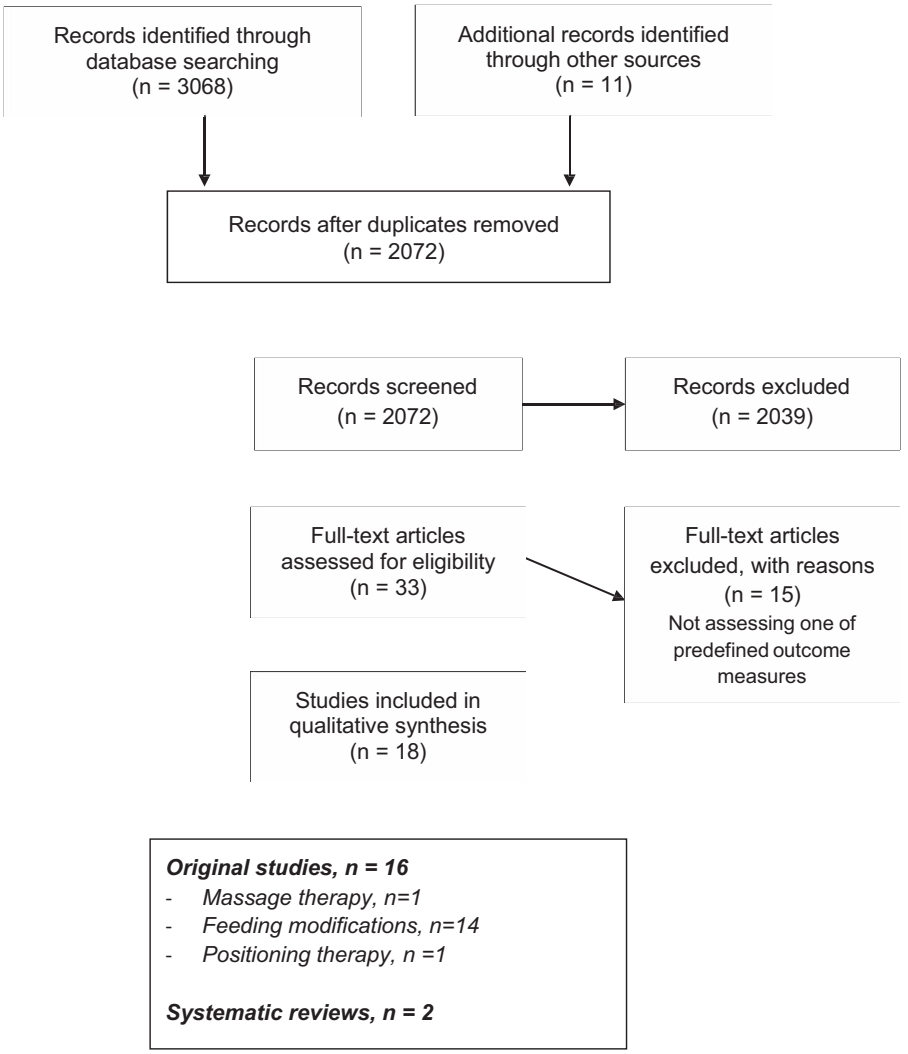


FIGURE 2. Flow-chart to identify articles related to non-pharmacologic therapies.

to be pathologic and referred to as GERD when the reflux leads to troublesome symptoms and/or complications, such as esophagitis or stricturing.

This definition of GERD was adopted in the 2009 published guidelines of NASPGHAN and ESPGHAN and in the 2015 published NICE guideline (1,3). However, as a direct consequence of its patient-centered and symptom-based nature, this definition is subject to several caveats, which are even more relevant in the pediatric population. In clinical practice, it may be difficult to differentiate GER from GERD in children, and the terms are used interchangeably by health professionals and parents alike. Symptoms of GERD are known to vary widely by age and are non-specific. As a consequence proving that reflux events cause one or multiple symptoms is often difficult (1,12). This is particularly true in nonverbal infants in whom defining *troublesome* is problematic. Reported symptoms of infant GERD vary widely and may include excessive crying, back arching, regurgitation and irritability. Many of these symptoms, however, occur in all babies with or without GERD, making a definitive diagnosis challenging. Therefore, the degree of concern of parents is often the factor driving the need for a diagnosis. For older children (particularly those older than the age of 8) and adolescents who can communicate more effectively, typical symptoms such as heartburn and regurgitation mimic those seen in adults with GERD (11,13–16).

Definitions of GER and GERD are therefore blurred for the pediatric population, making it difficult to identify infants and children who genuinely suffer from GERD and to estimate the true prevalence and burden of the problem. Moreover, to date no gold standard diagnostic tool exists for the diagnosis of GERD in infants and children. Despite these limitations, and given the need for definitions, the working group decided to adapt the definition of pediatric GERD as formulated in the 2009 consensus statements for all age groups. To date, no other definitions for pediatric GERD have been proposed, and validation studies on this definition have not been performed. In the present guideline, every effort was made to use the terms GER and GERD strictly as defined.

GERD is also known to be a prominent phenomenon in children who have other underlying medical conditions such as prematurity, neurologic impairment, and pulmonary problems, including cystic fibrosis. The present guideline was not intended

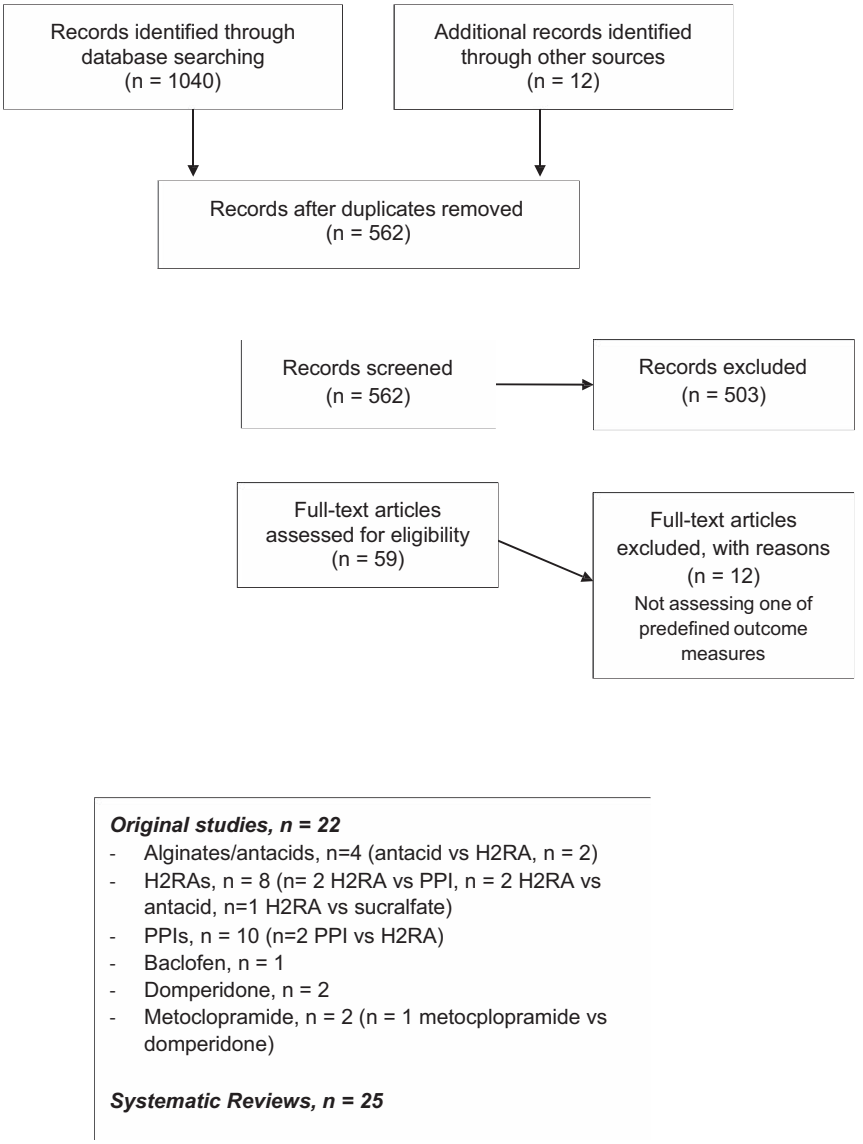


FIGURE 3. Flow-chart to identify articles related to pharmacologic therapies.

to specifically focus on patients with congenital anomalies, including esophageal atresia (EA) among others, since these are addressed in specific guidelines concerning these entities (3,17–19).

Definitions:	
GER:	the passage of gastric contents into the esophagus with or without regurgitation and vomiting.
GERD:	when GER leads to troublesome symptoms that affect daily functioning and/or complications.
Refractory GERD:	GERD, not responding to optimal treatment after 8 weeks.
Optimal Therapy:	Maximum pharmacologic and/or non-pharmacologic therapy based on the available health-care facilities in the region of practice of the subspecialist

(See under ''Summary of the Definitions'' for an overview of other definitions used in this guideline).

Recommendation:
Based on expert opinion, the working group recommends to use the definitions of GER/GERD as described in this section for all infants and children.
Voting: 7, 7, 7, 7, 8, 8, 8, 8, 8, 9. (moderate strength)

QUESTION 2: WHAT ARE THE ''RED FLAG'' FINDINGS AND DIAGNOSTIC CLUES TO DISTINGUISH INFANTS AND CHILDREN WITH GASTROESOPHAGEAL REFLUX DISEASE (OR CONDITIONS OTHER THAN GASTROESOPHAGEAL REFLUX DISEASE), FROM GASTROESOPHAGEAL REFLUX?

Clinical history of disease and physical examination in the evaluation of GERD is important to distinguish GER from GERD,

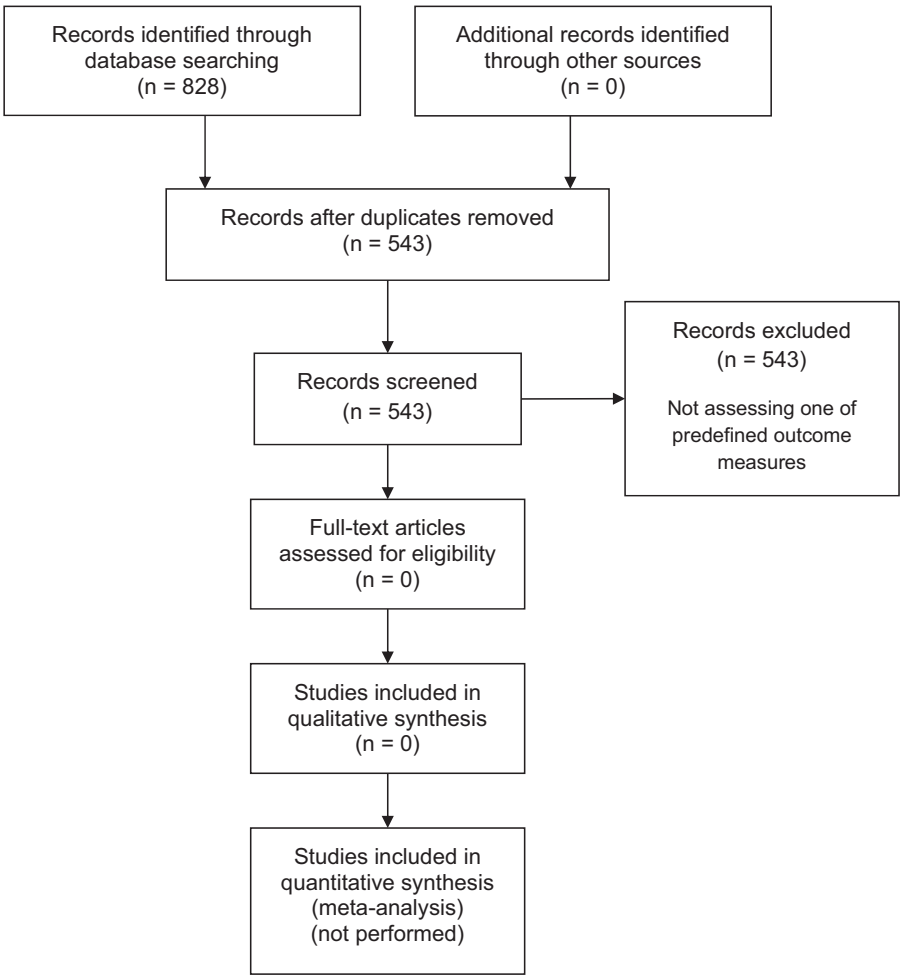


FIGURE 4. Flow-chart to identify articles related to surgical therapies.

to identify possible complications of GERD and also to exclude more worrisome disorders requiring further investigation and management. Infants and children present with a wide range of nonspecific symptoms that may be interpreted as GERD symptoms, but the reliability of these clinical manifestations as a consequence of GER is not always clear. As this may lead to both over- and underdiagnoses and –treatment, the working group considered it important to provide an overview of common symptoms and signs to identify GERD. Clarifying 'red flags' (alarm features) red flags should warrant further investigation by health-care professionals to rule out complications of GERD and to uncover underlying disorders presenting with signs or symptoms of GER, particularly regurgitation and/or vomiting (Algorithms 1 (infants) and 2 (children), Tables 1–3).

For this purpose, the working group critically reviewed evidence from existing guidelines, systematic reviews and consensus documents to establish a comprehensive list of symptoms and signs indicative of GERD (Question 2, Table 1) (1,3,20,21). Additionally, the working group highlighted a number of clinical manifestations and features, including gastrointestinal and systemic manifestations, which they considered to be recognized as 'red flags' suggesting possible other disorders apart from GERD in the infant or child presenting with regurgitation and/or vomiting (Question 2, Table 2).

It should be noted that a general concern is that the reported definitions of GERD and outcome measures used to assess treatment efficacy vary widely among studies with outcomes ranging from symptom resolution to reduction in the number of reflux events or healing of esophagitis. This heterogeneity makes comparisons among studies difficult.

Diagnostic Approach of Infants (age 0–12 Months) With Frequent Regurgitation and/or Vomiting

In the infant with recurrent regurgitation or 'spitting', a thorough history (Table 1) and physical examination with attention to warning signals suggesting other diagnoses (Tables 1 and 3) is generally sufficient to establish a clinical diagnosis of uncomplicated infant GER (Algorithm 1). The history should include the age of onset of symptoms, a thorough feeding and dietary history (eg, length of feeding period, volume of each feed, type of formula, quality of milk supply when breast feeding, methods of mixing the formula, size of the feeds, additives to the feeds, restriction of allergens, time interval between feeding), the pattern of regurgitation/spitting/vomiting (eg, nocturnal, immediately post prandial, long after meals, digested versus undigested), a family medical history, possible environmental triggers (including family psychosocial history and factors such as tobacco use and second-hand tobacco smoke-exposure), the patient's growth trajectory, prior

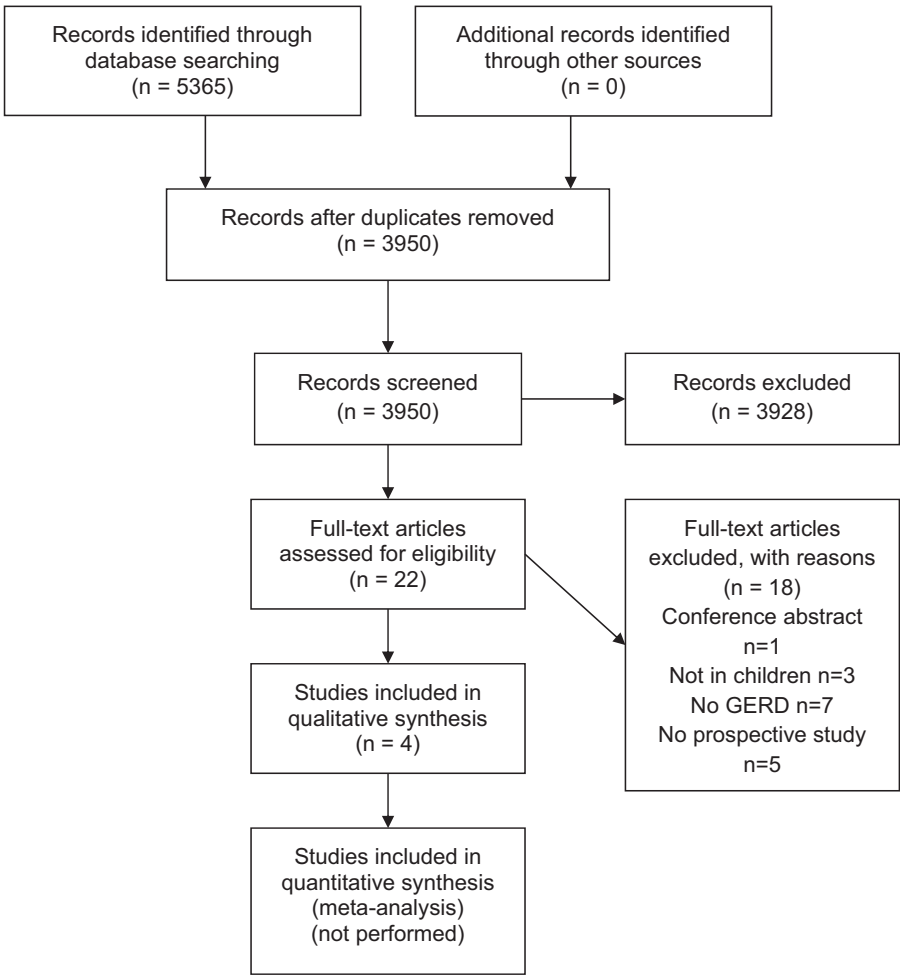


FIGURE 5. Flow-chart to identify articles related to GERD prognosis.

pharmacologic and dietary interventions and the presence of warning signs (Table 2) (22,23). Physiologic GER seldom starts before the age of 1 week or after the age of 6 months (24).

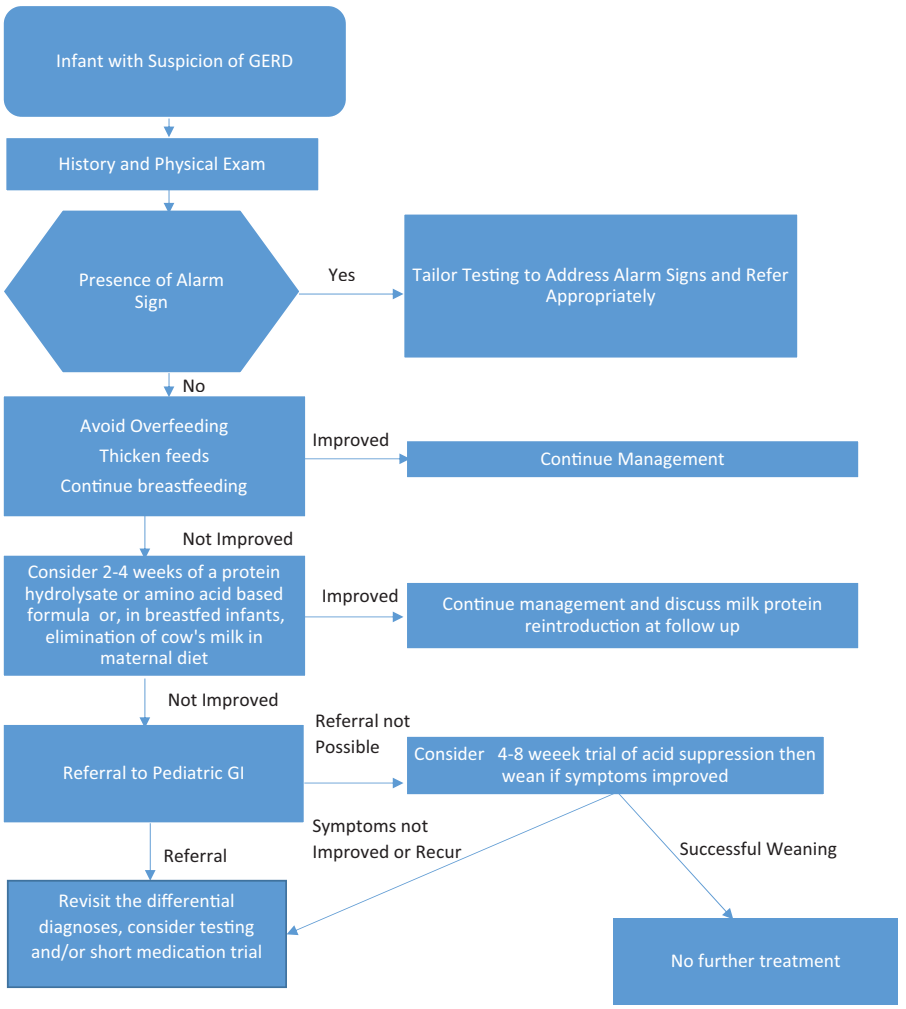
While most reflux in infants is benign, some infants merit additional testing. While the presence of warning signs obviously merits additional testing, the more difficult subgroup of patients is the group of infants presenting with fussiness, crying and arching with or without spitting but who otherwise are thriving. In this population, there is often intense pressure by families to start anti-reflux therapies or pursue diagnostic testing because of the perceived severity of symptoms. In the absence of warning signs, diagnostic testing and/or therapies including acid suppression are NOT needed if there is no impact of the symptoms on feeding, growth or acquisition of developmental milestones. In the presence of 'red flags' (Table 2), conditions other than GERD may be more likely (differential diagnosis of GERD, Table 3). The diagnostic approach of infants with frequent regurgitation or vomiting is presented in Algorithm 1.

Diagnostic Approach of Children (Age 12 Months–18 Years) with Frequent Regurgitation and/or Vomiting

Physiologic regurgitation and episodic vomiting are frequent in infants. Onset of GERD symptoms after the age of 6 months or persistence of symptoms beyond 12 months raises the possibility of alternative diagnoses to infant GER. Because these symptoms are not unique to GERD, referral to a pediatric gastroenterologist for evaluation to diagnose possible GERD and to rule out other diagnoses is recommended based on expert opinion. The goal of additional testing is to rule out mimickers or complications of GERD. Testing may include laboratory tests, contrast imaging, upper GI endoscopy and/or esophageal pH/MII, depending on presenting symptoms (Tables 2 and 3). The diagnostic approach of children with frequent regurgitation or vomiting is presented in Algorithm 2.

Diagnostic and Therapeutic Approach to Infants and Children With Possible Extraesophageal Reflux Disease

Because the outcome evaluated for these guidelines is based on the evaluation and treatment of bothersome GERD symptoms, extraesophageal symptoms were not included due to the heterogeneous nature of the symptoms and the lack of a clear way to prove that symptoms are actually related to movement of gastric contents from the stomach into the esophagus. However, because these symptoms are a frequent cause for referral and parental concern, the literature is reviewed and presented narratively, whenever possible.



ALGORITHM 1. Management of the symptomatic infant.

Recommendation:
Based on expert opinion, the working group recommends to use Tables 1–3 for symptoms and signs that may be associated with gastroesophageal reflux disease (GERD), for alarm symptoms and diagnostic clues to identify an alternative underlying disease which are responsible for the symptoms. **Voting: 7, 7, 8, 8, 8, 8, 8, 8, 9, 9. (weak recommendation)**

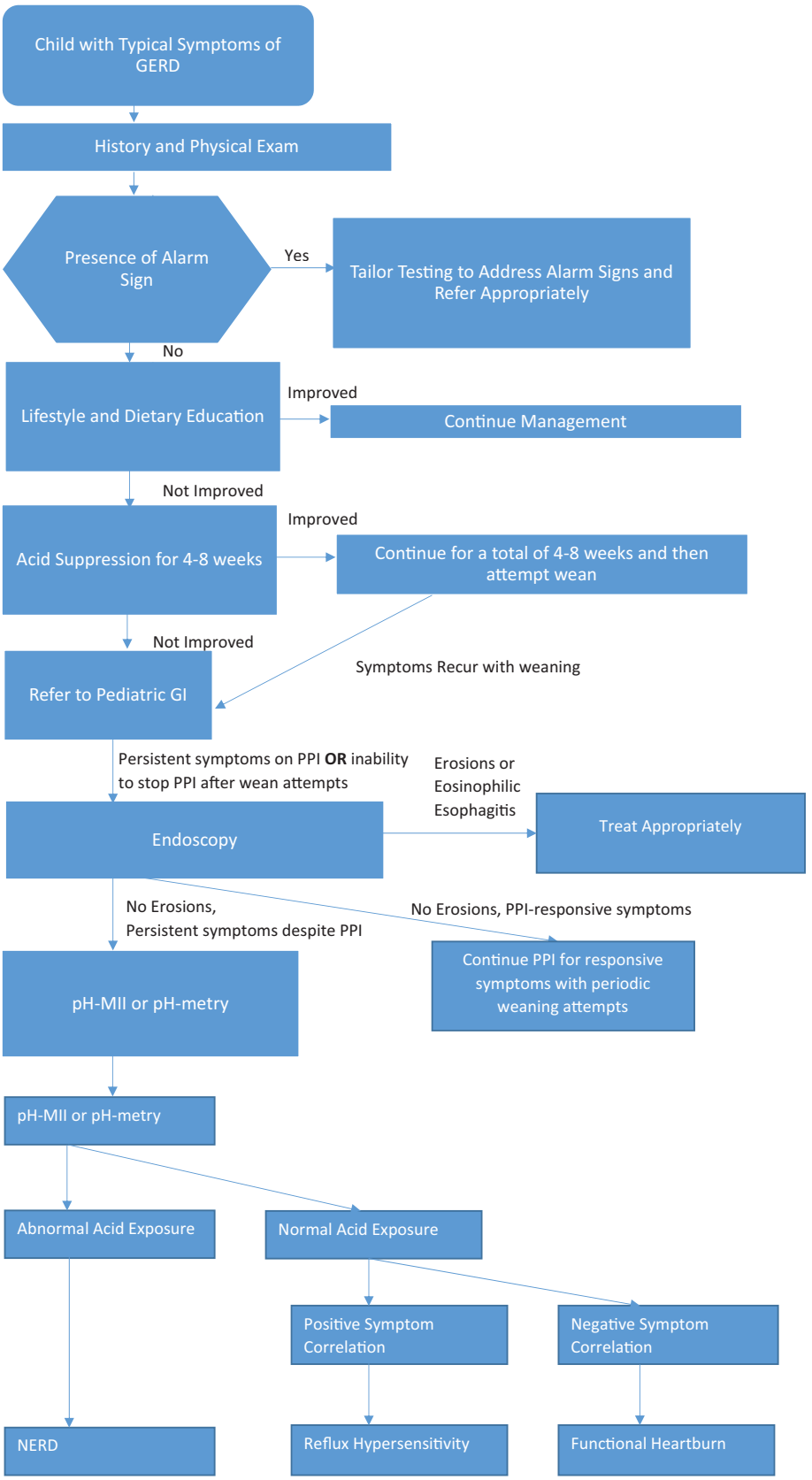
QUESTION 3: WHAT DIAGNOSTIC INTERVENTIONS HAVE ADDITIONAL VALUE TO HISTORY TAKING AND PHYSICAL EXAMINATION IN INFANTS AND CHILDREN WITH SUSPECTED GASTROESOPHAGEAL REFLUX DISEASE?

The diagnosis of GERD is based primarily on clinical suspicion, which can be strengthened by additional diagnostic investigations that are aimed to quantify and qualify GERD). Other diagnostic interventions may be utilized to rule out conditions other than GERD in the presence of specific diagnostic clues. In the absence of a single 'gold standard' investigation to diagnose GERD in infants or children, the diagnostic tests discussed in this section should be seen in this light.

Our search resulted in 2 original studies and 1 systematic review that were eligible for inclusion (25–27). After checking reference lists of this systematic review and the ESPGHAN/NASPGHAN 2009 and NICE 2015 guidelines (See Appendix A, Supplemental Digital Content 1, *http://links.lww.com/MPG/B265*, for summary of search strategy, results and study selection), 7 other original studies could be included, resulting in a total of 9 original studies with 8 studies reporting on pH-metry (27–34), 3 on endoscopy (28,30,33), 2 on GI-scintigraphy (27,28) and one each on biomarkers (26) and upper GI series (28). Characteristics of included studies can be found in Appendix B1 (Supplemental Digital Content 2, *http://links.lww.com/MPG/B266*). The QUADAS checklist can be found in Appendix C1 (Supplemental Digital Content 3, *http://links.lww.com/MPG/B267*) (7).

Barium contrast study:

The search identified 1 study comparing rates of gastroesophageal reflux events seen during barium imaging in symptomatic and asymptomatic infants and children ages 3 month old to



ALGORITHM 2. Diagnostic and therapeutic algorithm for typical reflux symptoms in the older child.

TABLE 1. Symptoms and signs that may be associated with gastroesophageal reflux disease in infants and children 0 to 18 years old

Symptoms	Signs
General	General
Discomfort/irritability*	Dental erosion
Failure to Thrive	Anemia
Feeding refusal	
Dystonic neck posturing (Sandifer syndrome)	
Gastrointestinal	Gastrointestinal
Recurrent regurgitation with/without vomiting in the older child	Esophagitis
Heartburn/chest pain†	Esophageal stricture
Epigastric pain†	Barrett esophagus
Hematemesis	
Dysphagia/odynophagia	
Airway	Airway
Wheezing	Apnea spells
Stridor	Asthma
Cough	Recurrent pneumonia associated with aspiration
Hoarseness	Recurrent otitis media

BRUE = brief resolved unexplained event; GERD = gastroesophageal reflux disease.
*If excessive irritability and pain is the single manifestation, it is unlikely to be related to GERD.
†Typical symptoms of GERD in older children.

17 years old (28). In this study, there were no definitions of how a positive test was defined so calculation of specificity or sensitivity was not possible.

Other Considerations for the Use of Barium Imaging

Other studies, while not meeting inclusion criteria, have shown that reflux events can be detected in as many as 50% of children undergoing radiologic imaging, regardless of symptoms. As such, routine use of upper GI barium contrast study in the evaluation of infants and children with GERD, especially uncomplicated GERD, is not supported by literature or clinical practice.

While the use of upper GI barium contrast to establish or negate a diagnosis of GERD in infants and children is not supported by literature nor clinical practice, the test does carry some utility in the evaluation of infants and children with alarm signs or in patients with symptoms that are particularly intense or not responsive to traditional therapies in order to evaluate for anatomic abnormalities. The test can be used to evaluate for other conditions that might mimic or predispose to GERD such as hiatal hernia, malrotation, pyloric stenosis, duodenal web, duodenal stenosis, antral web, esophageal narrowing, Schatzki's ring, achalasia, esophageal stricture, and esophageal extrinsic compression. One of the most important roles for barium imaging is in the evaluation of children who have had anti-reflux surgery who are symptomatic with persistent typical or atypical reflux symptoms, dysphagia or pain; barium imaging can be helpful to differentiate an obstructing fundoplication with esophageal stasis from a slipped or loose fundoplication (35,36).

TABLE 2. ''Red flag'' symptoms and signs that suggest disorders other than gastroesophageal reflux disease

Symptoms and signs	Remarks
General	
Weight loss	Suggesting a variety of conditions, including systemic infections
Lethargy	
Fever	
Excessive irritability/pain	
Dysuria	May suggest urinary tract infection, especially in infants and young children
Onset of regurgitation/vomiting >6 months or increasing/persisting >12–18 months of age	Late onset as well as symptoms increasing or persisting after infancy, based on natural course of the disease, may indicate a diagnosis other than GERD
Neurological	
Bulging fontanel/rapidly increasing head circumference	May suggest raised intracranial pressure for example due to meningitis, brain tumor or hydrocephalus
Seizures	
Macro/microcephaly	
Gastrointestinal	
Persistent forceful vomiting	Indicative of hypertrophic pyloric stenosis (infants up to 2 months old)
Nocturnal vomiting	May suggest increased intracranial pressure
Bilious vomiting	Regarded as symptom of intestinal obstruction. Possible causes include Hirschsprung disease, intestinal atresia or mid-gut volvulus or intussusception
Hematemesis	Suggests a potentially serious bleed from the esophagus, stomach or upper gut, possibly GERD-associated, occurring from acid-peptic disease*, Mallory-Weiss tear† or reflux-esophagitis.
Chronic diarrhea	May suggest food protein-induced gastroenteropathy‡
Rectal bleeding	Indicative of multiple conditions, including bacterial gastroenteritis, inflammatory bowel disease, as well as acute surgical conditions and food protein-induced gastroenteropathy rectal bleeding‡ (bleeding caused by proctocolitis)
Abdominal distension	Indicative of obstruction, dysmotility, or anatomic abnormalities

GERD = gastroesophageal reflux disease; NSAID = non-steroidal antiinflammatory drugs.
*Especially with NSAID use.
†Associated with vomiting.
‡More likely in infants with eczema and/or a strong family history of atopic disease.

TABLE 3. Differential diagnosis of gastroesophageal reflux disease*

Gastrointestinal obstruction	Other gastrointestinal disorders
Pyloric stenosis	Achalasia
Malrotation with volvulus	Gastroparesis
Intussusception	Gastroenteritis
Hirschsprung disease	Peptic ulcer
Antral/duodenal web	Eosinophilic esophagitis
Foreign body	Food allergy/intolerance
Incarcerated hernia	Inflammatory bowel disease
Superior mesenteric artery (SMA) syndrome	Pancreatitis
	Appendicitis
Neurologic	Infectious
Hydrocephalus	Sepsis/meningitis
Subdural hematoma	Urinary tract infection
Intracranial hemorrhage	Upper/lower airway infection
Intracranial mass	Otitis media
	Hepatitis
Metabolic/endocrine	Others
Galactosemia	Pediatric condition falsification (PCF)/factitious disorder by proxy (FDP)
Hereditary fructose intolerance	Child neglect or abuse
Urea cycle defects	Self-induced vomiting
Amino and organic acidemias	Cyclic vomiting syndrome
Fatty acid oxidation disorders	Rumination syndrome
Metabolic acidosis	
Congenital adrenal hyperplasia/adrenal crisis	
Toxic	Renal
Lead poisoning	Obstructive uropathy
Other toxins	Renal insufficiency
Cardiac	
Heart failure	
Vascular ring	
Autonomic dysfunction	

ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; GERD = gastroesophageal reflux disease; NASPGHAN = North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.
*Adapted from the ESPGHAN/NASPGHAN 2009 GERD guidelines.

Barium imaging in the evaluation of extraesophageal symptoms:

For patients with extraesophageal symptoms, barium imaging can serve several important roles, including evaluation for tracheoesophageal fistulae or of esophageal stasis putting patients at risk for aspiration. Videofluroscopic swallow studies (VFSS), while not assessing for gastroesophageal reflux, do assess for oropharyngeal dysphagia with resultant aspiration, the symptoms of which are mimickers of GERD (37,38). Pediatric studies have shown that neither the clinical history nor observed feeding sessions can accurately predict which patients have oropharyngeal dysphagia versus gastroesophageal reflux disease (37,39).

In conclusion, there is insufficient evidence to support the use of a barium contrast study for the primary diagnosis of GERD in infants and children.

Recommendations:

3.1 Based on expert opinion, the working group suggests not to use barium contrast studies for the diagnosis of GERD in infants and children.

Voting: 8, 8, 9, 9, 9, 9, 9, 9, 9, 9. (weak recommendation)

3.2 Based on expert opinion, the working group suggests to use barium contrast studies to exclude anatomical abnormalities.

Voting: 8, 8, 8, 9, 9, 9, 9, 9, 9, 9. (weak recommendation)

Ultrasonography:

The search did not identify any studies fulfilling our inclusion criteria.

Other considerations related to ultrasonography in the diagnosis of GERD:

Compared with the results of 24-hour esophageal pH testing as a diagnostic test for GERD, the sensitivity of color Doppler ultrasound performed for 15 minutes post-prandially is about 95% with a specificity of only 11%, and reflux frequency detected by ultrasound does not correlate with reflux index (RI) detected by pH monitoring (40,41). At present, ultrasound has no role as a routine diagnostic tool for GERD in children, but this test may be of use to evaluate for other conditions that might mimic GERD including, most importantly in the infant population, pyloric stenosis. Abdominal ultrasound may also pick up other diagnoses, which may trigger symptoms of discomfort and vomiting including diagnoses such as hydronephrosis, uretero-pelvic obstruction, gallstones and ovarian torsion. Similar to barium study, ultrasound can detect hiatal hernia, length and position of the LES relative to the diaphragm and magnitude of the gastroesophageal angle of His. It has also been proposed as a diagnostic test for gastric dysmotility, which may have implications from a reflux perspective.

In conclusion, there is no evidence to support ultrasonography for the diagnosis of GERD in infants and children.

Recommendations:

3.3 Based on expert opinion, the working group suggests not to use ultrasonography for the diagnosis of GERD in infants and children.
Voting: 8, 8, 8, 9, 9, 9, 9, 9, 9, 9. (weak recommendation)

3.4 Based on expert opinion, the working group suggests to use ultrasonography to exclude anatomical abnormalities.
Voting: 8, 8, 8, 9, 9, 9, 9, 9, 9, 9. (weak recommendation)

Esophago-gastro-duodenoscopy (EGD) with/without biopsy:

The search identified 3 studies meeting our inclusion criteria (28,33,42). EGD has 3 roles in the evaluation of symptomatic children: to diagnose erosive esophagitis, to diagnose microscopic esophagitis, and to diagnose other conditions mimicking GERD. Erosive esophagitis is defined as visible breaks in esophageal mucosa. Microscopic esophagitis is defined as the presence of eosinophils, papillary lengthening, and/or basal cell hyperplasia. All 3 studies included in this analysis reported on the visual presence of erosions, and 2 studies also reported on histologic esophagitis. In patients with GERD defined as the presence of troublesome symptoms, the likelihood of having erosive esophagitis endoscopically ranges from 15% to 71% among studies. Similarly, in patients with troublesome symptoms, the likelihood of finding (ie, sensitivity) microscopic esophagitis was 83% to 88%. In these studies, the negative predictive value (NPV) of a macroscopically and histologically normal endoscopy was relatively low ranging from 62% to 73%, which suggests that a normal endoscopy does not necessarily rule out the possibility of GERD (33,42). In the studies by Ravelli et al and Cucchiara et al, no data on the endoscopic appearance of the mucosa were provided for the control group (33,42). Arasu et al, reporting on the endoscopic mucosal appearance in control patients, found that the NPV was only 33% in diagnosing GERD (28). These findings indicate that biopsy without hallmarks of esophagitis or the absence of macroscopic lesions does not rule out the presence of GERD. In all 3 studies, if mentioned, histology and macroscopic appearance were normal in the control group, which automatically leads to a reported specificity and NPV of 100%. Visible, endoscopic erosions seen during EGD in the appropriate clinical context confirm a diagnosis of GERD. However, GERD may be present despite normal endoscopic appearance of the esophageal mucosa as well as in the absence of histological abnormalities.

In conclusion, there is insufficient evidence to support the use of EGD with/without biopsy for the diagnosis of GERD in infants and children.

Other considerations related to EGD in the diagnosis of GERD:

EGD is useful to evaluate the mucosa in the presence of alarm symptoms (such as hematemesis), to detect complications of GERD (such as strictures, Barrett esophagus), to diagnose conditions that predispose to GERD (such as hiatal hernia) or to diagnose conditions that might mimic GERD (such as eosinophilic esophagitis, infectious esophagitis). Visible breaks in the esophageal mucosa are the endoscopic sign of greatest inter-observer reliability based on adult studies (11). However, no studies in adults or in children support that microscopic esophagitis without evidence of erosive esophagitis is adequate to diagnose GERD defined as the presence of troublesome symptoms though microscopic esophagitis may, in some contexts, signify the presence of pathologic acid reflux defined by pH-metry (43). The primary role for esophageal histology is to rule out other conditions in the differential diagnosis, such as eosinophilic esophagitis, Crohn's disease, Barrett esophagus, infection and others.

When biopsies from endoscopically suspected esophageal metaplasia show columnar epithelium, the term Barrett esophagus should be applied and the presence or absence of intestinal metaplasia specified.

EGD under general anesthesia can be regarded as a safe procedure in pediatric patients. A study involving 13 pediatric facilities that used the PEDS-CORI (Pediatric Endoscopy Database System Clinical Outcomes Research Initiative) found an overall immediate complication rate of pediatric EGD of 2.3% over 10,236 procedures performed in 9,234 patients (complication rates of 1.7% for general anesthesia vs 3.7% for IV sedation) (44). Based upon a survey in almost 400 children undergoing EGD under general anesthesia, most common complications or adverse events were only minor, including sore throat or hoarseness in approximately one-third of patients (45). Nevertheless, EGD cannot be considered a non-invasive procedure, as it involves pre-procedure assessments, dietary restrictions, patient preparation, and specialized teams of pediatric gastroenterologists, pediatric intensive care physicians and pediatric endoscopy nurses (46).

The role of endoscopy in the evaluation of extraesophageal symptoms:

The rate of erosive esophagitis in children presenting with solely extraesophageal symptoms is not known and is complicated by the widespread use of Proton Pump Inhibitors (PPIs). Up to 32% of children presenting solely with extraesophageal symptoms have microscopic esophagitis, and up to 8% of children with these symptoms have eosinophilic esophagitis, only presenting with cough or other respiratory symptoms (47–49). Therefore, the main reason for endoscopy in this population with extraesophageal symptoms is to uncover reflux masqueraders such as eosinophilic esophagitis. Endoscopy can also be used to relieve esophageal outlet obstruction (from fundoplication, and untreated or partially treated achalasia) causing stasis with resultant cough and aspiration, or to diagnose candida esophagitis in children treated with inhaled steroids.

Performance of endoscopy on or off therapy:

One of the most controversial issues currently around the performance of endoscopy is whether it should be performed while the patient is on or off acid suppression. The field has evolved over time with a greater understanding of eosinophilic esophagitis and, more recently, PPI-responsive eosinophilic esophagitis (EoE). While originally the diagnosis of EoE was made upon the presence of esophageal eosinophils in patients with either a normal pH-metry study or unresponsiveness to an 8-week course of PPI therapy, recently a subgroup of EoE has emerged that is responsive to PPIs. Therefore, if patients are treated initially with a course of PPIs, esophageal biopsies may not show inflammation and the patient will thereby be misdiagnosed as having non-erosive reflux disease (NERD), hypersensitive esophagus, or may undergo additional unnecessary testing because the initial diagnosis was missed. In light of these concerns, recent guidelines for adults have suggested that patients undergo endoscopy off of acid suppression therapy (50,51). The benefit to this approach is that patients will receive a definitive diagnosis at the time of the first endoscopy but the negative side is that patients will need to undergo a second endoscopy to assess for healing after instituting therapy. Prospective studies are clearly needed to determine an algorithm that maximizes diagnostic yield, reduces unnecessary medication and procedure costs, and results in more rapid improvement in outcomes. At this time, there is insufficient prospective data to recommend a single approach, and the pros and cons to both approaches should thus be discussed with patients and their families.

Recommendations:

3.5 The working group suggests not to use esophago-gastro-duodenoscopy to diagnose GERD in infants and children.
Voting: 7, 8, 8, 8, 9, 9, 9, 9, 9, 9. (weak recommendation)

3.6 Based on expert opinion, the working group suggests to use esophago-gastro- duodenoscopy with biopsies to assess complications of GERD, in case an underlying mucosal disease is suspected, or prior to escalation of therapy.
Voting: 6, 8, 8, 9, 9, 9, 9, 9, 9, 9. (strong recommendation)

Extraesophageal biomarkers:

Using the GRADE criteria, the only study eligible for inclusion in this section was one on salivary pepsin in which the authors compared the rate of salivary pepsin positivity in preterm infants with clinical signs and symptoms of GERD (26). Salivary pepsin was detected in 45/101 (44.5%) infants. Mouth swabs were positive in 26/36 (72%) infants with GERD and in only 19/65 (29%) infants without GERD ($P < 0.001$). Overall, the sensitivity, specificity, positive predictive value and negative predictive value of pepsin to diagnose GERD were of 72%, 71%, 58%, and 82%, respectively. Because almost one-third of control patients was pepsin positive, the utility of salivary pepsin is still debated, and the technology is limited by a lack of normative values for salivary pepsin in the pediatric population.

Other considerations for the use of extraesophageal biomarkers:

- Pepsin
  Other studies, not fulfilling the conclusion criteria of the present guideline, measured the diagnostic value of salivary pepsin by comparing it to results from pH-MII testing and found this technique to be of limited sensitivity with results depending on concentration cut-off used (52,53). Apart from saliva, pepsin has also been measured in bronchoalveolar lavage (BAL) and middle ear fluid. Findings of these studies also most importantly suggest a lack of sensitivity (ranging from 57% to 84%) of the biomarker (54–60).
- Lipid-laden macrophage index
  Studies comparing the lipid-laden macrophage index in BAL fluid to impedance and endoscopy fail to show any relationship. This suggests that the lipid laden macrophage index is not a biomarker of gastroesophageal reflux and should therefore not be used for diagnosis (52,54,61).
- Bilirubin
  Continuous monitoring of bilirubin using fiberoptic measurements in the esophagus is limited by the required dietary restriction during testing, thereby limiting its reliability and sensitivity. This test is therefore not recommended for use in clinical practice (62,63).

In conclusion, evidence to support routine use of biomarkers such as salivary pepsin is insufficient to establish a diagnosis of extraesophageal reflux disease.

Recommendations:

3.7 The working group suggests that salivary pepsin should not be used for the diagnosis of GERD in infants and children.
Voting: 7, 7, 8, 8, 8, 8, 8, 9, 9, 9. (strong recommendation)

3.8 Based on expert opinion, the working group suggests not to use currently available extraesophageal biomarkers for the diagnosis of GERD in infants and children.
Voting: 7, 7, 8, 8, 8, 8, 8, 9, 9, 9. (strong recommendation)

Manometry/motility studies:

The search did not identify any studies fulfilling our inclusion criteria.

Other considerations related to esophageal manometry in the diagnosis of GERD:

Manometry and other motility studies are designed to discriminate between normal GI physiology and neuromuscular diseases and can be used to identify the lower esophageal sphincter in order to accurately place pH- or pH-impedance probes. The current gold standard for the evaluation of esophageal motility is high-resolution manometry, which utilizes a catheter with closely placed pressure sensors (1–2 cm apart) to allow a more detailed view of intraluminal pressure activity than conventional manometry. High resolution manometry was the key technique used to identify transient lower esophageal sphincter relaxations (TLESRs) as the predominant mechanism of GER in patients and it is also helpful in identifying other mechanisms of reflux such as hypotensive LES pressure or other risk factors for reflux such as the presence of a hiatal hernia. When combined with impedance, high resolution esophageal manometry (HRM) can also quantify the proportion of TLESRs associated with bolus movement into the esophagus, but is not predictive of GERD. Another possible application for HRM is in the pre- and post-operative evaluation of children undergoing fundoplication for the treatment of GERD. Although previous studies suggested that there was little role for manometry in predicting the outcome of fundoplication (64), newer modalities may confer some practical benefit. Loots et al, for example, used a novel pressure-flow analysis technique to identify esophageal motility parameters that are associated with post-operative complications such as dysphagia. They created a Dysphagia Risk Index that seemed better able to predict post-operative dysphagia in both adults supported by an uncontrolled pilot study of 10 children (65,66). Additionally, based upon pediatric studies, HRM with or without impedance may be of value to assess for ''R waves'' and retrograde bolus flow to diagnose rumination, a mimicker of intractable reflux symptoms (67–71).

HRM in the evaluation of extraesophageal symptoms HRM with impedance can rule out esophageal motility disorders whose presenting symptoms are often similar to GERD. HRM with impedance can not only detect abnormalities of peristalsis and esophageal outlet obstruction but also associated abnormalities in bolus transit. Esophageal stasis puts patients at high risk for aspiration, not from reflux but due to the retained fluid secondary to the dysmotility or obstruction, with signs and symptoms often being similar to GERD. Manometry can also be paired with pH-MII in 24-hour reflux studies to improve the cough-reflux correlation; manometrically coughs appear as high pressure, simultaneous pressure spikes on the pH-MII tracing. The accuracy of the device is increased by the fact that every cough-reflux pair can be detected (72).

In conclusion, there is no evidence to support the use manometry for the diagnosis of GERD in infants and children.

Recommendations:

3.9 Based on expert opinion, the working group suggests not to use manometry for the diagnosis of GERD in infants and children.
Voting: 8, 8, 8, 8, 8, 8, 8, 9, 9, 9. (strong recommendation)

3.10 Based on expert opinion, the working group suggests to consider the use of manometry when a motility disorder is suspected.
Voting: 6, 8, 8, 8, 8, 8, 8, 9, 9, 9. (strong recommendation)

Scintigraphy:

The search identified 2 studies on scintigraphy (27,28). Of these, one was carried out in children aged up to 17 years (28) and the other in infants/children up to 2 years with wheezing symptoms (27). In 1 study, there was no clear definition of GERD provided by authors making interpretation of the results difficult (27,28). In the study by Arasu et al, where positive scintigraphy (defined as 'any esophageal activity') was identified, sensitivity and specificity were only moderate (69% and 78%, respectively) (28). The other study did not provide cut-off values for test positivity, and no calculations on sensitivity or specificity could be performed (27,28).

Other considerations for the use of scintigraphy in the evaluation of GERD:

Gastric scintigraphy is the standard technique for the assessment of gastric emptying, but protocols also exist for the evaluation of GER in children (73–75). Although guidelines now exist for its use to diagnose reflux in children, clinical application has been limited by a lack of standardization of the technique (76). Apart from showing refluxed tracer into the esophagus, gastric scintigraphy may reveal impaired gastric emptying which may be a risk factor for GERD or may reveal tracer in the bronchi suggesting pulmonary aspiration either from direct aspiration of the tracer or from aspiration of refluxed gastric contents (77). Performance of gastric scintigraphy may be indicated when GERD symptoms are not responding to standard therapies and other diagnoses or triggers such as delays in gastric emptying are being considered.

In conclusion, there is insufficient evidence to support the use of scintigraphy for the diagnosis of GERD in infants and children.

Recommendation:
3.11 Based on expert opinion, the working group suggests scintigraphy should not be used for the diagnosis of GERD in infants and children.
Voting: 8, 8, 8, 9, 9, 9, 9, 9, 9, 9. (strong recommendation)

Trial of transpyloric or jejunal feeding:

The search did not identify any studies fulfilling our inclusion criteria.

Other considerations for the use of transpyloric feeding to diagnose GERD:

While transpyloric feeding is often used to treat intractable GERD (Question 6), the use of transpyloric feeding as a diagnostic test for GERD has not been studied. However, because transpyloric feeding reduces the reflux burden to a similar extent as fundoplication, additional studies using transpyloric feeding as a diagnostic test are needed (78,79)

In conclusion, there is no evidence to support the use of transpyloric feeding trials for the diagnosis of GERD in infants and children.

Recommendation:
3.12 Based on expert opinion, the working group suggests that transpyloric/jejunal feeding trials should not be used for the diagnosis of GERD in infants and children.
Voting: 6, 7, 8, 8, 8, 9, 9, 9, 9, 9. (moderate recommendation)

Proton pump inhibitor (PPI) trials:

The search did not identify any studies fulfilling our inclusion criteria.

Other considerations for the use of proton pump inhibitors as a diagnostic test for GERD:

Short 1 to 2-week trials of PPIs have been used diagnostically in adults with typical reflux symptoms (''PPI test''). This test is based on the hypothesis that if symptoms respond to PPIs, they are therefore GERD-related and a diagnosis is made. While no pediatric studies have been designed to validate this test, we did evaluate therapeutic trials in infants and children during which early time points for symptom resolution were assessed. The discussion below relates to acid suppression for diagnosis, and not for treatment of GERD. Because no studies meet inclusion criteria, the recommendations are based on assessment of intermediate endpoints of treatment trials.

- Results from studies in infants
  Five RCTs of PPIs in preterm and full term infants with treatment periods ranging from 2 to 4 weeks have been published. None of the trials show symptom reduction over placebo regardless of the trial length. Based on these results, a short trial of a PPI is not recommended as a diagnostic test for infants (80).
- Results from studies in children
  Several studies, both open-label and therapeutic RCTs, assessing the effect of PPIs on GERD symptom reduction in children with and without esophagitis, showed that the greatest symptomatic improvement occurs in the first 2 to 4 weeks of PPI administration, suggesting that this duration may be sufficient as a diagnostic test for GERD in this population (81–84) Other treatment trials have used longer courses of PPIs for treatment without assessment of symptom resolution at earlier endpoints so the assessment of a shorter ''PPI test'' for symptom resolution could not be evaluated (85). Because these studies were not powered to assess symptom resolution at interim time points and because of concern that some patients have persistent symptoms related to inflammation after only 2 to 4 weeks of therapy, a diagnostic trial window of 4 to 8 weeks was chosen by the working group. However, shorter courses may be applicable and preferred, particularly when the clinical suspicion for reflux is low or the concern for side effects is high.
- Results from studies in adults
  There are data supporting the use of a PPI trial in the diagnosis of GERD in adult patients presenting with typical symptoms. Initial studies suggest that a 1 to 2 week trial is adequate for the diagnosis with a sensitivity ranging from 78% to 83% compared with the reference test used (erosive esophagitis or pH-detected pathologic reflux) (86–88). In another adult study, PPI responsiveness after a 7 day trial in adults with non-erosive disease predicted an 85% probability of complete resolution of heartburn after 4 weeks; this study is of particular importance as it is the only one that applies symptom resolution as the ''gold standard'' for diagnosis of GERD, the definition used in these guidelines (89). Despite the possible value of a PPI trial as a diagnostic test for GERD, in adults with typical symptoms, more than 50% of patients with typical symptoms may not respond to acid suppression and require additional testing (90,91).
- PPI use as a diagnostic test for extraesophageal symptoms
  No data conclusively support the use of PPIs in the diagnosis of extraesophageal symptoms in the pediatric literature (92,93). Because of the heterogeneous nature of extraesophageal symptoms, patient selection and the assessment of clinical improvement in these symptoms, which may have a multitude of causes, are difficult. In pediatrics, only 1 randomized, blinded placebo controlled study by Holbrook et al addresses the use of PPIs in the treatment of asthma (93). While this was powered as a 24 week treatment trial, interval analyses at earlier time points

(1 or 2 months) after starting therapy show no symptomatic improvement suggesting that even short trials (ie, diagnostic trials) are not beneficial. In the infant population, one 2-week RCT of lansoprazole was powered to assess improvement in GERD symptoms but as secondary outcomes, Orenstein et al assessed changes in the extraesophageal symptoms of coughing, wheezing and hoarseness. The authors found no benefit of lansoprazole compared with placebo for extraesophageal symptoms, but again this study was not powered for these outcomes. Based on these 2 RCTS, insufficient evidence exists to support a short trial of PPIs as a diagnostic test for extraesophageal reflux symptoms. Finally, a recent Cochrane review failed to show a benefit of PPIs for cough in children (94).

In conclusion, there is no evidence to support empirical PPI therapy for the diagnosis of GERD in infants. Expert opinion suggests that in an older child or adolescent with typical symptoms suggesting GERD, a diagnostic trial of PPIs can be justified for 4 to 8 weeks.

Recommendations:

3.13 Based on expert opinion, the working group suggests that a trial of PPIs should not be used as a diagnostic test for GERD in infants.
Voting: 5, 6, 7, 7, 7, 8, 8, 9, 9, 9. (weak recommendation)

3.14 Based on expert opinion, the working group suggests a 4 to 8 week trial of PPIs for typical symptoms (heartburn, retrosternal or epigastric pain) in children as a diagnostic test for GERD.
Voting: 3, 7, 7, 7, 8, 8, 8, 9, 9, 9. (weak recommendation)

3.15 Based on expert opinion, the working group suggests that trial of PPIs should not be used as a diagnostic test for GERD in patients presenting with extraesophageal symptoms.
Voting: 7, 8, 8, 8, 8, 8, 8, 9, 9, 9. (weak recommendation)

pH-Metry/Wireless pH Recording

The search identified 7 studies assessing the value of pH-metry for the diagnosis of GERD in children (27–34). In 3 studies, no *P* values or cutoff values for test-positivity were provided, so neither sensitivity nor specificity data could be extracted for these studies (29,34,42). In the study by Ravelli et al, none of the controls underwent pH-metry, also hampering sensitivity and specificity analysis (33). Two studies used values of controls as normal values and inherently show a pH-metry specificity of 100% (31,32). The last and most recent study used the Reflux Index (RI, defined as the percentage of time that pH $<$ 4) to determine pathological GERD (where abnormal was defined as pH $<$ 4 for $>$10% for infants $<$1 year and 5% infants $>$1 year) (27). It should however be noted that for this population, although attempts have been made, no ''true'' normative values have been established because of the ethics of performing invasive studies in healthy infants and children (75,95). The authors found the RI measured by pH-metry had a sensitivity and specificity 50% and 82%, respectively, using history and physical examination as the gold standard method for diagnosing GERD.

Other considerations for the use of pH-metry as a diagnostic test for GERD:

Limitations to pH-metry technology include:

1. Determination of the value pH-metry as a diagnostic tool for GERD and to differentiate it from GER is difficult because of lack of a gold standard for comparison. Early pH-metry studies used esophageal manometry, endoscopy, scintigraphy, symptom presence and barium imaging as the gold standard methods to diagnose reflux events (28,29,31). All of these ''gold standards'' have significant limitations, with high rates of false positivity.
2. Obtaining data in healthy controls is not ethically feasible because of the invasive nature of pH-metry, hindering determination of true ''normal'' values.
3. Non-acid reflux particularly in young infants and children is common, and pH-metry is blind to reflux episodes with pH $>$ 4, which comprises 45% to 89% of pediatric reflux episodes (96).
4. pH-metry poorly identifies full column reflux (97,98) and fails to correlate symptoms with esophageal acid events (97), making it an inadequate tool for the diagnosis of extraesophageal symptoms.
5. While correlation of symptoms with reflux events is one of the main indications for pH- metry, patients/parents often fail to report symptoms, a factor which compromises symptom correlation (72). In addition, the appropriate time frame in which to consider a symptom correlated with reflux is debated (99,100).

Indications for pH-metry:

Despite these limitations, the working group considers several indications for performance of pH-metry in the evaluation of GERD when pH-MII is not available (See also under pH-MII):

1. Diagnosis of acid related disorders:
   pH-metry can be helpful in correlating symptoms with acid reflux episodes. This is of particular importance in differentiating NERD from other acid disorders, such as functional heartburn and hypersensitive esophagus or in conditions that are clearly acid related such as dental erosions (101,102). In addition, pH-metry can be helpful in clarifying the role of acid in patients with esophageal eosinophilia (103–105).
2. Correlate persistent symptoms with acid GER events (see also under pH-MII)
3. Efficacy of acid suppression
   In patients with persistent symptoms or esophagitis in high risk patients (eg, EA, cystic fibrosis, or neurologically compromised patients) despite acid suppression, performance of pH-metry may be helpful in determining the degree of breakthrough acid in patients on therapy as these patients may be inadequately acid suppressed on standard medication doses (106,107). (Limitations—see also under pH-MII)

In conclusion, there is insufficient evidence to support the routine use of pH-metry for the diagnosis of GERD in infants and children.

Other pH-based diagnostic testing options:

Wireless pH recording has been proposed as an alternative to pH probe monitoring. During endoscopy, the wireless recording device is clipped to the esophagus. The advantage of the device is that the patient does not have a catheter in the nose, so for some children (eg, those with developmental delay or autism or in patients with cystic fibrosis and chronic cough) the wireless device is preferable. In addition, for patients with exercise induced GERD symptoms, the wireless recording device is often more comfortable when exercising (including swimming). Finally, the wireless device records pH changes for a minimum of 48 hours but some studies have reported up to 5 days of recording. Pediatric studies have shown that the wireless pH recording results are comparable to the pH probe in patients that underwent both simultaneously (108). Pediatric studies have also shown that 2 days of recording may allow for improved reflux detection due to the additional recording

time (109). Complications of the device occurred in 0% to 15% of patients, including esophageal tears, chest pain, and device failure (failure to record or early detachment) (108–110). While concerns have been raised about performing the studies after sedation, pediatric studies have failed to show a significant anesthesia effect beyond 2 to 6 hours after placement (111,112).

Oropharyngeal pH monitoring has also been proposed as a less invasive test to measure changes in pharyngeal pH as an indicator of extraesophageal reflux. A catheter is placed in the nose with the sensor lying immediately above the uvula. In a single pediatric study by Chiou et al, 15 patients underwent simultaneous oropharyngeal pH monitoring and pH-MII testing (97). The authors failed to show any relationship between changes in the oropharyngeal pH and esophageal reflux events detected by pH-MII suggesting that oropharyngeal monitoring does not represent GER events. Adult studies have since shown similar results (113,114). Therefore, because of this inadequate sensitivity, oropharyngeal monitoring is not recommended.

pH of exhaled breath condensate has been proposed as a method for diagnosing extraesophageal reflux, but preliminary data indicate that it lacks the sensitivity needed to discriminate between patients with and without pathologic reflux (115).

Other testing for extraesophageal symptoms:

Airway appearance: While earlier studies in adults and children suggested that there may be a relationship between the appearance of the larynx and evidence of GER, these studies were limited because they were neither prospective nor blinded and the diagnosis of reflux was made using insensitive tools such as oropharyngeal pH monitoring or barium imaging. In a single prospective pediatric study, in which airway exams were blindly scored by 3 otolaryngologists in children undergoing pH-MII testing for respiratory symptoms, no relationship was found between laryngeal appearance scored by using a validated scoring system, the reflux finding score, and any reflux parameter by pH-MII. These findings suggest that the appearance of the airway does not correlate with pathologic reflux (116).

Recommendations:

3.16 Based on expert opinion, when pH-MII is not available, the working group suggests to consider to use pH-metry only to

1. Correlate persistent troublesome symptoms with acid gastroesophageal reflux events (See also under pH-MII) **Voting: 6, 7, 7, 7, 7, 8, 8, 9, 9. (strong recommendation)**
2. Clarify the role of acid reflux in the etiology of esophagitis and other signs and symptoms suggestive for GERD. **Voting: 6, 7, 7, 7, 7, 8, 8, 9, 9. (strong recommendation)**
3. Determine the efficacy of acid suppression therapy. **Voting: 6, 7, 7, 7, 7, 9, 8, 8, 9. (strong recommendation)**

pH-Impedance Monitoring (pH-MII)

The search did not identify any studies fulfilling our inclusion criteria.

Other considerations when using pH-MII for the diagnosis of GERD:

- pH based testing versus pH-MII
  The advantage of pH-MII above the sole monitoring of the esophageal pH lays its ability to accurately detect (1) refluxate with pH $<$ 4 and greater than 4, (2) full column refluxate, (3) liquid and gas reflux, and (4) drops in esophageal pH due to reflux versus swallow-related drops in pH. Because of these advantages, in validation studies, pH-MII had a high sensitivity compared to pH-metry for the detection of reflux episodes, particularly when non-acid reflux was prevalent (eg, patients taking acid suppression, infants who are fed frequently) (117–125). With the advent of pH-MII, the importance of refluxate with pH $>$ 4 was realized. In the literature, 2 terms are used interchangeably to describe reflux with pH $>$ 4: non-acid reflux and weakly acidic reflux. For the purposes of this discussion, we will use the term non-acid reflux, which may also include (weakly) acidic reflux.
  Despite the advantages of pH-MII over pH-metry, there are still some limitations to the technology:
  1. pH-MII technology is not available in all medical centers.
  2. As with pH-metry, defining reference ranges is limited by the lack of true control patients. Nevertheless, some attempts to establish normal values in pediatrics have been made, albeit all in symptomatic children (126,127).
  3. In patients with motility disorders or significant esophagitis, pH-MII (both software and manually analyzed) may underestimate the amount of reflux episodes as a result of low baseline impedance values, compromising the ability for baselines to drop by more than 50%, the accepted definition of reflux by impedance. While a low impedance baseline may alert the clinician to the presence of esophagitis, it does not avert the need for endoscopy (128,129).
  4. Despite availability of guidelines (130), considerable diversity exists in performance and interpretation of pH-MII recordings among users, with diverging results of inter- and intra-observer reproducibility of studies (130–133). Additionally, analysis is time-consuming and is best performed by those with considerable expertise.
  5. No studies have yet been performed in pediatrics that convincingly show that the results of pH-MII testing influence clinical outcomes (134,135).
  6. While correlation of symptoms with reflux events is one of the main indications for pH- MII, patients/parents fail to report more than 50% of symptoms (as with all reflux testing) compromising symptom correlation (72). In addition, the appropriate time window by which it can be established that a symptom is correlated with reflux is debated (99,100).

- Clinical considerations to perform pH-MII
  Despite the above limitations, the working group endorses several indications for the performance of pH-MII in the evaluation of GERD.

1. Differentiate patients with NERD, hypersensitive esophagus and functional heartburn in patients with normal endoscopy.
   The recently published Rome IV criteria for esophageal disorders included new classifications for adults with typical GERD symptoms including chest pain and heart burn. In patients with persistent typical symptoms despite acid suppression, pH-MII can clarify the diagnosis of NERD (pathologic reflux regardless of symptom correlation), hypersensitive esophagus (*positive* symptom correlation with either acid or nonacid reflux events but no pathologic reflux), and functional heartburn (*negative* symptom correlation and no pathologic reflux; see "Summary of the Definitions" for full definitions) (136). A single pediatric study examines the incidence of the Rome IV subgroups in pediatrics. Mahoney et al used these new Rome IV criteria to classify 45 children with typical reflux symptoms with no evidence of endoscopic erosions. Of these 45 patients, 27% of were categorized with

NERD, 29%, with reflux hypersensitivity and 44% with functional heartburn (137). Distinguishing these disease entities may have therapeutic impact. Based upon adult literature, reflux hypersensitivity may be treated with traditional reflux therapies (medications, fundoplication), whereas functional heartburn may be treated with neuromodulators (138–140).

2. Determine the efficacy of acid suppression therapy.
While pH-metry can be used to determine if there is persistent esophageal acid exposure despite therapy, pH-MII catheters can determine this as well as how much non-acid reflux is present in children taking acid suppression. Rosen et al found that the mean-sensitivity of MII-pH was $76 \pm 13\%$ compared to pH-metry whose mean-sensitivity was $80 \pm 18\%$. When patients taking acid suppression were studied, the mean-sensitivity of the pH-metry dropped to $47 \pm 36\%$, whereas the mean-sensitivity of MII-pH in treated patients was $80 \pm 21\%$ (123). Therefore, pH-MII should be considered as a diagnostic test in symptomatic patients taking acid suppression.
3. Correlate persistent troublesome symptoms with acid and non-acid gastroesophageal reflux events
Several studies in infants and children using pH-MII in the postprandial period highlight the importance of non-acid reflux events in this period, making pH-MII the preferred choice for measurement of reflux events in children with predominant postprandial symptoms that would be missed by standard pH-metry alone (119,124,141–143). The 7 impedance sensors distributed throughout the esophagus on the pH-MII catheter allow accurate detection of full column reflux events, which may be important in patients with extraesophageal symptoms (97,118).
4. Clarify the role of acid and non-acid reflux in the etiology of esophagitis and other signs and symptoms suggestive for GERD.
pH-MII monitoring plays an important role in the correlation of symptoms with both acid and non-acid reflux events with improved symptom correlation compared to pH-metry alone. The combination of pH-MII has proven useful for the evaluation of symptom correlations between reflux episodes and symptoms such as pain/irritability, apnea, cough, other respiratory symptoms, and behavioral symptoms (118,144–147). pH-MII, as with pH-metry, may also clarify the role of acid and non-acid reflux in the generation of esophagitis, though data are conflicting on the relationship between esophagitis and acid and non-acid reflux events measured by pH-MII (148,149).
   - **Study to be done on or off acid suppression?**
   No pediatric studies have examined if pH-MII testing should be performed on or off acid suppression. If the goal of testing is to determine the efficacy of therapy in persistently symptomatic patients, testing should be performed *on* acid suppression. If the goal is symptom correlation, several adult studies support the performance of pH-MII testing *off* acid suppression because of an increased yield of acid-related symptoms (150,151).
   - **Symptom association:**
   Three main symptom indices are used to correlate reflux episodes with symptoms: the symptom index (SI), symptom sensitivity index (SSI), and symptom association probability (SAP) (152–154). While some conflicting data exist depending on the symptom index chosen, pH-MII results in a higher degree of symptom association compared with pH-metry alone. However the theoretical benefits of individual symptom indices is still being debated. Although pediatric studies suggest the SI and the SAP are most frequently positive, no studies prove that one index is superior to another in predicting response to therapies in children. Due to a lack of evidence showing benefit in predicting outcomes, no index is recommended over another at this time (130).

In conclusion, there is insufficient evidence to support the use of pH-MII as a single technique for the diagnosis of GERD in infants and children.

3.17 Recommendations:
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
Voting: 6, 7, 7, 7, 8, 8, 8, 9, 9. (strong recommendation)
2. Clarify the role of acid and non-acid reflux in the etiology of esophagitis and other signs and symptoms suggestive for GERD.
Voting: 6, 7, 7, 7, 8, 8, 8, 9, 9. (weak recommendation)
3. Determine the efficacy of acid suppression therapy.
Voting: 6, 6, 7, 7, 7, 9, 8, 8, 9. (weak recommendation)
4. Differentiate NERD, hypersensitive esophagus and functional heartburn in patients with normal endoscopy.
Voting: 6, 6, 6, 7, 7, 7, 8, 9, 9, 9, 9. (weak recommendation)

QUESTION 4: WHAT NON-PHARMACOLOGIC TREATMENT OPTIONS ARE EFFECTIVE AND SAFE FOR THE REDUCTION OF SIGNS AND SYMPTOMS OF GASTROESOPHAGEAL REFLUX DISEASE?

Three original studies and 2 systematic reviews were eligible for inclusion. After checking reference lists of these systematic reviews and the ESPGHAN/NASPGHAN 2009 and NICE 2015 guidelines (See Appendix A, Supplemental Digital Content 1, *http://links.lww.com/MPG/B265*, for summary of search strategy, results and study selection), 16 original studies could be included 1 trial on positional therapy, 1 on massage therapy and 14 on feeding modifications (1,3,155–170). Characteristics of included studies can be found in Appendix B2 (Supplemental Digital Content 2, *http://links.lww.com/MPG/B266*). GRADE profiles can be found in Appendix D1 (Supplemental Digital Content 4, *http://links.lww.com/MPG/B268*).

Feeding modifications including formula or food thickeners, reduced feeding volumes or more frequent feedings and extensively hydrolyzed or amino-acid based formula, the latter of which should be reserved for patients with severe symptoms not responsive to a protein hydrolysate formula.

Thickened Feeding

The search identified 14 studies on the use of thickened feedings. No studies on the use of reduced feeding volumes, more frequent feedings, or extensively hydrolyzed or amino acid–based formula met our inclusion criteria. All studies were conducted in infants with signs and symptoms of GER as defined by the authors (1,156–169). Although no studies meet the inclusion criteria specifically assessing the use of thickened feedings in infants or children in GERD, based on expert opinion, the results found on

the occurrence of regurgitation/vomiting in infants with GER are most likely to be extrapolated to infants with GERD. The overall quality of evidence of included studies was low to very low and methodology and definitions for GER varied widely among studies (Appendices B2 and D1, Supplemental Digital Content 2 and 4, *http://links.lww.com/MPG/B266*, *http://links.lww.com/MPG/B268*). No definitive data showed that 1 particular thickening agent is more effective than another. In 10 studies, visible vomiting and/or regurgitation was used as an outcome measure (157,160,161,163–167,169,170). Three studies showed a reduction in the number of episodes of regurgitation per day (Pooled Mean Difference: −1.18, 95% CI −1.96 to −0.66), (160,161,164) and 2 studies showed a reduction in vomiting per day (Pooled Mean Difference −0.93 (95% CI −1.31 to −0.55) (160,166). Ostrom et al compared soy formula with added fiber (as a thickener) to cow's milk in a double blinded randomized controlled trial and found a significant reduction in the percentage of feedings with regurgitation and the number of subjects with any regurgitation at the end of the 4 week trial in those patients that received the soy formula with fiber ($P < 0.03$) (161). In contrast, Ummarino et al performed an open label randomized controlled trial of thickened feedings versus patient/family reassurance versus magnesium alginate with simethicone. In this study, the authors found that thickening reduced median symptom scores over the course of the 8-week study to a greater extent than reassurance alone ($P < 0.001$) (170). Grade of severity of regurgitation was reduced in another study, albeit not significantly (MD −1.10, 95% CI −2.49 to 0.29) (157). The remaining studies did not report sufficient data to draw group-group comparisons at the end of study period compared with baseline.

While the previously discussed studies focused on symptom scores and the amount of regurgitation, 4 studies used crying/distress as an outcome measure, although only 2 studies presented adequate data upon which it was possible to draw conclusions (159,161,167,168). In a randomized trial, regurgitation, vomiting, and other symptoms such as irritability were significantly reduced in the corn starch-thickened formula group compared with enriched formula-fed patients 4 and 8 weeks after initiating the formula changes (159). Ostrom et al found, in their 4-week trial, no significant differences in GERD symptoms in infants receiving soy formula with fiber compared with cow's milk formula without added fiber ($P > 0.05$) (161).

In summary, across all studies, thickening of feedings improves visible regurgitation but the impact on non-regurgitation symptoms is less clear (ie, as determined by predefined outcome measures and/or occurrence of side-effects and adverse events), (158,159,162–165,167,168).

Other Considerations With Thickeners

- The efficacy of thickeners as assessed by pH-MII
  The search yielded 1 systematic review published after 2008 on the use of thickened feedings for the treatment of GER in healthy infants (171). As this study applied different inclusion and exclusion criteria, 14 studies were included for meta-analysis and the conclusion of the analysis was that the thickening: (1) reduced vomiting and visible regurgitations per day, (2) increased the number of days without regurgitation, and (3) reduced symptoms such as crying and irritability. Horvath et al also highlighted that thickening does not improve the acid reflux parameters measured by pH-metry including the RI, number of acid gastroesophageal reflux episodes per hour, or number of reflux episodes lasting >5 minutes. In this systematic review, there was a reduction in the duration of the longest reflux episode of pH < 4 based on the pooled results of 2 RCTs (n = 116) (171). One argument for a lack of improvement in pH-metry parameters is that thickening would be expected to reduce post-prandial reflux, which is typically non-acid and therefore may be missed by pH-metry. However, in 2 trials of thickening performed using pH-MII parameters as outcomes, thickening still did not result in reducing the total reflux burden when comparing feeding periods with and without thickening within individual patients (172,173).

Safety of Thickeners

- Cereal based
  Recent reports have raised concerns about the safety of rice cereal as a thickening agent for infants and children. Safety concerns were raised because of elevated levels of inorganic arsenic in all forms of rice including infant cereals. Arsenic exposure has been linked to neurotoxicity and long-term cancer risk in areas with environmental arsenic contamination. In April 2016, the United States Food and Drug Administration (FDA) proposed an action level, or limit, of 100 parts per billion for inorganic arsenic in infant rice cereal, which corresponds to a level proposed by the European Commission for rice destined for the production of food for infants and young children. Despite this FDA warning, rice cereal still enjoys advantages as a thickener, including its ability to dissolve more thoroughly than other cereals without clogging nipples, its affordability, and its long track record of use in infants. Whenever possible, using rice cereal with low or no arsenic is recommended.
- Commercial thickeners
  The search did not identify any studies on the efficacy of thickening of breastmilk. In a cross- over study, Corvaglia et al evaluated the effect of thickening of human milk by precooked starch in reducing GER in 5 preterm infants and found no significant reduction in the number of pH-MII detected reflux episodes with thickened feeds when compared to unthickened feeds (173). In the vast majority of infants presenting with physiological GER, breastfeeding should be further encouraged. However, for babies with significant reflux such that thickening is being considered, breastmilk can be thickened with xanthum gum or carob bean based thickeners but not with cereal, the latter of which is digested by the amylases in breast milk. While these commercial thickeners are available for use in breast milk, some cautions exist. Carob bean thickeners are approved for use in infants after 42 weeks gestation. Xanthum gum thickeners are approved for infants greater than 1 year old because of concerns of necrotizing enterocolitis (174,175).

Reduction of Ingested Volume

A reduction of the ingested volume per feeding is a common recommendation that can be found in many reviews, guidelines and recommendations for GERD treatment (1,3,176). No RCTs have studied reduced feeding volumes. Omari et al showed that in preterm and term infants with GERD, using more frequent feedings led to a reduced RI in this specific group (119). Although no data relate ingested volume to frequency and volume of regurgitation, avoiding overfeeding by adjusting feeding frequency and volume for age and weight while maintaining an appropriate total daily amount of formula or breastmilk is recommended (Algorithm 1).

Elimination of Cow 's Milk Protein

No RCTs evaluate extensively hydrolyzed or amino acid based formulas for the treatment of GERD. However, a subset

of infants with allergy to cow's milk protein (CMPA) experience regurgitation and vomiting indistinguishable from that associated with physiologic GER or GERD and it is for this reason that, even in acid suppression trials, cow's milk elimination trials are often performed prior to randomization for reflux medications (177). In these infants, vomiting frequency decreases significantly (usually within 2 weeks) after the elimination of cow's milk protein from the diet, and reintroduction causes recurrence of symptoms. Because regurgitation is sometimes the sole manifestation of CMPA in healthy-appearing infants, non-breast-fed infants with suspected CMPA should receive a formula with an extensively hydrolyzed protein. In breast-fed infants, the mother can achieve similar results by restricting all dairy including casein and whey from her diet. According to the recently published ESPGHAN guidelines on CMPA, amino acids-based formulae should be reserved for the patients with intractable or severe symptoms (178). While no trials compare the use of protein hydrolysate formulas to milk based formulas in the treatment of symptoms of GERD, children with suspected CMPA who are given an amino acid based formula for 24 hours followed by a cow's milk containing formula for 24 hours have significantly more reflux events measured by pH-MII during the cow's milk feeding compared to the amino acid based feeds (179). Corvaglia et al studied 18 infants with symptoms of feeding intolerance, constipation or distension that were treated for 1 week with a hydrolyzed protein formula (180). After this 1 week trial, if the infants had GERD symptoms, they underwent pH-MII testing while receiving cow's milk formula alternating with protein hydrolysate formula as part of a randomized cross over design trial. The authors found that RI improves during hydrolysate feeds compared with the cow's milk feedings, but they found no other differences in any of the reflux parameters as measured by pH-MII. ESPGHAN guidelines recommend against the use of soy-based infant formula, and in Europe soy based formulas are no longer commercially available (181,182). Among 10% to 15% of the infants with CMPA will also become allergic to soy (183). Rice hydrolysates are commercially available, but the data are too limited to be considered in these guidelines. Any patient placed on a protein hydrolysate formula or an amino acid based formula needs close follow up to determine how and when dairy can be safely introduced. Studies have shown that infants and children on CMP restriction may have increased disordered eating patterns and may even develop anaphylaxis to milk protein (184,185).

In conclusion, the use of thickeners may improve slightly the occurrence of overt regurgitation/vomiting as symptoms of GER in infants. It is uncertain whether the use of food thickeners improves other signs and symptoms of GER and whether their use leads to side effects in infants. While evidence supporting modification of feeding volumes or intervals is lacking, these modifications are without risk or cost, so feeding modification should be considered before more costly or risky interventions. While there is no evidence to support the use of extensively hydrolyzed formula or amino acid–based formula for the treatment of GERD in infants and children who do not have CMPA, symptoms of GERD and CMPA are identical. Therefore, a trial of extensively hydrolyzed formula or amino acid–based formula is indicated in patients who have not responded to conventional GERD therapies. For each of these non-pharmacologic therapies, a minimum 2-week trial is recommended to assess for symptom improvement before considering other therapeutic alternatives.

Recommendations:

4.1 The working group suggests to use thickened feed for treating visible regurgitation/vomiting in infants with GERD (Algorithm 1).
Voting: 6, 7, 7, 8, 8, 8, 9, 9, 9, 9. (weak recommendation)

4.2 Based on expert opinion, the working group suggests to modify feeding volumes and frequency according to age and weight to avoid overfeeding in infants with GERD (Algorithm 1).
Voting: 7, 7, 8, 8, 8, 8, 8, 9, 9, 9. (weak recommendation)

4.3 Based on expert opinion, the working group suggests a 2 to 4 week trial of formula with extensively hydrolyzed protein (or amino-acid based formula) in formula fed infants suspected of GERD after optimal non-pharmacological treatment has failed (Algorithm 1, or see ESPGHAN 2012 CMPA guidelines).
Voting: 4, 6, 7, 8, 8, 8, 8, 9, 9, 9. (weak recommendation)

Positioning Therapy

One study was identified that met the inclusion criteria (156). Loots et al conducted a study of infants with a positive symptom correlation on pH-MII testing who were randomized to left side or head elevation positioning in addition to medications (PPI or Mylanta). The primary outcome of the study, measured 14 days after initiation of treatment, was change in reflux measured by pH-MII testing, but symptom improvement was also assessed. Regardless of the medication given, left lateral positioning (LLP) resulted in reduction in the total number of reflux episodes. Vomiting also declined in infants given Mylanta and placed in LLP (156).

Other considerations on the effect of positioning on reflux parameters:

- pH-MII and motility parameters
  As mentioned above, LLP reduced the total number of reflux episodes measured by pH-MII. In a study by Omari et al, the authors measured by impedance and LES pressures in 10 preterm infants placed in the right and left lateral decubitus positions (186). In this study, both the number of reflux episodes and the TLESRs significantly decreased in infants in LLP compared to right lateral positioning (RLP). A subsequent study by van Wijk et al found identical effects of positioning on reflux by impedance, and the effect of positioning was immediate; when babies were switched from RLP to LLP and vice versa, the impact on reflux and TLESRs was immediate (187). No studies met our inclusion criteria on the impact of positioning on symptom reduction as the primary outcome. An uncontrolled trial by Vandenplas et al showed that a 40° specially constructed antireflux bed resulted in a significant decrease of objective reflux parameters, reflux symptoms and antiacid medications in infants that tolerated this position (188). Corvaglia et al showed that prone and left side position were associated with a decreased number of reflux episodes measured by impedance in premature infants (189).
- Safety
  Despite possible benefits to positioning in the treatment of reflux, no position other than supine position is recommended for infants because of the risk of sudden infant death syndrome

(SIDS). Supine sleeping is universally recommended by the National Health Service and the American Academy of Pediatrics as the safest position to prevent the risk of SIDS. Because elevating the head of an infant's crib while the infant is supine may result in the infant rolling to the foot of the crib into a position that may comprise respiration, elevating the head of the crib is not recommended by the American Academy of Pediatrics (189).

No studies are published on positioning therapy in older children. However, in adults, head-of-the-bed elevation modestly decreases time with supine acid exposure compared with a flat position (from 21% to 15%, $P < 0.05$) (190). In another small study by Loots et al in 10 adult GERD patients, TLESRs, reflux events, distension of proximal stomach, and gastric emptying were increased in the right lateral position compared to left lateral position, while this effect was not found in 10 healthy controls (191).

In conclusion, it is uncertain whether the use of positioning therapy (left side or head elevation positioning) improves the occurrence of crying/distress as signs and symptoms of GERD in infants.

Recommendations:

4.4 The working group recommends not to use positional therapy (ie, head elevation, lateral and prone positioning) to treat symptoms of GERD in sleeping infants.
Voting: 6, 6, 7, 8, 8, 8, 9, 9, 9, 9. (strong recommendation)

4.5 Based on expert opinion, the working group suggests to consider the use of head elevation or left lateral positioning to treat symptoms of GERD in children.
Voting: 7, 8, 8, 8, 9, 9, 9, 9, 9, 9. (weak recommendation)

Other Non-Pharmacological Interventions Including Life-Style Modifications (Alcohol and Tobacco Use/Exposure), Massage therapy, Complementary Therapy (Hypnotherapy, Homeopathy, Acupuncture, Herbal Medicine), Pre- and Probiotics.

The search yielded 1 study on the use of massage therapy in infants with a diagnosis of GERD according to their treating pediatrician, but no studies met our inclusion criteria on any of the other interventions (155). In this single study by Neu et al, 36 infants with GERD diagnosed by I-GERQ-R were randomized to massage therapy or sham therapy including rocking and holding. Both groups experienced improvement in GERD symptoms, measured by I-GERQ-R scores, and no difference was found between groups after the 6-week intervention. This study was limited by its small size and short length of intervention.

Other considerations for non-pharmacologic therapies:

- Probiotics
  No studies met the criteria for inclusion. However, 1 placebo-controlled RCT investigated the efficacy of *Lactobacillus reuteri* DSM 17938 given as drops daily for 90 days in 589 term newborns (age < 1 week) in the prevention of colic, regurgitation, and functional constipation. Since this study was a prevention study conducted in infants < 3 months of age, regardless of the presence of GERD, this study did not meet inclusion criteria. Nevertheless, regurgitation frequency was addressed as a primary outcome in the study. At the conclusion of the 3-month trial, the mean number of regurgitations per day in the *L reuteri* DSM 17938 and placebo groups were significantly different: 2.9 versus 4.6; $P < 0.01$ (192). Significant improvement was also noted in crying time per day ($P < 0.01$), but this is a symptom not unique to GERD. No studies have been published on the effect of infant formula with probiotics on GERD symptoms.
- Weight loss in obesity
  In children, obesity has been associated with a small increase in risk of GERD symptoms compared to non-obese children (193,194). However, the impact of obesity on GERD complications such as erosive esophagitis is less clear (3,195,196). No pediatric intervention studies determine if weight reduction changes GERD symptoms. No pediatric studies show a relationship between obesity and reflux events by pH-metry or pH-MII. A review of lifestyle changes in adults with GERD concluded that only weight loss improved pH-metry profiles and symptoms (197).

In conclusion, it is uncertain whether the use of massage therapy reduces crying/distress or other signs and symptoms of GERD in infants based on the I-GERQ- R questionnaire. While there is a lack of evidence supporting non-pharmacologic interventions, some interventions (such as tobacco avoidance) are low to no cost and risk and may merit a trial before considering more costly or risky therapies. Other interventions massage therapy, complementary therapy (hypnotherapy, homeopathy, acupuncture, and herbal medicine), dietary supplementation, pre-and probiotics have not been adequately studied and may pose more risk and cost so therefore cannot be recommended for the reduction of symptoms of GERD in infants and children.

Recommendations:

4.6 The working group suggests not to use massage therapy to treat infant GERD.
Voting: 7, 7, 7, 8, 8, 8, 9, 9, 9, 9. (weak recommendation)

4.7 Based on expert opinion, the working group suggests not to use currently available lifestyle interventions or complementary treatments such as prebiotics, probiotics, or herbal medications to treat GERD.
Voting: 5, 6, 7, 7, 8, 9, 9, 9, 9, 9. (weak recommendation)

4.8 Based on expert opinion, the working group suggests informing caregivers and children that excessive body weight is associated with an increased prevalence of GERD.
Voting: 6, 7, 7, 7, 7, 8, 8, 9, 9, 9. (weak recommendation)

Parental Guidance, Education, and Support

The search did not identify any studies fulfilling our inclusion criteria.

- Other considerations on education
  Patient and parental education, guidance, and support are always considered to be required as part of the treatment of GERD. It is important to inform caregivers about diagnostic and treatment options, side effects, complications and prognosis (also see section Prognosis). These measures are usually sufficient to manage healthy, thriving infants with symptoms likely to result from physiologic GER (1). A RCT on physician counseling of families of patients with chronic conditions, such as asthma, has shown that patient education on specific pathophysiology of the disorder, specific methods to prevent or treat symptoms, and patient empowerment, can help improve parent understanding of the disorder, decrease patient symptoms of the chronic disorder and

decrease health care utilization (198,199). However, no studies specifically in pediatric GERD patients have been performed.

In conclusion, there is no evidence to support parental guidance, education and support for the reduction of signs and symptoms of GERD in infants and children.

Recommendation:
4.9 Based on expert opinion, the working group recommends providing patient/parental education and support as part of the treatment of GERD (Algorithm 1).
Voting: 8, 8, 9, 9, 9, 9, 9, 9, 9, 9. (strong recommendation)

QUESTION 5: WHAT ARE EFFECTIVE AND SAFE PHARMACOLOGIC TREATMENT OPTIONS FOR THE REDUCTION OF SIGNS AND SYMPTOMS OF GASTROESOPHAGEAL REFLUX DISEASE?

Ten original studies and 25 systematic reviews were eligible for inclusion. After checking reference lists of these systematic reviews and the ESPGHAN/NASPGHAN 2009 and NICE 2015 guidelines (See Appendix A, Supplemental Digital Content 1, *http://links.lww.com/MPG/B265*, for summary of search strategy, results and study selection), 12 additional original studies could be included, resulting in a total of 22 original studies. Characteristics of included studies can be found in Appendix B3 (Supplemental Digital Content 2, *http://links.lww.com/MPG/B266*). GRADE profiles can be found in Appendix D (Supplemental Digital Content 4, *http://links.lww.com/MPG/B268*).

Algorithm 1 and 2 display the therapeutic approach to respectively the infant and child with GERD. For recommended dosages for the different drugs we refer to Table 4.

Anti-acids and Alginates

Alginates and antacids are designed to neutralize acid and contain either sodium/potassium bicarbonate, or aluminium, magnesium or calcium salts and are typically used to treat acid related disorders such as heartburn or dyspepsia. The search yielded 2 studies assessing the use of alginates (1 containing 225 mg sodium alginate and 87.5 mg magnesium alginate (170) and 1 containing magnesium alginate and simethicone (200) versus placebo 1 study also assessed the use of alginates versus rice-starch thickened formula (170). Two additional studies assessed the use of alginates versus H2RAs (see section 5) (201,202). A recent Cochrane review on the currently available pharmacological interventions used to treat children with GER was also reviewed (203). No studies meeting our inclusion criteria on the use of anti-acids were identified.

Ummarino, et al, assessed GER symptoms using I-GERQ-R questionnaire scores. While they reported that median I-GERQ-R scores were more significantly reduced in the intervention group compared with no intervention ($P < 0.0001$) or thickened feedings ($P < 0.002$), no comparison between groups at end of study period was made (170). Ummarino, et al, reported on the number of infants with persisting symptoms at week 4 and 8, showing a significant decrease in the number of infants regurgitating at week 8 when treated with alginates compared with no intervention (RR = 0.04, 95% CI 0.01 to 0.25) and compared with thickened feedings (RR = 0.26, 95% CI 0.26 to 0.88) (170). The other study, by Miller et al, found the number of vomiting/regurgitation episodes in 24 hours at 2 weeks was significantly lower compared with baseline ($P = 0.009$), however the mean frequency of episodes did not differ statistically (200). In both studies, no significant differences were found in the number of infants with more than 1 adverse (AE; RR = 1.30, 95% CI = 0.87 to 1.93) or serious adverse event (SAE; RR = 1.10, 95% CI 0.16 to 7.43) or in the number of infants withdrawing from the study due to the occurrence of a(n) (S)AE

TABLE 4. Dosages of most frequently used drugs for the treatment of gastroesophageal reflux disease

Drugs	Recommended pediatric dosages	Maximum dosages (based upon adult dosage)
Histamine-2 Receptor Antagonists (H2RAs)		
Ranitidine	5–10 mg/kg/day	300 mg
Cimetidine	30–40 mg/kg/day	800 mg
Nizatidine	10–20 mg/kg/day	300 mg
Famotidine	1 mg/kg/day	40 mg
Proton Pump Inhibitors (PPIs)		
Omeprazole	1–4 mg/kg/day	40 mg
Lansoprazole	2 mg/kg/day for infants	30 mg
Esomeprazole	10 mg/day (weight <20kg) or 20 mg/day (weight >20kg)	40 mg
Pantoprazole	1–2 mg/kg/day	40 mg
Prokinetics		
Metoclopramide	0.4-0.9 mg/kg/day	60 mg
Domperidone	0.8–0.9 mg/kg/day	30 mg
Baclofen	0.5 mg/kg/day	80 mg
Antacids		
Mg alginate plus simethicone	2.5 ml 3×/day (weight < 5kg) or 5 ml 3×/day (weight >5 kg)	NA
Sodium alginate	225 mg sodium alginate and magnesium alginate 87.5 mg) in a total 0.65 g One sachet/day (weight <4.54 kg) or Two sachet/day (weight >4.54 kg)	NA

NA = no data available.