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Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)

Co-Chairs: *Yvan Vandenplas and †Colin D. Rudolph
Committee Members: ‡Carlo Di Lorenzo, §Eric Hassall, ||Gregory Liptak, ¶Lynnette Mazur, #Judith Sondheimer, **Annamaria Staiano, ††Michael Thomson, ‡‡Gigi Veereman-Wauters, and §§Tobias G. Wenzl

*UZ Brussel Kinderen, Brussels, Belgium, †Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, WI, USA, ‡Division of Pediatric Gastroenterology, Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA, §Division of Gastroenterology, Department of Pediatrics, British Columbia Children's Hospital/University of British Columbia, Vancouver, BC, Canada, ||Department of Pediatrics, Upstate Medical University, Syracuse, NY, USA, ¶Department of Pediatrics, University of Texas Health Sciences Center Houston and Shriners Hospital for Children, Houston, TX, USA, #Department of Pediatrics, University of Colorado Health Sciences Center, Denver, CO, USA, **Department of Pediatrics, University of Naples "Federico II," Naples, Italy, ††Centre for Paediatric Gastroenterology, Sheffield Children's Hospital, Western Bank, Sheffield, UK, ‡‡Pediatric Gastroenterology & Nutrition, Queen Paola Children's Hospital-ZNA, Antwerp, Belgium, and §§Klinik für Kinder- und Jugendmedizin, Universitätsklinikum der RWTH Aachen, Aachen, Germany

ABSTRACT

Objective: To develop a North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) international consensus on the diagnosis and management of gastroesophageal reflux and gastroesophageal reflux disease in the pediatric population.

Methods: An international panel of 9 pediatric gastroenterologists and 2 epidemiologists were selected by both societies, which developed these guidelines based on the Delphi principle. Statements were based on systematic literature searches using the best-available evidence from PubMed, Cumulative Index to Nursing and Allied Health Literature, and bibliographies. The committee convened in face-to-face meetings 3 times. Consensus was achieved for all recommendations through nominal group technique, a structured, quantitative method. Articles were evaluated using the Oxford Centre for Evidence-based Medicine Levels of Evidence. Using the Oxford Grades of Recommendation, the quality of evidence of each of the recommendations made by the committee was determined and is summarized in appendices.

Results: More than 600 articles were reviewed for this work. The document provides evidence-based guidelines for the diagnosis and management of gastroesophageal reflux and gastroesophageal reflux disease in the pediatric population.

Conclusions: This document is intended to be used in daily practice for the development of future clinical practice guidelines and as a basis for clinical trials. ***JPGN 49:498–547, 2009.*** **Key Words:** Clinical practice guidelines—Diagnostic tests—Gastroesophageal reflux (GER)—Gastroesophageal reflux disease (GERD)—Therapeutic modalities. © 2009 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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Address correspondence and reprint requests to Colin D. Rudolph, MD, PhD, Professor of Pediatrics & Vice Chair for Clinical Affairs, Chief, Pediatric Gastroenterology, Hepatology, and Nutrition, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Wisconsin, Medical College of Wisconsin, 9000 W Wisconsin Ave, Milwaukee, WI 53226 (e-mail: crudolph@mcw.edu).

Carlo Di Lorenzo, Eric Hassall, Gregory Liptak, Lynnette Mazur, Judith Sondheimer, Annamaria Staiano, Michael Thomson, Gigi Veereman-Wauters, and Tobias G. Wenzl contributed equally to the development of these guidelines. Abstract adapted by Gregory Liptak.

Authors' disclosures are listed in Appendix D.

SYNOPSIS

This synopsis contains some essentials of the guidelines, but does not convey the details, nuances, and complexity of the issues addressed in the complete guidelines, and therefore can be interpreted only with reference to the full article.

1. RATIONALE The purpose of these guidelines is to provide pediatricians and pediatric subspecialists with a common resource for the evaluation and management of patients with gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD). These guidelines are not intended as a substitute for clinical judgment or as a protocol for the management of all pediatric patients with GER and GERD.

2. METHODS "Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)" is a document developed by a committee of 9 pediatric gastroenterologists from NASPGHAN and ESPGHAN and 2 pediatric epidemiologists from the United States. Using the best-available evidence from the literature, the committee critically evaluated current diagnostic tests and therapeutic modalities for GER and GERD.

3. DEFINITIONS AND MECHANISMS GER is the passage of gastric contents into the esophagus with or without regurgitation and vomiting. GER is a normal physiologic process occurring several times per day in healthy infants, children, and adults. Most episodes of GER in healthy individuals last <3 minutes, occur in the postprandial period, and cause few or no symptoms. In contrast, GERD is present when the reflux of gastric contents causes troublesome symptoms and/or complications. Every effort was made to use these 2 terms strictly as defined.

4. DIAGNOSIS

4.1. History and Physical Examination In infants and toddlers, there is no symptom or symptom complex that is diagnostic of GERD or predicts response to therapy. In older children and adolescents, as in adult patients, history and physical examination may be sufficient to diagnose GERD if the symptoms are typical.

4.2. Esophageal pH Monitoring This test is a valid quantitative measure of esophageal acid exposure, with established normal ranges. However, the severity of pathologic acid reflux does not correlate consistently with symptom severity or demonstrable complications. In children with documented esophagitis, normal esophageal pH monitoring suggests a diagnosis other than GERD. Esophageal pH monitoring is useful for evaluating the efficacy of antisecretory therapy. It may be useful to correlate symptoms (eg, cough, chest pain) with acid reflux episodes and to select those infants and children with wheezing or respiratory symptoms in whom GER is an aggravating factor. The sensitivity, specificity, and clinical utility of pH monitoring for diagnosis and management of possible extraesophageal complications of GER are not well established.

4.3. Combined Multiple Intraluminal Impedance (MII) and pH Monitoring This test detects acid, weakly acid, and nonacid reflux episodes. It is superior to pH monitoring alone for evaluation of the temporal relation between symptoms and GER. Whether combined esophageal pH and impedance monitoring will provide useful measurements that vary directly with disease severity, prognosis, and response to therapy in pediatric patients has yet to be determined.

4.4. Motility Studies Esophageal manometry may be abnormal in patients with GERD but the findings are not sufficiently sensitive or specific to confirm a diagnosis of GERD, nor to predict response to medical or surgical therapy. It may be useful to diagnose a motility disorder in patients who have failed acid suppression and who have a normal endoscopy, or to determine the position of the lower esophageal sphincter to place a pH probe. Manometric studies are useful to confirm a diagnosis of achalasia or other motor disorders of the esophagus that may mimic GERD.

4.5. Endoscopy and Biopsy Endoscopically visible breaks in the distal esophageal mucosa are the most reliable evidence of reflux esophagitis. Mucosal erythema, pallor, and increased or decreased vascular pattern are highly subjective and nonspecific findings that are variations of normal. Histologic findings of eosinophilia, elongated rete pegs, basilar hyperplasia, and dilated intercellular spaces, alone or in combination, are insufficiently sensitive or specific to diagnose reflux esophagitis. Conversely, absence of these histologic changes does not rule out GERD. Endoscopic biopsy is important to identify or rule out other causes of esophagitis, and to diagnose and monitor Barrett esophagus (BE) and its complications.

4.6. Barium Contrast Radiography This test is not useful for the diagnosis of GERD but is useful to confirm or rule out anatomic abnormalities of the upper gastrointestinal (GI) tract that may cause symptoms similar to those of GERD.

4.7. Nuclear Scintigraphy The standards for interpretation of this test are poorly established. According to limited published literature, scintigraphy may have a role in the diagnosis of pulmonary aspiration in patients with chronic and refractory respiratory symptoms. A negative test does not rule out possible pulmonary aspiration of refluxed material. Gastric emptying studies by themselves do not confirm the diagnosis of GERD and are recommended only in individuals with symptoms of gastric retention. Nuclear scintigraphy is not recommended for the routine evaluation of pediatric patients with suspected GERD.

4.8. Esophageal and Gastric Ultrasonography These tests are not recommended for the routine evaluation of GERD in children.

4.9. Tests on Ear, Lung, and Esophageal Fluids Evaluation of middle ear or pulmonary aspirates for lactose, pepsin, or lipid-laden macrophages have been proposed as the tests for GERD. No controlled studies have proven that reflux is the only reason these compounds appear in ear or lung fluids, and no controlled studies have shown that the presence of these substances confirms GER as the cause of ear, sinus, or pulmonary disease. Diagnosis of duodeno-gastroesophageal reflux by detection of bilirubin in the esophagus is not recommended for the routine evaluation for possible GERD in children. The role of bile reflux in causing GERD that is resistant to proton pump inhibitors (PPIs) therapy has not been established.

4.10. Empiric Trial of Acid Suppression as a Diagnostic Test Expert opinion suggests that in an older child or adolescent with typical symptoms suggesting GERD, an empiric trial of PPIs is justified for up to 4 weeks. However, improvement of heartburn, following treatment, does not confirm a diagnosis of GERD because symptoms may improve spontaneously or respond by a placebo effect. There is no evidence to support an empiric trial of acid suppression as a diagnostic test in infants and young children where symptoms suggestive of GERD are less specific.

5. TREATMENT

5.1. Lifestyle Changes

5.1.1. & 5.1.2. Lifestyle Changes in the Infant Parental education, guidance, and support are always required and usually sufficient to manage healthy, thriving infants with symptoms likely because of physiologic GER. Milk protein sensitivity is sometimes a cause of unexplained crying and vomiting in infants. Therefore, formula-fed infants with recurrent vomiting may benefit from a 2- to 4-week trial of an extensively hydrolyzed protein formula that has been evaluated in controlled trials. Use of a thickened formula (or commercial anti-regurgitation formulae, if available) may decrease visible regurgitation but does not result in a measurable decrease in the frequency of esophageal reflux episodes. Prone positioning decreases the amount of acid esophageal exposure measured by pH probe compared with that measured in the supine position. However, prone and lateral positions are associated with an increased incidence of sudden infant death syndrome (SIDS). The risk of SIDS outweighs the benefit of prone or lateral sleep position on GER; therefore, in most infants from birth to 12 months of age, supine positioning during sleep is recommended.

5.1.3. Lifestyle Changes in Children and Adolescents In older children, there is no evidence to support the routine elimination of any specific food for management of GERD. In adults, obesity, large meal volume, and late night eating are associated with symptoms of GERD. Prone or left-side sleeping position and/or elevation of the head of the bed may decrease GER, as shown in adult studies.

5.2. Pharmacologic Therapies The major pharmacologic agents currently used for treating GERD in children are gastric acid–buffering agents, mucosal surface barriers, and gastric antisecretory agents. Acid-suppressant agents are the mainstay of treatment for all but the patient with occasional symptoms. The potential adverse effects of acid suppression, including increased risk of community-acquired pneumonias and GI infections, need to be balanced against the benefits of therapy.

5.2.1. Histamine-2 Receptor Antagonists (H2RAs) H2RAs exhibit tachyphylaxis or tolerance but PPIs do not. Tachyphylaxis is a drawback to chronic use. H2RAs have a rapid onset of action and, like buffering agents, are useful for on-demand treatment.

5.2.2. Proton Pump Inhibitors For healing of erosive esophagitis and relief of GERD symptoms, PPIs are superior to H2RAs. Both medications are superior to placebo. Administration of long-term acid suppression without a diagnosis is inadvisable. When acid suppression is required, the smallest effective dose should be used. Most patients require only once-daily PPI; routine use of twice-daily doses is not indicated. No PPI has been approved for use in infants younger than 1 year of age, and there are special concerns pertaining to prescription of PPIs in infants, as described in the Guideline.

5.2.3. Prokinetic Therapy Potential adverse effects of currently available prokinetic agents outweigh the potential benefits of these medications for treatment of

GERD. There is insufficient evidence of clinical efficacy to justify the routine use of metoclopramide, erythromycin, bethanechol, cisapride, or domperidone for GERD. Baclofen reduces the frequency of transient relaxations of the lower esophageal sphincter (TLESR), but it has not been evaluated in controlled trials for treatment of GERD in children.

5.2.4. Other Agents Buffering agents, alginate, and sucralfate are useful on demand for occasional heartburn. Chronic use of buffering agents or sodium alginate is not recommended for GERD because some have absorbable components that may have adverse effects with long-term use. Special caution is required in infants. If long-term use is required, more effective therapy is available.

5.3. Surgical Therapy Antireflux surgery may be of benefit in selected children with chronic-relapsing GERD. Indications include failure of optimized medical therapy, dependence on long-term medical therapy, significant nonadherence to medical therapy, or pulmonary aspiration of refluxate. Children with respiratory complications, including asthma or recurrent aspiration related to GERD, are generally considered most likely to benefit from antireflux surgery when medical therapy fails but additional study is required to confirm this assumption. Children with underlying disorders predisposing to the most severe GERD are at the highest risk for operative morbidity and postoperative failure. Before surgery it is essential to rule out non-GERD causes of symptoms and ensure that the diagnosis of chronic-relapsing GERD is firmly established. It is important to provide families with appropriate education and a realistic understanding of the potential complications of surgery, including symptom recurrence.

6. EVALUATION AND MANAGEMENT OF PEDIATRIC PATIENTS WITH SUSPECTED GERD The following sections describe the relation between reflux and several common signs, symptoms, or symptom complexes of infants and children.

6.1. Recurrent Regurgitation and Vomiting The practitioner's challenge is to distinguish regurgitation and vomiting caused by GER from vomiting caused by numerous other disorders.

6.1.1. Infants With Uncomplicated Recurrent Regurgitation A history of disease and physical examination, with attention to warning signs, are generally sufficient to allow the clinician to establish the diagnosis of uncomplicated GER. Parental education, reassurance, and anticipatory guidance are recommended. In formula-fed infants, thickened formula (or antiregurgitation formula if available) reduces the frequency of overt regurgitation and vomiting.

6.1.2. Infants With Recurrent Vomiting and Poor Weight Gain A diagnosis of physiologic GER should not be made in an infant with vomiting and poor weight gain. Expert opinion suggests that initial evaluation in an infant with normal physical examination but poor weight gain should include diet history, urinalysis, complete blood count, serum electrolytes, blood urea nitrogen, and serum creatinine. Additional testing should be based on suggestive historical details or results of screening tests. Management may include a 2-week trial of extensively hydrolyzed formula or amino acid–based formula to exclude cow's milk allergy, increased caloric density of formula and/or thickened formula, and education as to appropriate daily formula volume required for normal growth. Careful follow-up of interval weight change and caloric intake is essential. If management fails to improve symptoms and weight gain, referral to a pediatric gastroenterologist is recommended.

6.1.3. Infants With Unexplained Crying and/or Distressed Behavior Reflux is not a common cause of unexplained crying, irritability, or distressed behavior in otherwise healthy infants. Other causes include cow's milk protein allergy, neurologic disorders, constipation, and infection (especially of the urinary tract). Following exclusion of other causes, an empiric trial of extensively hydrolyzed protein formula or amino acid–based formula is reasonable in selected cases, although evidence from the literature in support of such a trial is limited. There is no evidence to support the empiric use of acid suppression for the treatment of irritable infants. If irritability persists with no explanation other than suspected GERD, expert opinion suggests the following options: the practitioner may continue anticipatory guidance and training of parents in the management of such infants with the anticipation of improvement with time; additional investigations to ascertain the relation between reflux episodes and symptoms or to diagnose esophagitis may be indicated (pH monitoring $\pm$ impedance monitoring, endoscopy); a time-limited (2-week) trial of antisecretory therapy may be considered, but there is a potential risk of adverse effects. Clinical improvement following empiric therapy may be due to spontaneous symptom resolution or a placebo response. The risk/benefit ratio of these approaches is not clear.

6.1.4. The Child Older Than 18 Months of Age With Chronic Regurgitation or Vomiting Physiologic regurgitation, episodic vomiting, or regurgitation followed by swallowing of refluxate in the mouth are frequent in infants. Whether of new onset or persisting from infancy, these symptoms are less common in children older than 18 months of age. Although these

symptoms are not unique to GERD, evaluation to diagnose possible GERD and to rule out alternative diagnoses is recommended based on expert opinion. Testing may include upper GI endoscopy and/or esophageal pH/MII, and/or barium upper GI series.

6.2. Heartburn Extrapolation from adult data suggests that in older children and adolescents, on-demand therapy with buffering agents, sodium alginate, or H2RA may be used for occasional symptoms. Adolescents with typical symptoms of chronic heartburn should be treated with lifestyle changes if applicable (diet changes, weight loss, smoking avoidance, sleeping position, no late night eating) and a 2- to 4-week trial of PPI. If symptoms resolve, PPIs may be continued for up to 3 months. Heartburn that persists on PPI therapy or recurs after this therapy is stopped should be investigated further by a pediatric gastroenterologist.

6.3. Reflux Esophagitis In pediatric patients with endoscopically diagnosed reflux esophagitis or established nonerosive reflux disease, PPIs for 3 months constitute initial therapy. Not all reflux esophagitis are chronic or relapsing, and therefore trials of tapering the dose and then withdrawal of PPI therapy should be performed at intervals. Most but not all of the children with chronic-relapsing reflux disease have one of the GERD-predisposing disorders described below. In most cases of chronic-relapsing esophagitis, symptom relief can be used as a measure of efficacy of therapy, but in some circumstances repeat endoscopy or diagnostic studies may be indicated. Recurrence of symptoms and/or esophagitis after repeated trials of PPI withdrawal usually indicate that chronic-relapsing GERD is present, if other causes of esophagitis have been ruled out. At that point, therapeutic options include long-term PPI therapy or antireflux surgery.

6.4. Barrett Esophagus BE occurs in children with less frequency than it does in adults. Multiple biopsies documented in relation to endoscopically identified esophagogastric landmarks are advised to confirm or rule out the diagnosis of BE and dysplasia. In BE, aggressive acid suppression is advised by most experts. Symptoms are a poor guide to the severity of acid reflux and esophagitis in BE, and pH studies are often indicated to guide treatment. BE per se is not an indication for surgery. Dysplasia is managed according to adult guidelines.

6.5. Dysphagia, Odynophagia, and Food Refusal Dysphagia, or difficulty in swallowing, occurs in association with oral and esophageal anatomic abnormalities, neurologic and motor disorders, oral and esophageal inflammatory diseases, and psychological stressors or disorders. Of the mucosal disorders, eosinophilic esophagitis is increasingly recognized to be a more common cause of dysphagia or odynophagia than GERD, although this finding is not consistently reported in all geographic regions. Odynophagia, or pain caused by swallowing, must be distinguished from heartburn (substernal pain caused by esophageal acid exposure) and dysphagia. Although odynophagia may be a symptom of peptic esophagitis, it is more often associated with other conditions such as oropharyngeal inflammation, esophageal ulcer, eosinophilic esophagitis, infectious esophagitis, and esophageal motor disorders. Although GERD is not a prevalent cause of difficulty in swallowing or pain with swallowing, an evaluation including barium upper GI series and possibly upper endoscopy should be considered if physical examination and history of disease do not reveal a cause. Therapy with acid suppression without earlier evaluation is not recommended. In the infant with feeding refusal, acid suppression without earlier diagnostic evaluation is not recommended.

6.6. Infants With Apnea or Apparent Life-threatening Event In the majority of infants with apnea or apparent life-threatening events (ALTEs), GER is not the cause. In the uncommon circumstance in which a relation between symptoms and GER is suspected or in those with recurrent symptoms, MII/pH esophageal monitoring in combination with polysomnographic recording and precise, synchronous symptom recording may aid in establishing cause and effect.

6.7. Reactive Airways Disease In patients with asthma who also have heartburn, reflux may be a contributing factor to the asthma. Despite a high frequency of abnormal reflux studies in patients with asthma who do not have heartburn, there is no strong evidence to support empiric PPI therapy in unselected pediatric patients with wheezing or asthma. Only 3 groups—those with heartburn, those with nocturnal asthma symptoms, and those with steroid-dependent difficult-to-control asthma—may derive some benefit from long-term medical or surgical antireflux therapy. Finding abnormal esophageal pH exposure by esophageal pH monitoring, with or without impedance, before considering a trial of long-term PPI therapy or surgery may be useful, although the predictive value of these studies for this purpose has not been established. The relative efficacy of medical versus surgical therapy for GERD in children with asthma is unknown.

6.8. Recurrent Pneumonia Recurrent pneumonia and interstitial lung disease may be the complications of GER due to aspiration of gastric contents. No test can determine whether GER is causing recurrent pneumonia. An abnormal esophageal pH test may increase the probability that GER is a cause of recurrent pneumonia but is not proof thereof. Nuclear scintigraphy can detect

aspirated gastric contents when images are obtained for 24 hours after enteral administration of a labeled meal. Aspiration during swallowing is more common than aspiration of refluxed material. A trial of nasogastric feeding may be used to exclude aspiration during swallowing as a potential cause of recurrent disease. A trial of nasojejunal therapy may help in determining whether surgical antireflux therapy is likely to be beneficial. In patients with severely impaired lung function, antireflux surgery may be necessary to prevent further pulmonary damage, despite lack of definitive proof that GER is causative.

6.9. Upper Airway Symptoms The data linking reflux to chronic hoarseness, chronic cough, sinusitis, chronic otitis media, erythema, and cobblestone appearance of the larynx come mainly from case reports and case series. The association of reflux with these conditions and response to antisecretory therapy have not been proven by controlled studies. Patients with these symptoms or signs should not be assumed to have GERD without consideration of other potential etiologies.

6.10. Dental Erosions An association between GERD and dental erosions has been established. The severity of dental erosions seems to be correlated with the presence of GERD symptoms and, in adults, with the severity of proximal esophageal or oral exposure to an acidic pH. Young children and children with neurologic impairment appear to be at the greatest risk. Factors other than reflux that cause similar dental erosions include juice drinking, bulimia, and racial and genetic factors affecting the characteristics of enamel and saliva.

6.11. Dystonic Head Posturing (Sandifer Syndrome) Sandifer syndrome (spasmodic torsional dystonia with arching of the back and opisthotonic posturing, mainly involving the neck and back) is an uncommon but specific manifestation of GERD. It resolves with antireflux treatment.

7. GROUPS AT HIGH RISK FOR GERD

Certain conditions are predisposed to severe, chronic GERD. These include neurologic impairment, obesity, repaired esophageal atresia or other congenital esophageal disease, cystic fibrosis, hiatal hernia, repaired achalasia, lung transplantation, and a family history of GERD, BE, or esophageal adenocarcinoma. Although many premature infants are diagnosed with GERD because of nonspecific symptoms of feeding intolerance, apnea spells, feeding refusal, and pain behavior, there are no controlled data that confirm reflux as a cause. Although reflux may be more common in infants with bronchopulmonary dysplasia, there is no evidence that antireflux therapy affects the clinical course or outcome of this condition.

PEDIATRIC GER GUIDELINE

1. RATIONALE

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) published the first clinical practice guidelines on pediatric gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) in 2001 (1). Consensus-based guidelines on several aspects of GER and GERD were developed in Europe at about the same time but were not officially endorsed by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (2,3). In 2007, the Councils of ESPGHAN and NASPGHAN established a joint committee to review, update, and unify these guidelines as a means of improving uniformity of practice and quality of patient care (4,5).

The committee used the 2001 NASPGHAN guidelines as an outline, adding new sections on certain pediatric populations at high risk for GERD. In all deliberations, the committee attempted to distinguish physiologic GER events from GERD. Furthermore, in response to evidence that the diagnosis of GERD is applied excessively to healthy infants with bothersome but harmless symptoms of physiologic GER (6–9), the committee reevaluated the 2001 diagnostic and therapeutic algorithms to clarify the distinction between physiologic GER and GERD. In its recommendations for testing, the committee confronted the ongoing problem that current reflux tests may identify variations from normal but cannot predict symptom severity, natural history, or response to therapy.

These guidelines are designed to assist pediatric health care providers in the diagnosis and management of GER and GERD. They are intended to serve as general guidelines and not as a substitute for clinical judgment, or as a protocol applicable to all patients.

2. METHODS

2.1. Selection of Committee Members

The NASPGHAN–ESPGHAN Joint Guideline Committee included 5 European and 4 North American

pediatric gastroenterologists with extensive experience in GER and GERD, selected by their respective societies, and 2 North American primary care pediatricians experienced in clinical epidemiology. Both pediatric epidemiologists, members of the American Academy of Pediatrics Section on Epidemiology, were selected because of their contribution to the previous NASPGHAN GERD guidelines.

2.2. Guideline Preparation Process

The previous guidelines developed by NASPGHAN (1) and ESPGHAN (2,3) were used as the foundation for the current guidelines. Articles written in English and published between March 1999 (the date of the previous review) and October 2008 were identified using PubMed and Cumulative Index to Nursing and Allied Health Literature. Letters, editorials, case reports, and reviews were eliminated from the initial evaluation. Additional articles were identified by members of the committee from bibliographies found in other articles and study results in the public domain on the US National Institutes of Health Web site. These included review articles as well as articles that involved the care of adults. A total of 377 articles related to therapy and 195 articles related to etiology, diagnosis, and prognosis were reviewed for this guideline.

Using the best-available evidence from the literature, the committee evaluated current diagnostic tests and therapeutic modalities for GER and GERD. Evidence of a causal relation between GER/GERD and several common symptoms or symptom complexes were evaluated. Diagnostic tests were evaluated by the following criteria: ability to confirm a diagnosis of GERD; ability to exclude other diagnoses with similar presentation; ability to detect complications of GERD; and ability to predict disease severity, natural history of disease, and response to treatment. Therapy was evaluated considering efficacy, appropriate clinical indications, and potential risks and complications.

The committee convened face to face 3 times and had several conference calls. It based its recommendations on its study of the literature review combined with expert opinion and the evidence available in the adult literature when pediatric evidence was insufficient. Consensus was achieved for all of the recommendations through nominal group technique, a structured quantitative method (10). Articles were evaluated using the Oxford Centre for Evidence-based Medicine Levels of Evidence (11). Using the Oxford Grades of Recommendation (11), the quality of evidence of each of the recommendations made by the committee was determined and is summarized in Appendices A to C. Sections of the document were written by individual committee members, then reviewed and edited by a separate committee member; in most instances both a NASPGHAN and an ESPGHAN member participated in preparing the initial draft of each section. These sections and other evidence available in previously prepared tables that listed references and graded the quality of each reference were distributed, then reviewed and discussed to achieve consensus agreement in conference sessions. The document was then distributed to the entire NASPGHAN membership for comment. Further revisions were made based on their suggestions following telephone conference and e-mail communications among committee members. Complete voting anonymity could not be maintained through the revision process because voting was done by e-mail, but only 1 of the co-chairs (C.D.R.) was aware of e-mail votes. Following final committee approval, the document was endorsed by the Executive Councils of NASPGHAN and ESPGHAN.

2.3. Management of Potential Conflict of Interest

Disclosures of potential conflicts of interest of committee members or immediate family were documented and shared with committee members before the first meeting of the committee and updated before the review of the final document. Disclosures included paid or donated services of any kind, research support, stock ownership or options, and intellectual property rights. During the process of preparing the guidelines, the scientific data were reviewed by all of the members of the committee, and recommendations were voted on by all of the members. No section of the document was written solely by any 1 member. Chairs or committee members did not require that any individual be removed from discussions or voting based on potential conflicts of interest. Potential conflicts of interest are listed in Appendix D. No industry support was used for the production of these guidelines.

3. DEFINITIONS AND MECHANISMS

GER is the passage of gastric contents into the esophagus with or without regurgitation and vomiting. GER is a normal physiologic process occurring several times per day in healthy infants, children, and adults. Most episodes of GER in healthy individuals last <3 minutes, occur in the postprandial period, and cause few or no symptoms (12). In contrast, GERD is present when the reflux of gastric contents causes troublesome symptoms and/or complications (13). Every effort was made to use these 2 terms strictly as defined.

Regurgitation in pediatrics is defined as the passage of refluxed gastric contents into the pharynx or mouth and sometimes expelled out of the mouth. Regurgitation is generally assigned as effortless and nonprojectile, although it may sometimes be forceful in infants (13). Other terms such as ''spitting-up,'' ''posseting,'' and ''spilling,'' are considered equivalent to regurgitation. Spitting up, which occurs daily in about 50% of the infants

younger than 3 months of age, is the most visible symptom of regurgitation. Regurgitation resolves spontaneously in most healthy infants by 12 to 14 months of age (14–18).

Reflux episodes sometimes trigger vomiting, a coordinated autonomic and voluntary motor response, causing forceful expulsion of gastric contents through the mouth. Vomiting associated with reflux is probably a result of the stimulation of pharyngeal sensory afferents by refluxed gastric contents. Rumination refers to the effortless regurgitation of recently ingested food into the mouth with subsequent mastication and reswallowing. Rumination syndrome is a distinct clinical entity with regurgitation of ingested food within minutes following meals because of the voluntary contraction of the abdominal muscles (19,20).

Reflux episodes occur most often during transient relaxations of the lower esophageal sphincter (LES) unaccompanied by swallowing, which permit gastric contents to flow into the esophagus (21–23). A minor proportion of reflux episodes occur when the LES pressure fails to increase during a sudden increase in intra-abdominal pressure or when LES resting pressure is chronically reduced. Alterations in several protective mechanisms allow physiologic reflux to become GERD: insufficient clearance and buffering of refluxate, delayed gastric emptying, abnormalities in epithelial restitution and repair, and decreased neural protective reflexes of the aerodigestive tract. In hiatal hernia (HH), all of the antireflux barriers at the LES (including the crural support, intraabdominal segment, and angle of His) are compromised (24–27) and transient LES relaxations (TLESR) also occur with greater frequency (25). Erosive esophagitis by itself may promote esophageal shortening and consequent hiatal herniation (25). HH is prevalent in adults and children with severe reflux complications (28–31), and hernia size is a major determinant of GERD severity (30,32).

Significant clusterings of reflux symptoms, HH, erosive esophagitis, Barrett esophagus (BE), and esophageal adenocarcinoma occur in families, suggesting some heritability of GERD and its complications (33–37). A large Swedish Twin Registry study found an increased concordance for reflux in monozygotic compared with dizygotic twins (33). Several other pediatric patient populations appear to be at higher risk for GERD than healthy infants, children, or adolescents. These include individuals with neurologic impairment (NI), obesity, certain genetic syndromes, esophageal atresia (EA), chronic lung diseases, and those with a history of premature birth. These are discussed in Section 7.

4. DIAGNOSIS

The diagnosis of GERD is often made clinically based on the bothersome symptoms or signs that may be associated with GER (Table 1). However, subjective symptom descriptions are unreliable in infants and children younger than 8 to 12 years of age, and many of the purported symptoms of GERD in infants and children are nonspecific. The diagnosis of GERD is inferred when tests show excessive frequency or duration of reflux events, esophagitis, or a clear association of symptoms and signs with reflux events in the absence of alternative diagnoses.

TABLE 1. *Symptoms and signs that may be associated with gastroesophageal reflux*

Symptoms
Recurrent regurgitation with/without vomiting
Weight loss or poor weight gain
Irritability in infants
Ruminative behavior
Heartburn or chest pain
Hematemesis
Dysphagia, odynophagia
Wheezing
Stridor
Cough
Hoarseness
Signs
Esophagitis
Esophageal stricture
Barrett esophagus
Laryngeal/pharyngeal inflammation
Recurrent pneumonia
Anemia
Dental erosion
Feeding refusal
Dystonic neck posturing (Sandifer syndrome)
Apnea spells
Apparent life-threatening events

Although many tests have been used to diagnose GERD, few studies compare their utility. Importantly, it is not known whether tests can predict an individual patient's response to therapy. Tests are useful to document the presence of pathologic reflux or its complications to establish a causal relation between reflux and symptoms, to evaluate therapy, and to exclude other conditions. Because no test can address all of these questions, tests must be carefully selected according to the information sought, and the limitations of each test must be recognized.

4.1. History and Physical Examination

The major role of the history of disease and physical examination in the evaluation of GERD is to exclude other more worrisome disorders that present with vomiting and to identify complications of GERD (Table 2). Typical presenting symptoms of reflux disease in childhood vary with age and underlying medical condition (13,38); however, the underlying pathophysiology of GERD is thought to be similar at all ages including the premature infant (23,39). In 1 study, regurgitation or vomiting, abdominal pain, and cough but not heartburn

TABLE 2. *Warning signals requiring investigation in infants with regurgitation or vomiting*

Bilious vomiting
Gastrointestinal bleeding
Hematemesis
Hematochezia
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Hepatosplenomegaly
Bulging fontanelle
Macro/microcephaly
Seizures
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

were the most frequently reported symptoms in children and adolescents with GERD. Cough and anorexia or feeding refusal were more common in children 1 to 5 years of age than in older children (40).

Symptoms and signs associated with reflux (Table 1) are nonspecific. For example, not all of the children with GER have heartburn or irritability. Conversely, heartburn and irritability can be caused by conditions other than GER. Regurgitation, irritability, and vomiting are common in infants with physiologic GER or GERD (14,18,41,42) but are indistinguishable from regurgitation, irritability, and vomiting caused by food allergy (43,44), colic (45,46), and other disorders. The severity of reflux or esophagitis found on diagnostic testing does not directly correlate with the severity of symptoms (47–49).

GERD is often diagnosed clinically in adults based on a history of heartburn, defined as substernal, burning chest pain, with or without regurgitation. Recent adult and pediatric consensus guidelines have applied the terms ''typical reflux syndrome'' or ''reflux chest pain syndrome'' to this presentation (13,50). Based on expert opinion, the diagnosis of GERD can be made in adolescents presenting with typical heartburn symptoms as in adults (49,51–55). However, a clinical diagnosis based on a history of heartburn cannot be used in infants, children, or nonverbal adolescents (eg, those with NI) because these individuals cannot reliably communicate the quality and quantity of their symptoms. The verbal child can communicate pain, but descriptions of quality, intensity, location, and severity generally are unreliable until at least 8 and possibly 12 years of age (56–60).

As in adults, individual symptoms in children generally are not highly predictive of findings of GERD by objective studies. For example, in a study of irritable infants younger than 9 months of age, regurgitation >5 times per day had a sensitivity of 54% and specificity of 71% for a reflux index (RI) >10% by esophageal pH testing, whereas feeding difficulties had a sensitivity of 75% and specificity of 46% (61). A similar poor correlation of symptoms and esophageal acid exposure was observed during an omeprazole treatment study in irritable infants; similar reductions in crying occurred in both treated and untreated infants, and the extent of reduction in crying did not correlate with extent of reduction of the RI in the treated patients (46).

Because individual symptoms do not consistently correlate with objective findings or response to medical treatment, parent- or patient-reported questionnaires based on clusters of symptoms have been developed. Orenstein et al (51,62) developed a diagnostic questionnaire for GERD in infants. A score of >7 (of 25 possible) on the initial instrument demonstrated a sensitivity of 0.74 and specificity of 0.94 during primary validation. The questionnaire has undergone several revisions (54). The questionnaire has been shown to be reliable for documentation and monitoring of reported symptoms. However, when applied to a population in India, it had a sensitivity and specificity of only 43% and 79%, respectively, compared with pH-monitoring results (52). In another study of infants referred for symptoms of reflux disease and controls, the questionnaire had a sensitivity and specificity of 47% and 81% for a RI >10% and 65% and 63% for a reflux index >5%. The questionnaire score failed to identify 26% of the infants with GERD. The score was positive in 17 of 22 infants with normal biopsies and pH studies and in 14 of 47 infants with normal pH studies. No single symptom was significantly associated with esophagitis (49). In another study, the questionnaire was unable to identify a group of infants responsive to proton pump inhibitor (PPI) therapy (9). Thus, no symptom or cluster of symptoms has been shown to reliably predict complications of reflux or to predict those infants likely to respond to therapy.

A 5-item questionnaire developed for children 7 to 16 years of age had a sensitivity of 75% and a specificity of 96% compared with pH monitoring during primary validation (63). No subsequent independent confirmatory validation has been performed. Other diagnostic questionnaires, such as the GERD symptom questionnaire (53), have not been compared with objective standards like endoscopy, pH monitoring, or esophageal multiple intraluminal impedance (MII) monitoring. Some researchers have used questionnaires to monitor symptoms of children during GERD therapy (64). Whether this method is preferable to monitoring individual symptoms is uncertain. Although daily symptom diaries are frequently used in adults to monitor the effects of therapy, these have not been validated in children.

4.2. Esophageal pH Monitoring

Intraluminal esophageal pH monitoring measures the frequency and duration of acid esophageal reflux

episodes. Most commercially available systems include a catheter for nasal insertion with 1 or more pH electrodes (antimony, glass, or ion-sensitive field effect) arrayed along its length and a system for data capture, analysis, and reporting. Slow electrode response times (antimony being the slowest) do not alter the assessment of total reflux time substantially but may affect the accuracy of correlation between symptoms and reflux episodes (65). Esophageal pH monitoring is insensitive to weakly acid and nonacid reflux events. Recently, wireless sensors that can be clipped to the esophageal mucosa during endoscopy have allowed pH monitoring without a nasal cannula for up to 48 hours. Placement of wireless electrodes requires sedation or anesthesia, and comfort has been an issue in some studies (66–68). The size of current wireless electrodes precludes their use in small infants. Benefits, risks, and indications for wireless electrode monitoring have not been fully defined in children. Data on reproducibility of conventional and wireless pH studies are contradictory (68–72).

By convention, a drop in intraesophageal pH <4.0 is considered an acid reflux episode. This cutoff was initially chosen because heartburn induced by acid perfusion of the esophagus in adults generally occurs at pH <4.0 (73). Although interpretation of pH monitoring data is simplified by computerized analysis, visual inspection of the tracing is required to detect artifacts and evaluate possible clinical correlations. Common parameters obtained from pH monitoring include the total number of reflux episodes, the number of reflux episodes lasting >5 minutes, the duration of the longest reflux episode, and the RI (percentage of the entire record that esophageal pH is <4.0). GER events that occur while supine or upright or while awake or asleep are often discriminated by the automated software used in both adults and children, but the clinical value of such differentiation has not been established (74–80).

The RI is the most commonly used summary score. Several scoring systems for pH-monitoring studies have been developed (74,75,81), but no system is clearly superior to measuring the RI (82). Normal pediatric ranges are established for glass and antimony electrodes but not for ion-sensitive field effect or wireless technologies. The normal pediatric ranges previously in general use were obtained using glass electrodes (65,83), but such data poorly correlate with that obtained by the antimony electrodes now in common use (84). Moreover, normal data depend on the definition of a ''normal population.'' In the first study by Vandenplas et al (83), showing a low RI in young infants, the definition of ''normal infant'' was an infant who did not regurgitate or vomit. In the second study, a ''normal population'' was defined as an infant who had not been treated for reflux (65). Although the definition of the first study was biased toward a ''too normal'' population, the second study included all of the untreated infants, thus possibly some infants with GERD. A study by Sondheimer (85) showed a different range of normal values for infants. Most of the data, provided in previous sections, pertain to infants, in whom frequency of feeding and buffering of refluxate can confound findings between studies (76). For these reasons, specific ''cutoff'' values that discriminate between physiologic GER and pathologic GERD are suspect; rather, it is likely that a continuum exists such that normal ranges should be regarded as guidelines for interpretation rather than absolutes. In pH studies performed with antimony electrodes, an RI $>7\%$ is considered abnormal, an RI $<3\%$ is considered normal, and an RI between 3% and 7% is indeterminate.

Abnormal esophageal pH monitoring has not been shown to correlate with symptom severity in infants. In a study of infants with suspected GERD, an abnormal pH study (RI $>10\%$) was associated only with pneumonia, apnea with fussing, defecation less than once per day, and constipation (49). An abnormal RI is more frequently observed in adults and children with erosive esophagitis than in normal adults and children or those with nonerosive reflux disease (NERD), but there is substantial overlap among groups (79,86,87). In childen with documented esophagitis, normal esophageal pH monitoring suggests a diagnosis other than GERD (88,89). The RI is often abnormal in children with difficult-to-control asthma and in otherwise healthy infants with daily wheezing (90). Esophageal pH monitoring may be abnormal in patients with conditions other than GERD, such as gastric outlet obstruction, motility disorders, and esophagitis due to other disorders, including eosinophilic esophagitis (EoE) (91–94). Although multiple case series report the use of esophageal pH monitoring to select the children reported to benefit from antireflux surgery (95–99), the reliability of such data to predict improvement following either medical or surgical antireflux therapy has not been established.

The application of various methods of analysis of esophageal pH-monitoring results, including the symptom index (SI), symptom sensitivity index (SSI), and symptom association probability (SAP), may help in correlating symptoms with acid reflux. A prospective study in adults found that when compared with symptom improvement following high-dose PPI therapy, the sensitivities of the SI, SSI, and SAP were 35%, 74%, and 65% and specificities were 80%, 73%, and 73%, respectively (100). The clinical utility of pH studies and their ability to determine a causal relation between specific symptoms (eg, pain, cough) and reflux remain controversial in adults (101), and are not validated in pediatric patients.

Esophageal pH monitoring provides a quantitative measure of esophageal acid exposure with established normal ranges, but the severity of pathologic acid reflux does not correlate consistently with symptom severity or demonstrable complications. In childen with documented

esophagitis, normal esophageal pH monitoring suggests a diagnosis other than GERD (88,89). Esophageal pH monitoring is useful for evaluating the efficacy of antisecretory therapy. It may be useful to correlate symptoms (eg, cough, chest pain) with acid reflux episodes, and to select those children with wheezing or respiratory symptoms in which acid reflux may be an aggravating factor. The sensitivity and specificity of pH monitoring are not well established.

4.3. Combined Multiple Intraluminal Impedance and pH Monitoring

MII is a procedure for measuring the movement of fluids, solids, and air in the esophagus (102). It is a relatively new technology that provides a more detailed description of esophageal events with a more rapid response time than current pH-monitoring technology. MII measures changes in the electrical impedance (ie, resistance) between multiple electrodes located along an esophageal catheter. Esophageal impedance tracings are analyzed for the typical changes in impedance caused by the passage of liquid, solid, gas, or mixed boluses. If the impedance changes of a liquid bolus appear first in the distal channels and proceed sequentially to the proximal channels, they indicate retrograde bolus movement, which is GER. The direction and velocity of a bolus can be calculated using the defined distance between electrodes and the time between alterations in the impedance pattern of sequential electrode pairs. The upward extent of the bolus and the physical length of the bolus can also be evaluated (103). MII can detect extremely small bolus volumes (104).

MII and pH electrodes can and should be combined on a single catheter. The combined measurement of pH and impedance (pH/MII) provides additional information as to whether refluxed material is acidic, weakly acidic, or nonacidic (105–109). Recent studies have found variable reproducibility (110,111). Evaluation of MII recordings is aided by automated analysis tools (112), but until the currently available automatic analysis software has been validated, a visual reading of the data is required. Normal values for all of the age groups have not yet been established (113).

The risks and side effects of MII are low and the same as those of isolated pH monitoring. The combination of pH/MII with simultaneous monitoring of symptoms using video-polysomnography or manometry has proven useful for the evaluation of symptom correlations between reflux episodes and apnea, cough, other respiratory symptoms, and behavioral symptoms (23,24,114–116). The technology is especially useful in the postprandial period or at other times when gastric contents are nonacidic. The relation between weakly acid reflux and symptoms of GERD requires clarification. Measurement of other parameters such as SI or SAP may be of additional value to prove symptom association with reflux, especially when combined with MII (117). Whether combined esophageal pH and impedance monitoring will provide useful measurements that vary directly with disease severity, prognosis, and response to therapy in pediatric patients has yet to be determined.

4.4. Motility Studies

Esophageal manometry measures esophageal peristalsis, upper and lower esophageal sphincter pressures, and the coordinated function of these structures during swallowing. Although esophageal manometry has been an important tool in studying the mechanisms of GERD, GERD cannot be diagnosed by esophageal manometry. Manometric studies were critical in identifying TLESR as a causative mechanism for GERD (21). A variety of nonspecific esophageal motor abnormalities have been found in children with developmental delay and NI, a group at high risk for severe GERD (118). Esophageal motor abnormalities are also common in patients with esophagitis (119,120). In these 2 situations esophageal motor dysfunction may be a secondary phenomenon related to esophagitis because it has been observed to resolve upon treatment of esophagitis (119). Recent studies indicate that there is no role for manometry in predicting outcome of fundoplication (121). Manometric studies are also important in confirming a diagnosis of achalasia or other motor disorders of the esophagus that may mimic GERD (122).

Esophageal manometry may be abnormal in patients with GERD, but the findings are not sufficiently sensitive or specific to confirm a diagnosis of GERD, nor to predict response to medical or surgical therapy. It may be useful in patients who have failed acid suppression and who have negative endoscopy to search for a possible motility disorder, or to determine the position of the LES to place a pH probe. Manometric studies are useful to confirm a diagnosis of achalasia or other motor disorders of the esophagus that may mimic GERD.

4.5. Endoscopy and Biopsy

Upper gastrointestinal (GI) endoscopy allows direct visual examination of the esophageal mucosa. Mucosal biopsies enable evaluation of the microscopic anatomy (123). Macroscopic lesions associated with GERD include esophagitis, erosions, exudate, ulcers, strictures, HH, areas of possible esophageal metaplasia, and polyps. Although endoscopy can detect strictures, subtle degrees of narrowing may be better shown on barium contrast study, during which the esophagus can be distended with various techniques, such as a radioopaque pill and barium-soaked bread or marshmallows. Malrotation and achalasia cannot be diagnosed by endoscopy. These

and other anatomic and motility disorders of the esophagus are better evaluated by barium radiology or motility studies.

Recent global consensus guidelines define reflux esophagitis as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the gastroesophageal junction (13,50,124). Evidence from adult studies indicates that visible breaks in the esophageal mucosa are the endoscopic signs of greatest interobserver reliability (125–127). Operator experience is an important component of interobserver reliability (128,129). Mucosal erythema or an irregular Z-line is not a reliable sign of reflux esophagitis (126,127). Grading the severity of esophagitis, using a recognized endoscopic classification system, is useful for evaluation of the severity of esophagitis and response to treatment. The Hetzel-Dent classification (125) has been used in several pediatric studies (29,130,131), whereas the Los Angeles classification (124) is generally used for adults, but it is suitable also for children. The presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of NERD or esophagitis of other etiologies (93,132,133).

The diagnostic yield of endoscopy is generally greater if multiple samples of good size and orientation are obtained from biopsy sites that are identified relative to major esophageal landmarks (28,123,134). Several variables have an impact on the validity of histology as a diagnostic tool for reflux esophagitis (133,135). These include sampling error because of the patchy distribution of inflammatory changes and a lack in standardization of biopsy location, tissue processing, and interpretation of morphometric parameters. Histology may be normal or abnormal in NERD because GERD is an inherently patchy disease (133,136). Histologic findings of eosinophilia, elongation of papillae (rete pegs), basal hyperplasia, and dilated intercellular spaces (spongiosis) are neither sensitive nor specific for reflux esophagitis. They are nonspecific reactive changes that may be found in esophagitis of other causes or in healthy volunteers (49,89,132,133,135,137–141). Recent studies have shown considerable overlap between the histology of reflux esophagitis and EoE (93,94,132,142). Many histologic parameters are influenced by drugs used to treat esophagitis or other disorders.

GERD is likely the most common cause of esophagitis in children, but other disorders such as EoE, Crohn disease, and infections also cause esophagitis (Table 3) (132). EoE and GERD have similar symptoms and signs and can be best distinguished by endoscopy with biopsy. A key difference, endoscopically, is that EoE is generally not an erosive disease but has its own typical endoscopic features such as speckled exudates, trachealization of the esophagus, or linear furrowing. In up to 30% of cases, however, the esophageal mucosal appearance is normal (93). When EoE is considered as a part of the differential diagnosis, it is advisable to take esophageal biopsies from the proximal and distal esophagus (93). Mucosal eosinophilia may be present in the esophageal mucosa in asymptomatic infants younger than 1 year of age (143), and in symptomatic infants eosinophilic infiltrate may be because of milk-protein allergy (142).

TABLE 3. *Causes of esophagitis*

Gastroesophageal reflux	Graft-versus-host disease
Eosinophilic esophagitis	Caustic ingestion
Infections	Postsclerotherapy/banding
Candida albicans	Radiation/chemotherapy
Herpes simplex	Connective tissue disease
Cytomegalovirus	Bullous skin diseases
Crohn disease	Lymphoma
Vomiting, bulimia	
Pill induced	

There is insufficient evidence to support the use of histology to diagnose or exclude GERD. The primary role for esophageal histology is to rule out other conditions in the differential diagnosis, such as EoE, Crohn disease, BE, and infection. This conclusion concurs with that of a global pediatric consensus group that included some members of the present committee (E.H., Y.V., C.D.R.) (13). When symptoms suggestive of GERD are present in adolescents or adults in the absence of erosive esophagitis, the clinical entity is known as NERD. In NERD, there is no evidence that esophageal histology makes a difference to clinical care decisions; that is, patient treatment is guided by symptoms, whether or not reactive histologic changes are present on biopsy.

At endoscopy, accurate documentation of esophagogastric landmarks is necessary for the diagnosis of HH and endoscopically suspected esophageal metaplasia (ESEM) (123,134,144–147). This is of particular importance in children with severe esophagitis, in whom landmarks may be obscured by bleeding or exudate, or when landmarks are displaced by anatomic abnormalities or HH (28,123,134). In these circumstances, a course of high-dose PPIs for at least 12 weeks is advised, followed by a repeat endoscopy, to remove the exudative camouflage and better visualize the landmarks (134,148).

When biopsies from ESEM show columnar epithelium, the term BE should be applied and the presence or absence of intestinal metaplasia specified (13,50). Thus, BE may be diagnosed in the presence of only cardia-type mucosa (149,150). BE occurs with greatest frequency in children with underlying conditions putting them at high risk for GERD (see Section 7) (28,31).

4.6. Barium Contrast Radiography

The upper GI series is neither sensitive nor specific for diagnosing GERD. The sensitivity, specificity, and

positive predictive value of the upper GI series range from 29% to 86%, 21% to 83%, and 80% to 82%, respectively, when compared with esophageal pH monitoring (151–157). The brief duration of the upper GI series produces false-negative results, whereas the frequent occurrence of nonpathological reflux during the examination produces false-positive results.

Therefore, routine performance of upper GI series to diagnose reflux or GERD is not justified (158). However, the upper GI series is useful to detect anatomic abnormalities such as esophageal stricture, HH, achalasia, tracheoesophageal fistula, intestinal malrotation, or pyloric stenosis, which may be considered in the differential diagnosis of infants and children with symptoms suggesting GERD.

4.7. Nuclear Scintigraphy

In gastroesophageal scintigraphy, food or formula labeled with ^{99}technetium is introduced into the stomach and areas of interest—stomach, esophagus, and lungs—are scanned for evidence of reflux and aspiration. The nuclear scan evaluates only postprandial reflux and demonstrates reflux independent of the gastric pH. Scintigraphy can provide information about gastric emptying, which may be delayed in children with GERD (159–161). A lack of standardized techniques and the absence of age-specific norms limit the value of this test. Sensitivity and specificity of a 1-hour scintigraphy for the diagnosis of GERD are 15% to 59% and 83% to 100%, respectively, when compared with 24-hour esophageal pH monitoring (162–165). Late postprandial acid exposure detected by pH monitoring may be missed with scintigraphy (166).

Gastroesophageal scintigraphy scanning can detect reflux episodes and aspiration occurring during or shortly after meals, but its reported sensitivity for microaspiration is relatively low (167–169). Evidence of pulmonary aspiration may be detected during a 1-hour scintigraphic study or on images obtained up to 24 hours after administration of the radionuclide (170). A negative test does not exclude the possibility of infrequently occurring aspiration (168). One study of children with refractory respiratory symptoms found that half had scintigraphic evidence of pulmonary aspiration (169). However, aspiration of both gastric contents and saliva also occurs in healthy adults during deep sleep (171,172).

Gastric emptying studies have shown prolonged half-emptying times in children with GER. Delayed gastric emptying may predispose to GERD. Tests of gastric emptying are not a part of the routine examination of patients with suspected GERD, but may be important when symptoms suggest gastric retention (173–176).

Nuclear scintigraphy is not recommended in the routine diagnosis and management of GERD in infants and children.

4.8. Esophageal and Gastric Ultrasonography

Ultrasonography is not recommended as a test for GERD but can provide information not available through other technology. Ultrasonography of the gastroesophageal junction can detect fluid movements over short periods of time and thereby can detect nonacid reflux events. It can also detect HH, length and position of the LES relative to the diaphragm, and magnitude of the gastroesophageal angle of His. Barium upper GI series can provide the same information. When 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 postprandially is about 95% with a specificity of only 11%, and there is no correlation between reflux frequency detected by ultrasound and reflux index detected by pH monitoring (177,178). Intraluminal esophageal ultrasound is used in adults to evaluate esophageal wall thickness and muscle shortening, parameters that vary with inflammation, scarring, and malignancy (179). At present, there is no role for ultrasound as a routine diagnostic tool for GERD in children.

4.9. Tests on Ear, Lung, and Esophageal Fluids

Recent studies have suggested that finding pepsin, a gastric enzyme, in middle ear effusions of children with chronic otitis media, indicates that reflux is playing an etiologic role (180–183). One recent study showed no relation between the presence of pepsin in the middle ear and symptoms of GERD (184), and this relation has not been validated in controlled treatment trials. Similarly, the presence of lactose, glucose, pepsin, or lipid-filled macrophages in bronchoalveolar lavage fluids has been proposed to implicate aspiration secondary to reflux as a cause of some chronic pulmonary conditions (185–187). No controlled studies have proven that reflux is the only reason these compounds appear in bronchoalveolar lavage fluids or that reflux is the cause of pulmonary disease when they are present.

Continuous monitoring of bilirubin in the esophagus has been suggested as a means of detecting esophageal reflux of duodenal juice or duodenogastroesophageal reflux. Duodenal juice components appear to damage the esophagus in a pH-dependent manner (188). Two uncontrolled pediatric case series have suggested that duodenogastroesophageal reflux produced GERD that was refractory to therapy with PPIs (189,190). One study indicated that therapy with PPIs decreased the esophageal damage caused by duodenogastroesophageal reflux (190). At present, there is insufficient evidence to recommend continuous monitoring of the esophagus for bilirubin in the routine evaluation of GERD. The role of bile reflux in children resistant to PPI treatment has not been established.

4.10. Empiric Trial of Acid Suppression as a Diagnostic Test

In adults, empiric treatment with acid suppression, that is, without diagnostic testing, has been used for symptoms of heartburn (191), chronic cough (192,193), noncardiac chest pain (194), and dyspepsia (195). However, empiric therapy has only modest sensitivity and specificity as a diagnostic test for GERD, depending upon the comparative reference standard used (endoscopy, pH monitoring, symptom questionnaires) (196), and the appropriate duration of a ''diagnostic trial'' of acid suppression has not been determined. A meta-analysis evaluating pooled data from 3 large treatment trials among the adults with NERD showed that 85% of the patients who had symptom resolution after 1 week of PPI treatment remained well for the entire 4 weeks of PPI treatment, thus ''confirming'' the diagnosis of GERD (197). However, 22% of the patients who had no improvement after 1 week of treatment did improve by the fourth week of treatment. An uncontrolled trial of esomeprazole therapy in adolescents with heartburn, epigastric pain, and acid regurgitation showed complete resolution of symptoms in 30% to 43% by 1 week, but the responders increased to 65% following 8 weeks of treatment (55). Another uncontrolled treatment trial of pantoprazole in children ages 5 to 11 years reported greater symptom improvement at 1 week with one 40-mg dose compared with one 10-mg or 20-mg dose (64). After 8 weeks all of the treatment groups improved. Similar improvement in symptoms over time has been observed in adults with erosive esophagitis (198,199). One study of infants with symptoms suggestive of GERD who were treated empirically with a PPI showed no efficacy over placebo (9).

The treatment period required to achieve uniform therapeutic responses with PPI therapy probably varies with disease severity, treatment dose, and specific symptoms or complications (200). The 2-week ''PPI test'' lacks adequate specificity and sensitivity for use in clinical practice. In an older child or adolescent with symptoms suggesting GERD, an empiric PPI trial is justified for up to 4 weeks. Improvement following treatment does not confirm a diagnosis of GERD because symptoms may improve spontaneously or respond by a placebo effect. There is no evidence to support an empiric trial of pharmacologic treatment in infants and young children as a diagnostic test of GERD.

5. TREATMENT

Management options for physiologic GER and for GERD discussed in this section include lifestyle changes, pharmacologic therapy, and surgery. Lifestyle changes in infants with physiologic GER include nutrition, feeding, and positional modifications. In older children and adolescents, lifestyle changes include modification of diet and sleeping position, weight reduction, and smoking cessation.

Medications for use in GERD include agents to buffer gastric contents or suppress acid secretion. Agents affecting GI motility are discussed. Surgical therapy includes fundoplication and other procedures to eliminate reflux.

5.1. Lifestyle Changes

Parental education, guidance, and support are always required and usually sufficient to manage healthy, thriving infants with symptoms likely because of physiologic GER.

5.1.1. Feeding Changes in Infants

About 50% of the healthy 3- to 4-month-old infants regurgitate at least once per day (16,18) and up to 20% of caregivers in the United States seek medical help for this normal behavior (16). Breast-fed and formula-fed infants have a similar frequency of physiologic GER, although the duration of reflux episodes measured by pH probe may be shorter in breast-fed infants (201–203).

A subset of infants with allergy to cow's milk protein experience regurgitation and vomiting indistinguishable from that associated with physiologic GER (9,69,142,204–206). 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 (206,207). Studies support the use of extensively hydrolyzed or amino acid formula in formula-fed infants with bothersome regurgitation and vomiting for trials lasting up to 4 weeks (206–208). Cow's milk protein and other proteins pass into human breast milk in small quantities. Breast-fed infants with regurgitation and vomiting may therefore benefit from a trial of withdrawal of cow's milk and eggs from the maternal diet (209,210). The symptoms of infant reflux are almost never so severe that breast-feeding should be discontinued. There are no studies specifically evaluating soy protein allergy in infants with regurgitation and vomiting, or the role of soy protein–based formula in the treatment of infants with regurgitation. Moreover, there are no data on allergy to possible formula-thickening agents such as rice cereals.

One study in infants showed that large volume feedings promote regurgitation, probably by increasing the frequency of TLESR and reduced feeding volume and decreased reflux frequency (211). Severe reduction in feeding volume during an extended period may deprive the infant of needed energy and adversely affect weight gain. Infants with inadequate weight gain because of losses by regurgitation may benefit from increasing the energy density of formula when volume or frequency of feedings is decreased as a part of therapy.

Adding thickening agents such as rice cereal to formula does not decrease the time with pH <4 (reflux index) measured by esophageal pH studies, but it does decrease the frequency of overt regurgitation (211–215). Studies with combined pH/MII show that the height of reflux in the esophagus is decreased with thickened formula as well as the overt frequency of regurgitation, but not the frequency of reflux episodes (114). One study reported an improvement in esophageal pH parameters with cornstarch-thickened formula (216). Another study showed no change in esophageal impedance parameters of premature infants receiving cornstarch-thickened human milk (217).

In the United States, rice cereal is the most commonly used thickening agent for formula (214). Rice cereal–thickened formula produces a decrease in the volume of regurgitation but may increase coughing during feedings (218). Formula with added rice cereal may require a nipple with an enlarged hole to allow adequate flow. Excessive energy intake is a potential problem with long-term use of feedings thickened with rice cereal or cornstarch (219). Thickening a 20-kcal/oz infant formula with 1 tablespoon of rice cereal per ounce increases the energy density to ~34 kcal/oz (~1.1 kcal/mL). Thickening with 1 tablespoon per 2 oz of formula increases the energy density to ~27 kcal/oz (~0.95 kcal/mL).

Commercial antiregurgitant (AR) formulae containing processed rice, corn or potato starch, guar gum, or locust bean gum are available in Europe, Asia, and the United States. These formulae decrease overt regurgitation and vomiting frequency and volume compared with unthickened formulae (1,220,221) or formulae thickened with rice cereal (216,222–226). However, a natural history study showed only a nonsignificant decrease in episodes of regurgitation and no change in infant comfort among infants fed with a formula thickened with bean gum versus those fed with a formula thickened with rice cereal or regular formula (227). When ingested in normal volumes, AR formulae contain an energy density, osmolarity, protein, calcium, and fatty acid content appropriate to an infant's nutritional needs, whereas a formula with added thickener has a higher energy density, and in normal ingested volumes this may provide more energy than needed. A largely untested potential advantage of AR formulae is that they do not require a substantially increased sucking effort, obviating the need for use of a large-bore nipple hole. In vitro studies have shown a decrease in the absorption of minerals and micronutrients from formulae commercially thickened with indigestible but not digestible carbohydrates (228,229). The clinical significance of these findings is unclear because a 3-month follow-up study of children on formula thickened with indigestible carbohydrate showed normal growth and nutritional parameters (230).

The use of AR formulae and formulae with added thickener results in a decrease of observed regurgitation. Although the actual number of esophageal reflux episodes may not decrease, the reduction in regurgitation may be a welcome improvement in quality of life for caregivers. The impact of thickened formula on the natural history of physiologic GER or GERD has not been studied. The allergenicity of commercial thickening agents is uncertain, and the possible nutritional risks of long-term use require additional study.

Infants with GERD who are unable to gain weight despite conservative measures and in whom nasogastric or nasojejunal feeding may be beneficial are rare (231). Similarly, nasojejunal feeding is occasionally useful in infants with recurrent reflux-related pneumonia to prevent recurrent aspiration. Although these approaches to therapy are widely used, there are no controlled studies comparing them to pharmacologic or surgical treatments.

5.1.2. Positioning Therapy for Infants

Several studies in infants have demonstrated significantly decreased acid reflux in the flat prone position compared with flat supine position (232–236). There is conflicting evidence as to whether infants placed prone with the head elevated have less reflux than those kept prone but flat (232–234,237). The amount of reflux in supine infants with head elevated is equal to or greater than in infants supine and flat (232,234,238,239). The semisupine positioning as attained in an infant car seat exacerbates GER (240). Although the full upright position appears to decrease measured reflux, 1 study suggested that using formula thickened with rice cereal is more effective in decreasing the frequency of regurgitation than upright positioning after feeds (223).

In the 1980s, prone positioning was recommended for the treatment of GERD in infants because studies showed less reflux in this position. Prone sleep positioning is associated with longer uninterrupted sleep periods and supine sleep positioning with more frequent arousals and crying (241). However, concerns regarding the association between prone positioning and sudden infant death syndrome (SIDS) required a reassessment of the benefits and risks of prone positioning for reflux management. The Nordic Epidemiological SIDS Study demonstrated that the odds ratio of mortality from SIDS was more than 10 times higher in prone-sleeping infants and 3 times higher in side-sleeping infants than in supine-sleeping infants (242–244). Therefore, prone positioning is acceptable if the infant is observed and awake, particularly in the postprandial period, but prone positioning during sleep can only be considered in infants with certain upper airway disorders in which the risk of death from GERD may outweigh the risk of SIDS. Prone positioning may be beneficial in children older than 1 year of age with GER or GERD whose risk of SIDS is negligible.

Esophageal pH and combined pH/MII monitoring show that reflux is quantitatively similar in the left-side-down and prone positions. Measured reflux in these 2 positions is less than in the right-side-down and supine positions (234,245–247). Two impedance studies of preterm infants found that postprandial reflux was greater in the right-side-down than in the left-side-down position (173,235). Based on these findings, 1 study recommended that infants be placed right-side-down for the first hour after feeding to promote gastric emptying and then switched to left-side-down thereafter to decrease reflux (173). These findings notwithstanding, it is important to note that side-lying is an unstable position for an infant who may slip unobserved into the prone position. Bolstering an infant with pillows to maintain a side-lying position is not recommended (248).

5.1.3. Lifestyle Changes in Children and Adolescents

Lifestyle changes often recommended for children and adolescents with GER and GERD include dietary modification, avoidance of alcohol, weight loss, positioning changes, and cessation of smoking. Most studies investigating these recommendations have been performed in adults, thus their applicability to children of all ages is uncertain. A review of lifestyle changes in adults with GERD concluded that only weight loss improved pH profiles and symptoms (249). Although alcohol, chocolate, and high-fat meals reduce LES pressure, only a few studies have evaluated the impact of these factors on symptoms. Tobacco smoke exposure is associated with increased irritability in infants, yet neither tobacco nor alcohol cessation has been shown to improve esophageal pH profiles or symptoms. One uncontrolled study (250) found that a low-carbohydrate diet reduced distal esophageal acid exposure and improved symptoms in obese individuals with GERD. Gastric bypass surgery significantly improved symptoms of GERD in obese adults (251). Another study (252) detected more overnight reflux in adults eating a late evening meal than in adults eating an earlier evening meal. The difference was especially obvious in overweight adults.

Current evidence generally does not support (or refute) the use of specific dietary changes to treat reflux beyond infancy. Expert opinion suggests that children and adolescents with GERD should avoid caffeine, chocolate, alcohol, and spicy foods if they provoke symptoms (253–264). In an overweight individual, weight loss does decrease reflux, and is therefore recommended (250–252,265–267). Smoking should be avoided in those with GERD because it has been linked to adenocarcinoma of the esophagus in adults (268,269). Three studies have shown that chewing sugarless gum after a meal decreases reflux (270–272). It is not known whether any lifestyle changes have an additive benefit in children or adolescents receiving pharmacological therapy.

The effectiveness of positioning for treatment of GER and GERD in children older than 1 year of age has not been studied. It is unclear whether the benefits of positional therapy identified in adults and infants younger than 1 year can be extrapolated to children in general (215). Some studies have shown that adults who sleep with the head of the bed elevated have fewer and shorter episodes of reflux and fewer reflux symptoms (273–275). Other studies in adults have shown that reflux increases in the right lateral decubitus position (245,276). It is likely therefore that adolescents, like adults, may benefit from the left lateral decubitus sleeping position with elevation of the head of the bed.

5.2. Pharmacologic Therapies

The major pharmacologic agents currently used for treating GERD in children are gastric acid buffering agents, mucosal surface barriers, and gastric antisecretory agents. Since the withdrawal of cisapride from commercial availability in most countries, prokinetic agents have been less frequently used, although domperidone is commercially available in Canada and Europe.

Comparisons between pharmacologic agents for GERD in children have been impaired by small sample size, absence of controls, and use of unreliable endpoints such as esophageal histology (Section 3.4).

5.2.1. Histamine-2 Receptor Antagonists

Histamine-2 receptor antagonists (H2RAs) decrease acid secretion by inhibiting histamine-2 receptors on gastric parietal cells. In 1 study of infants, ranitidine (2 mg/kg per dose orally) reduced the time that gastric pH was <4.0 by 44% when given twice daily and by 90% when given 3 times per day (277). One dose of ranitidine (5 mg/kg) has been shown to increase gastric pH for 9 to 10 hours in infants (278). Pharmacokinetic studies in 4- to 11-year-old children suggest that peak plasma ranitidine concentration occurs 2.5 hours after dosing with a half-life of 2 hours. Gastric pH begins to increase within 30 minutes of administration and the effect lasts for 6 hours (279). Tachyphylaxis, or diminution of the response, to intravenous ranitidine and escape from its acid-inhibitory effect have been observed after 6 weeks (280), and tolerance to oral H2RAs in adults is well recognized (281,282). Numerous randomized controlled trials (RCTs) in adults have demonstrated that cimetidine, ranitidine, and famotidine are superior to placebo for relief of symptoms and healing of esophageal mucosa (283–285). However, the efficacy of H2RAs in achieving mucosal healing is much greater in mild esophagitis than in severe esophagitis (286). One randomized trial of infants and children with erosive esophagitis compared the efficacy of cimetidine ($30–40\,mg \cdot kg^{-1} \cdot day^{-1}$) to placebo (287). Significant improvement in clinical and

histopathology scores occurred only in the cimetidine-treated group. Another randomized study in 24 children with mild to moderate esophagitis demonstrated that nizatidine ($10\,mg \cdot kg^{-1} \cdot day^{-1}$) was more effective than placebo for the healing of esophagitis and symptom relief (288). There are case series providing additional support for the efficacy of H2RAs in infants and children (289–294). Although no RCTs in children demonstrate the efficacy of ranitidine or famotidine for the treatment of esophagitis, expert opinion is that these agents are as effective as cimetidine and nizatidine. Extrapolation of the results of a large number of adult studies to older children and adolescents suggests that H2RAs may be used in these patients for the treatment of GERD symptoms and for healing esophagitis, although H2RAs are less effective than PPIs for both symptom relief and healing of esophagitis (283,295,296).

The fairly rapid tachyphylaxis that develops with H2RAs is a drawback to chronic use. In some infants, H2RA therapy causes irritability, head banging, headache, somnolence, and other side effects that, if interpreted as persistent symptoms of GERD, could result in an inappropriate increase in dosage (293). H2RAs, particularly cimetidine, are associated with an increased risk of liver disease (297,298) and cimetidine with gynecomastia (299). Other adverse effects of suppression of gastric acid are discussed in the section on PPIs.

5.2.2. Proton Pump Inhibitors

PPIs inhibit acid secretion by blocking Na^+–K^+-ATPase, the final common pathway of parietal cell acid secretion, often called the proton pump. Studies in adults have shown that PPIs produce higher and faster healing rates for erosive esophagitis than H2RAs, which in turn are better than placebo (122). The superior efficacy of PPIs is largely because of their ability to maintain intragastric pH at or above 4 for longer periods and to inhibit meal-induced acid secretion, a characteristic not shared by H2RAs. In contrast with H2RAs, the effect of PPIs does not diminish with chronic use. The potent suppression of acid secretion by PPIs also results in decrease of 24-hour intragastric volumes, thereby facilitating gastric emptying and decreasing volume reflux (300). Despite their efficacy in the management of acid-related disorders, PPIs have limitations as a consequence of their pharmacologic characteristics. They must be taken once per day before breakfast and must be protected from gastric acid by enteric coatings. Bioavailability of PPIs is decreased if they are not taken before meals. However, taking the medications before meals effectively delays absorption and onset of their antisecretory effect. Most available PPIs are therefore regarded as ''delayed release'' preparations. Achievement of maximal acid suppressant effect can take up to 4 days (301). However, a summary of adult data suggests that PPIs can also be used for ''on-demand'' treatment of symptoms (302). One commercially available ''immediate-release'' PPI is uncoated omeprazole with added bicarbonate (302). There are no data available concerning its use in children. Dexlansoprazole MR is said to be less dependent on being taken on an empty stomach. This new medication has 2 delayed-release mechanisms, and therefore a longer duration of acid suppression (303). The clinical importance of this modification has yet to be determined. There are no pediatric clinical trials and the drug is not approved for use in children.

PPIs currently approved for use in children in North America are omeprazole, lansoprazole, and esomeprazole. At this moment, in Europe, only omeprazole and esomeprazole are approved. No PPI has been approved for use in infants younger than 1 year of age. Most studies of PPIs in children are open-label and uncontrolled. In children, as in adults, PPIs are highly efficacious for the treatment of symptoms due to GERD and the healing of erosive disease. PPIs have greater efficacy than H2RAs. These data and recommendations regarding administration of PPIs are detailed in Section 6.3. Children 1 to 10 years of age appear to require a higher dose per kilogram for some PPIs than adolescents and adults. Young children require higher per kilogram doses to attain the same acid blocking effect or area under the curve (304–306). This may not apply to all of the PPIs (307). There are few pharmacokinetic data for PPIs in infants, but studies indicate that infants younger than 6 months may have a *lower* per-kilogram dose requirement than older children and adolescents (308,309).

The number of PPI prescriptions written for infants has increased manyfold in recent years despite the absence of evidence for acid-related disorders in the majority (6–8). Infant responses to many stimuli, including GER, are nonspecific (310). Double-blind randomized placebo-controlled trials of PPI efficacy in infants with GERD-like symptoms showed that PPI and placebo produced similar improvement in crying, despite the finding that acid suppression only occurred in the PPI group (9,46,308). In the largest double-blind randomized placebo-controlled trial of PPI in infants with symptoms purported to be due to GERD, response rates in those treated for 4 weeks with lansoprazole or placebo were identical (54%) (9). Thus, no placebo-controlled treatment trial, in which enrollment was based on ''typical'' GERD symptoms, has demonstrated symptom improvement in infants. This result may be because of a lack of specificity of symptom-based diagnosis of GERD, especially with esophagitis, in this age group (see above discussion on history). Double-blind randomized placebo-controlled trials show that PPI therapy is not beneficial for the treatment of infants with symptoms that previously were purported but not proven to be due to GERD.

There are potential risks associated with acid suppression resulting from PPI therapy in infants (9,46). There

are 4 main categories of adverse effects related to PPIs: idiosyncratic reactions, drug–drug interactions, drug-induced hypergastrinemia, and drug-induced hypochlorhydria. Idiosyncratic side effects occur in up to 14% of children taking PPIs (28,311,312). The most common are headache, diarrhea, constipation, and nausea, each occurring in 2% to 7%. These may resolve with decreased dose or change to a different PPI. Parietal cell hyperplasia (313,314) and occasional fundic gland polyps (315) are benign changes resulting from PPI-induced acid suppression and hypergastrinemia. Enterochromaffin cell-like hyperplasia is also a result of acid suppression. A prospective study monitoring patients treated for up to 2 years (316) and retrospective studies of patients treated up to 11 years (28) have found only mild grades of enterochromaffin-like cell hyperplasia. A recent retrospective study using sensitive staining techniques (317) showed enterochromaffin cell-like hyperplasia in the gastric body of almost half of children receiving long-term PPI continuously for a median of 2.84 years (up to 10.8 years); the hyperplasia was of the lowest 2 grades (not clinically significant), and no patient developed atrophic gastritis or carcinoid tumors.

Increasing evidence suggests that hypochlorhydria, that is, acid suppression, associated with H2RAs or PPIs may increase rates of community-acquired pneumonia in adults and children, gastroenteritis in children, and candidemia and necrotizing enterocolitis in preterm infants (318–322). In 1 study, PPIs but not H2RAs were associated with bacterial enterocolitis in adults. Doubling of the PPI dose increased the risk (323). Infants treated with PPI in a study (9) had a significantly higher rate of all adverse effects compared with the placebo group. Lower respiratory tract infections were the most frequent among these adverse effects, although the difference in respiratory tract infection rate between treated and placebo groups did not achieve statistical significance. PPIs have been shown to alter the gastric and intestinal bacterial flora in adults (324). The effect of PPI therapy on the flora of infants and childen or the consequences of any alterations have not been evaluated.

Other adverse effects have been reported in elderly patients on chronic PPI therapy, such as deficiency of vitamin B_{12} and increased incidence of hip fractures (325,326), but these findings have not been corroborated by recent studies (327,328). In a retrospective case review, 18 cases of biopsy-proven PPI-induced acute interstitial nephritis causing acute renal failure were reported, and the authors suggest this entity may go unrecognized as ''unclassified acute renal failure'' (329). PPIs are considered to be the most common cause of acute interstitial nephritis in adults (330). This adverse effect is considered to be an idiosyncratic reaction, more frequent in elderly adults. No childhood cases have been described. Animal studies suggest that acid suppression may predispose to the development of food allergy (331), but this remains to be confirmed by human studies.

5.2.3. Prokinetic Therapy

Cisapride is a mixed serotonergic agent that facilitates the release of acetylcholine at synapses in the myenteric plexus, thus increasing gastric emptying and improving esophageal and intestinal peristalsis. Clinical studies of cisapride in children with GERD showed significant reduction in the RI (332) but with less consistent reduction in symptoms (333,334). After cisapride was found to produce prolongation of the QTc interval on electrocardiogram, a finding increasing the risk of sudden death (335), its use was restricted to limited-access programs supervised by a pediatric gastroenterologist and to patients in clinical trials, safety studies, or registries.

Domperidone and metoclopramide are antidopaminergic agents that facilitate gastric emptying. Metoclopramide has cholinomimetic and mixed serotonergic effects. Metoclopramide and placebo equally reduced symptom scores of infants with reflux. Metoclopramide did reduce the RI on pH probe examination but did not normalize it (336). A meta-analysis of 7 RCTs of metoclopramide in developmentally healthy children 1 month to 2 years of age with symptoms of GER found that metoclopramide reduced daily symptoms and the RI but was associated with significant side effects (215). Metoclopramide commonly produces adverse side effects in infants and children, particularly lethargy, irritability, gynecomastia, galacctorhea, and extrapyramidal reactions and has caused permanent tardive dyskinesia (337–340). A recent systematic review of studies on domperidone (341) identified only 4 RCTs in children, none providing ''robust evidence'' for efficacy of domperidone in pediatric GERD. Domperidone occasionally causes extrapyramidal central nervous system side effects (342).

Bethanechol, a direct cholinergic agonist studied in a few controlled trials, has uncertain efficacy and a high incidence of side effects in children with GERD (338, 343,344). Erythromycin, a dopamine-receptor antagonist, is sometimes used in patients with gastroparesis to hasten gastric emptying. Its role in the therapy of GER and GERD has not been investigated.

Baclofen is a γ-amino-butyric-acid receptor agonist that reduces both acid and nonacid reflux in healthy adults and in adults with GERD (345). In children, it was shown to accelerate gastric empyting for 2 hours after dosing, without any deleterious effect on LES resting pressure or esophageal peristalsis (346). In a small group of children with GERD and NI, it was reported to decrease the frequency of emesis (347). Although no side effects were noted in 1 study, baclofen is known to cause dyspeptic symptoms, drowsiness, dizziness, and fatigue, and to lower the threshold for seizures. Such side effects preclude its routine use (348).

Currently, there is insufficient evidence to justify the routine use of cisapride, metoclopramide, domperidone, bethanechol, erythromycin, or baclofen for GERD (215,333,341,349,350).

5.2.4. Other Agents

Antacids directly buffer gastric contents, thereby reducing heartburn and healing esophagitis. On-demand use of antacids may provide rapid symptom relief in some children and adolescents with NERD (351). Although this approach appears to carry little risk, it has not been formally studied in children. Intensive, high-dose antacid regimens (eg, magnesium hydroxide and aluminum hydroxide; 700 mmol/1.73 m^2/day) are as effective as cimetidine for treating peptic esophagitis in children ages 2 to 42 months (352,353). No studies of antacids to date have used combined esophageal pH/MII to assess outcome. Prolonged treatment with aluminum-containing antacids significantly increases plasma aluminum in infants (354,355), and some studies report plasma aluminum concentrations close to those that have been associated with osteopenia, rickets, microcytic anemia, and neurotoxicity (356–358). Milk-alkali syndrome, a triad of hypercalcemia, alkalosis, and renal failure, can occur due to chronic or high-dose ingestion of calcium carbonate. Although these side effects are less common than they were in the era before acid-suppressive drugs (359), all of the antacid buffering agents should be used with particular caution in infants and young children. Because safe and convenient alternatives are available that are more acceptable to patients, chronic antacid therapy is generally not recommended for patients with GERD.

Most surface protective agents contain either alginate or sucralfate. Alginates are insoluble salts of alginic acid, a component of algal cell walls. In older studies of alginic acid therapy in pediatric patients with GERD, the liquid preparations used also contained buffering agents, making it difficult to isolate the effect of the surface protective agent itself (360–363). Efficacy in these studies has varied widely. In 1 clinical study, a commercial liquid preparation containing only sodium-magnesium alginate significantly decreased the mean frequency and severity of vomiting in infants compared with placebo (364). Another placebo-controlled study of this preparation in infants showed that although symptoms improved with therapy, the only objective change on combined pH/MII evaluation was a marginal decrease in the height of reflux in the esophagus (365). Alginate is also available as tablets and is useful for on-demand treatment of symptoms.

Sucralfate is a compound of sucrose, sulfate, and aluminum, which, in an acid environment, forms a gel that binds to the exposed mucosa of peptic erosions. In adults, sucralfate decreased symptoms and promoted healing of nonerosive esophagitis (366). The only randomized comparison study in children demonstrates that sucralfate was as effective as cimetidine for treatment of esophagitis (367). The available data are inadequate to determine the safety or efficacy of sucralfate in the treatment of GERD in infants and children, particularly the risk of aluminum toxicity with long-term use.

None of the surface agents is recommended as a sole treatment for severe symptoms or erosive esophagitis.

5.3. Surgical Therapy

Fundoplication decreases reflux by increasing the LES baseline pressure, decreasing the number of TLESRs and the nadir pressure during swallow-induced relaxation, increasing the length of the esophagus that is intraabdominal, accentuating the angle of His, and reducing an HH if present (24,368). Fundoplication usually eliminates reflux, including physiologic reflux (369). Fundoplication does not correct underlying esophageal clearance, gastric emptying, or other GI dysmotility disorders (21,24,370–373).

Most of the literature on surgical therapy in children with GERD consists of retrospective case series in which documentation of the diagnosis of GERD and details of previous medical therapy are deficient, making it difficult to assess the indications for and responses to surgery (374–377). Children with underlying conditions predisposing to the most severe GERD (Section 5.1.1) comprise a large percentage of most of the surgical series, further confounding efforts to determine the benefits versus risks of surgical antireflux procedures in specific patient populations. The absence of systematic postoperative evaluation, including objective testing with pH or impedance studies and endoscopy, further complicates the assessment of surgical outcomes in most series (368,372,378).

In general, outcomes of antireflux surgery have been more carefully evaluated in adults than in children. In 1 study (379), at a mean of 20 ($\pm$10) months after surgery, 61% of the adults were satisfied with their outcome; 32% were taking medications for heartburn, 11% required esophageal dilatation, and 7% had repeat surgery. This study found that a substantial number of patients underwent fundoplication for questionable reasons. In another study of patients relieved of typical reflux symptoms postoperatively, up to two thirds developed new symptoms postoperatively, including excessive gas, abdominal bloating, increased flatus, dysphagia, difficulty with eructation, and vomiting (378–381). In a large multicenter controlled study, 62% of the adults were taking PPIs for reflux symptoms 7 years after antireflux surgery (381). In another study, 37% of adults were taking antireflux medications at a mean of 5.9 years following antireflux surgery (382). Another study showed a similarly high surgical failure rate (383).

A large open RCT compared the efficacy and safety of laparoscopic fundoplication versus esomeprazole (20 mg qd) for treatment of adults with GERD (384). Short-term outcomes were reported in an interim analysis of data at 3 years. More than 90% of both the surgically and medically treated adults showed good to excellent symptom control; 10% of the surgical group had dysphagia whereas dysphagia was uncommon in the medically treated group. Quality of life measures were similar in both groups (384). Death related to open or laparoscopic surgery occurs. In adults, the mortality of the first operation is reported to be between 1 in 1000 and 1 in 330 (385–387).

In children who were operated on, those with NI have more than twice the complication rate, 3 times the morbidity, and 4 times the reoperation rate of children without NI (388). Other studies show similar data (389–391). One case series with a follow-up period of 3.5 years reported that more than 30% of children with NI had major complications or died within 30 days of antireflux surgery (392). Twenty-five percent of those patients had operative failure and 71% had a return of 1 or more preoperative symptoms within 1 year of surgery.

Children with repaired EA also have a high rate of operative failure (393,394), although not as high as those with NI. Recurrence of pathologic reflux after antireflux surgery in children with NI or EA may not be obvious, and detection often requires a high index of suspicion, repeated evaluation over time, and use of more than 1 test (391,394).

In a recent retrospective review of 198 children, 74% of whom had underlying disorders, two thirds had GERD symptoms or required medical treatment for GERD within 2 months of antireflux surgery (374). Fundoplication in early infancy has a higher failure rate than fundoplication performed later in childhood (395,396), and appears to be more frequent in children with associated anomalies (396).

The impact of antireflux surgery on hospitalization for reflux-related events, especially adverse respiratory events, was reviewed using a large administrative database (397). A significant reduction in the number of adverse respiratory events was observed in the year following surgery in those operated at <4 years of age (1.95 vs 0.67 events per year). However, in older children, no benefit of surgery on the rate of hospitalization for adverse respiratory events was found. In fact, children with developmental delay were hospitalized more frequently in the year following antireflux surgery than before surgery (397). In a recent pediatric study, Nissen fundoplication did not decrease hospital admissions for pneumonia, respiratory distress or apnea, or failure to thrive, even in those with underlying neurological impairment (398).

Complications following antireflux surgery may be due to alterations in fundic capacity, altered gastric compliance and sensory responses that may persist from months to years. These include gas-bloat syndrome, early satiety, dumping syndrome, and postoperative retching and gagging. In a postoperative study of otherwise healthy children, that is, children with no underlying disorders, 36% had mild to moderate gas bloat symptoms, 32% were ''very slow'' to finish most meals, 28% were unable to burp or vomit, and 25% choked on some solids (399). Early and late operative failure may result from disruption of the wrap or slippage of the wrap into the chest (385,389–394,400–404). In otherwise healthy children evaluated at a mean of 10 months (1–35 months) following antireflux surgery, 67% had ''no complaints,'' but one third had objective evidence of operative failure (405). Operative complications include splenic or esophageal laceration, each of which occurs in about 0.2% of pediatric cases (406). Children with underlying disorders such as NI are at substantially greater risk for surgical mortality (388,400,406), as are those in early infancy (396). Mortality due to surgery in children without NI is difficult to assess because of the heterogeneous population in most surgical studies.

Laparoscopic Nissen fundoplication (LNF) has largely replaced open Nissen fundoplication (ONF) as the preferred antireflux surgery for adults and children, due to its decreased morbidity, shorter hospital stays, and fewer perioperative problems (124,377,378,386,387,395,401,407–409). However, LNF is attended by as high a failure rate as open surgery in adults (378,401). In a randomized study of ONF versus LNF in adults, patients who received LNF had a higher incidence of disabling dysphagia (410). In a series of 456 children undergoing surgery younger than 5 years of age, Diaz et al (395) reported that those with LNF had a higher reoperation rate than those with ONF. Average time to reoperation with LNF was 11 months versus 17 months for ONF. In children with 1 to 3 comorbidities the probability of reoperation was 18% to 24% after LNF, compared with 6% to 16% for ONF (395).

Total esophagogastric dissociation is an operative procedure that is useful in selected children with NI or other conditions causing life-threatening aspiration during oral feedings. The operation has been used either after failed fundoplication or as a primary procedure (411,412). The esophagogastric disconnection eliminates all of the reflux while allowing tube feedings or oral supplementation up to the patient's tolerance. This is a technically demanding operation, and because of the fragile nature of the children involved—most of whom have histories of aspiration and pulmonary compromise—it carries significant morbidity (411,412).

Endoluminal endoscopic gastroplication has been described in children as an alternative to surgical fundoplication. When a group of 16 children with GERD refractory to or dependent on medical therapy was evaluated after endoluminal gastroplication (413), 4

had recurrent symptoms requiring a repeat procedure 2 to 24 months postoperatively. Three years after surgery, 9 patients (56%) were taking no antireflux medication. Longer-term studies in adults have shown little or no difference in procedure time or failure rate between endoluminal and surgical antireflux procedures (414, 415). In some studies, sham-operated patients have done as well as operated patients (416,417). Other endoscopic GERD treatments have not been studied in children (368).

The annual number of antireflux operations has been on the increase in the United States, especially in children younger than 2 years of age (375,406). In contrast, in adults, rates of fundoplication are declining in the United States and have dropped 30% from their peak in 1999 (378). The greatest decline is in teaching hospitals and in young adult patients.

Antireflux surgery may be of benefit in children with confirmed GERD who have failed optimal medical therapy, or who are dependent on medical therapy over a long period of time, or who are significantly nonadherent with medical therapy, or who have life-threatening complications of GERD. Children with respiratory complications including asthma or recurrent aspiration related to GERD are generally considered most likely to benefit from antireflux surgery when medical therapy fails, but additional study is required to confirm this. Children with underlying disorders predisposing to the most severe GERD are at the highest risk for operative morbidity and operative failure. Before surgery it is essential to rule out non-GERD causes of symptoms, and ensure that the diagnosis of chronic-relapsing GERD is firmly established. It is important to provide families with appropriate education and a realistic understanding of the potential complications of surgery, including symptom recurrence.

6. EVALUATION AND MANAGEMENT OF THE PEDIATRIC PATIENT WITH SUSPECTED GERD

The following sections describe the relation between reflux and several common signs, symptoms or symptom complexes of infants and children. The evaluations appropriate to establish a diagnosis of GERD and recommendations for management in each case are outlined. Recommendations are based on the available evidence and the consensus opinion of the members of the guideline committee.

6.1. Recurrent Regurgitation and Vomiting

The practitioner's challenge is to distinguish regurgitation and vomiting caused by reflux or reflux disease from vomiting caused by numerous other disorders (Table 4). This can be confusing because reflux episodes sometimes trigger vomiting, a coordinated autonomic and voluntary motor response causing forceful expulsion of gastric contents. Vomiting associated with reflux is probably a result of the stimulation of pharyngeal sensory afferents by refluxed gastric contents (418,419). Laboratory and radiographic investigation may be necessary to exclude other causes of vomiting.

TABLE 4. *Differential diagnosis of vomiting in infants and children*

Gastrointestinal obstruction
Pyloric stenosis
Malrotation with intermittent volvulus
Intestinal duplication
Hirschsprung disease
Antral/duodenal web
Foreign body
Incarcerated hernia
Other gastrointestinal disorders
Achalasia
Gastroparesis
Gastroenteritis
Peptic ulcer
Eosinophilic esophagitis/gastroenteritis
Food allergy
Inflammatory bowel disease
Pancreatitis
Appendicitis
Neurologic
Hydrocephalus
Subdural hematoma
Intracranial hemorrhage
Intracranial mass
Infant migraine
Chiari malformation
Infectious
Sepsis
Meningitis
Urinary tract infection
Pneumonia
Otitis media
Hepatitis
Metabolic/endocrine
Galactosemia
Hereditary fructose intolerance
Urea cycle defects
Amino and organic acidemias
Congenital adrenal hyperplasia
Renal
Obstructive uropathy
Renal insufficiency
Toxic
Lead
Iron
Vitamins A and D
Medications—ipecac, digoxin, theophylline, etc
Cardiac
Congestive heart failure
Vascular ring
Others
Pediatric falsification disorder (Munchausen syndrome by proxy)
Child neglect or abuse
Self-induced vomiting
Cyclic vomiting syndrome
Autonomic dysfunction

TABLE 5. *History in the child with suspected gastroesophageal reflux disease*

Feeding and dietary history
Amount/frequency (overfeeding)
Preparation of formula
Recent changes in feeding type or technique
Position during feeding
Burping
Behavior during feeding
Choking, gagging, cough, arching, discomfort, refusal
Pattern of vomiting
Frequency/amount
Pain
Forceful
Blood or bile
Associated fever, lethargy, diarrhea
Medical history
Prematurity
Growth and development
Past surgery, hospitalizations
Newborn screen results
Recurrent illnesses, especially croup, pneumonia, asthma
Symptoms of hoarseness, fussiness, hiccups
Apnea
Previous weight and height gain
Other chronic conditions
Medications
Current, recent, prescription, nonprescription
Family psychosocial history
Sources of stress
Maternal or paternal drug use
Postpartum depression
Family medical history
Significant illnesses
Family history of gastrointestinal disorders
Family history of atopy
Growth chart including height, weight, and head circumference
Warning signals (Table 2)

6.1.1. The Infant With Uncomplicated Recurrent Regurgitation

In the infant with recurrent regurgitation or spitting, a thorough history (Table 5) and physical examination with attention to warning signals suggesting other diagnoses (Table 1) is generally sufficient to establish a clinical diagnosis of uncomplicated infant GER (Fig. 1). The typical presentation of uncomplicated infant GER is effortless, painless regurgitation in a healthy-appearing child with normal growth—the so-called happy spitter. Intermittently, an episode of vomiting, even forceful vomiting may occur. Irritability may accompany regurgitation and vomiting; however, in the absence of other warning symptoms, it is not an indication for extensive diagnostic testing. An upper GI series or other diagnostic tests are not required unless other diagnoses such as GI obstruction are suspected. Recurrent regurgitation due to GER generally decreases during the first year, resolving at 12 to 18 months of age (17,18). If ''warning signs'' for GERD or other diagnoses are present, or if regurgitation is not resolving by 12 to 18 months of age, consultation with a pediatric gastroenterologist is recommended.

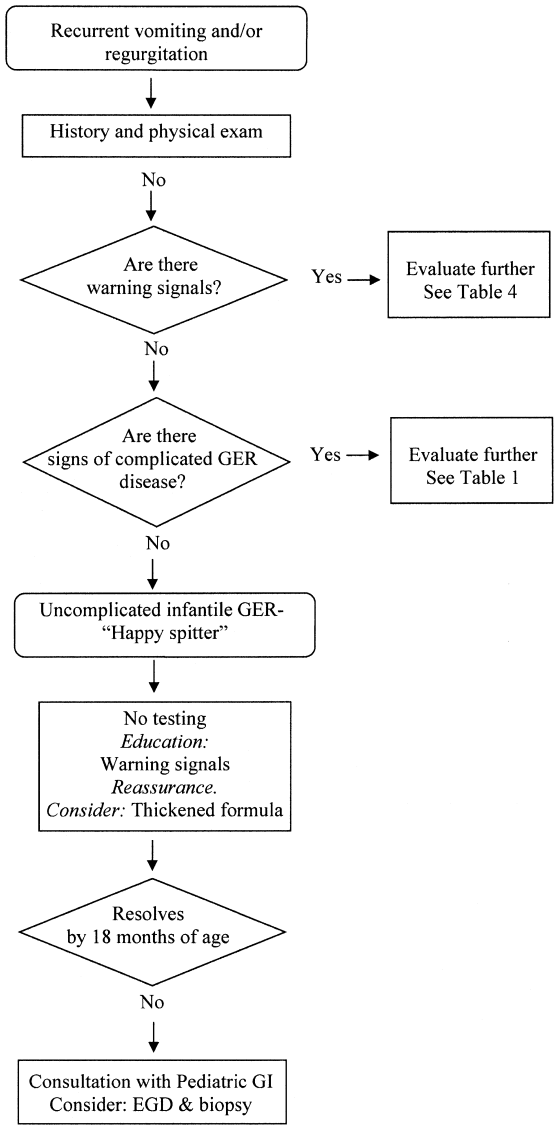

FIG. 1. Approach to the infant with recurrent regurgitation and vomiting.

Generally, only parental education, anticipatory guidance, and modification of feeding composition, frequency, and volume are necessary for the management of uncomplicated infant GER (208,420). Overfeeding exacerbates recurrent regurgitation and should be avoided (211). In some infants with persistent regurgitation, a thickened or commercial antiregurgitation formula may help control the frequency of regurgitation (Section 4.1.1). There is no evidence that antisecretory or promotility agents improve physiologic infant regurgitation. Prone positioning is not recommended because of its association with SIDS. Because regurgitation is sometimes the sole manifestation of cow's milk protein allergy in healthy-looking infants (420,421), a 2-week trial of

protein hydrolysate– or amino acid–based formula or a trial of milk-free diet for the breast-feeding mother is appropriate in infants not responding to previous management.

6.1.2. The Infant With Recurrent Regurgitation and Poor Weight Gain

The infant with recurrent regurgitation and poor weight gain should not be confused with the "happy spitter" described in Section 6.1.1. Whereas the history and physical examination may be identical, poor weight gain is not typical of uncomplicated infant GER and is a crucial warning sign that alters clinical management.

Because there are no well-controlled studies evaluating diagnostic or therapeutic strategies for these infants, the following approach is based on expert opinion (Fig. 2). A feeding history should be obtained that includes an estimate of energy offered and ingested per day, an estimate of energy loss through regurgitation, a description of formula preparation and feeding schedule, an assessment of breast milk sufficiency, and a description of infant sucking and swallowing behavior. Parents should be advised not to reduce intake to the point of energy deprivation in the attempt to prevent regurgitation. If problems identified by history seem to explain the symptoms and can be addressed, close outpatient monitoring of weight gain will determine whether further evaluation is indicated.

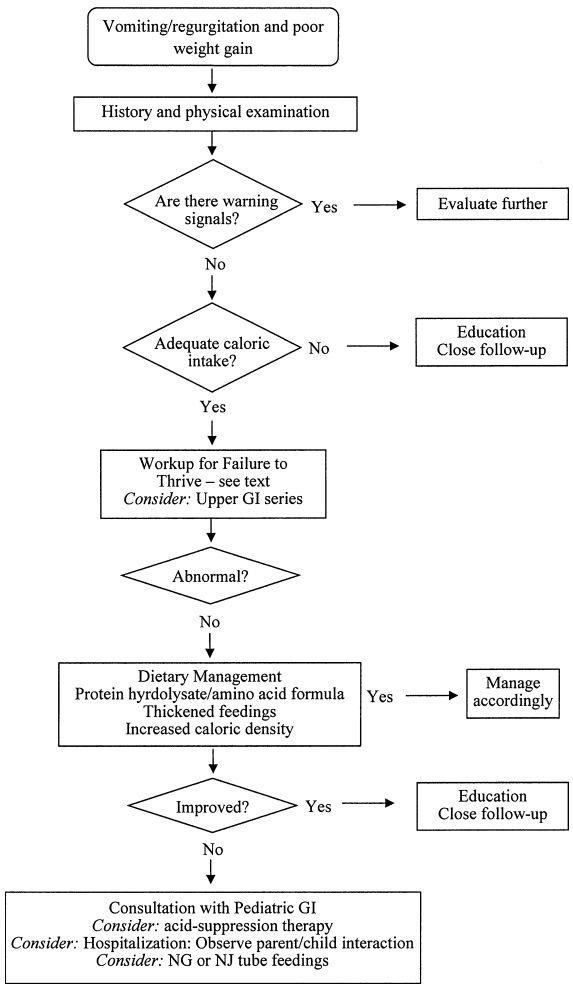

FIG. 2. Approach to the infant with recurrent regurgitation and weight loss.

If chronic regurgitation and inadequate weight gain persist after observation and despite adequate energy intake, evaluation for causes of failure to thrive compatible with the history is mandatory. Among possible etiologies in infancy are infections (especially urinary tract), food allergy, anatomic abnormalities, neurologic disorders, metabolic disease, and neglect or abuse (Table 4). A 2- to 4-week trial of extensively hydrolyzed or amino acid–based formula is appropriate. Depending on the results of investigations and response to dietary management, the infant should be referred to a pediatric specialist. Hospitalization for observation and testing is appropriate in some infants with persistent failure to thrive. Nasogastric or nasojejunal feeding is occasionally necessary to achieve weight gain in the infant with no other clear explanation for poor weight gain (231).

6.1.3. The Infant With Unexplained Crying and/or Distressed Behavior

Irritability and regurgitation are nonspecific symptoms that occur in healthy infants and are associated with a wide range of physiologic and pathologic conditions. For example, exposure to environmental factors, such as tobacco smoke may result in irritability in infants (422,423). Healthy young infants fuss or cry an average of 2 hours daily. There is substantial individual variation and some healthy infants cry as much as 6 hours per day. Likewise, there is variation in parental perceptions regarding the severity and duration of crying and its importance. The amount of daily crying typically peaks at 6 weeks of age (424,425). As with fussing, sleeping patterns of healthy infants show great individual and maturational variation as do parental expectations for sleep behavior (426).

The concept that infant irritability and sleep disturbances are manifestations of GER is largely extrapolated from adult descriptions of heartburn and sleep disturbances that improve with antacid therapy (50,427–429). Although 1 study in infants showed a correlation between infant grimacing and episodes of reflux (430), multiple other studies have shown no relation between crying and GERD determined by esophageal pH testing (61,84,140, 431) or the presence of esophagitis (47,84). Some small

descriptive studies have evaluated pH probe studies in infants with irritability and sleep disturbance. One compared infants with normal and abnormal pH probe studies and found a slight increase in nighttime waking, delayed onset of sleep, and greater daytime sleeping in those with abnormal pH probe studies (432). Another study found no increase in sleep disturbance in infants with abnormal esophageal pH tests (431). One dual pH probe study showed slightly poorer proximal acid clearance in colicky infants, but no abnormality in other parameters (433). Recently, a study of colicky infants found abnormal pH test results only in those with excessive regurgitation or feeding difficulties (61).

There are few studies addressing the appropriate management of infants with irritability and reflux symptoms. One study showed a greater decrease in crying time in infants treated with a 1-mg/kg dose of famotidine than in infants given 0.5 mg/kg. Although the authors concluded from this study that famotidine was effective in treating infant crying, differences in age between treatment groups, absence of placebo control, and a lack of difference between the treatment group and a group withdrawn from medications cast doubt on this conclusion (293). Placebo-controlled studies have evaluated acid-suppressive therapy in irritable infants. A study of infants with irritability and normal esophageal pH tests found that combined ranitidine and cisapride treatment was not superior to placebo or counselling for persistent crying (45). A double-blind placebo-controlled trial of omeprazole in irritable infants who either had esophagitis or an RI $>5\%$ found no difference in crying between treated and placebo groups despite highly effective acid suppression in the treated group (46). A large double-blind study of 162 infants randomized to 4 weeks of placebo or lansoprazole showed an identical 54% response rate in each group, using an endpoint of $>50\%$ reduction of measures of feeding-related symptoms (crying, irritability, arching) and other parameters of the I-GERQ questionnaire (9). Furthermore, this study showed a small but significant increase in the numbers of infants that experienced lower respiratory symptoms during the treatment trial.

The available evidence does not support an empiric trial of acid suppression in infants with unexplained crying, irritability, or sleep disturbance. A symptom diary (61,434) or hospital observation (45,435) may be useful to confirm the history, which is subjective to observation bias.

Disorders other than GERD that are likely to cause irritability include cow's milk protein allergy (142,436), infections (especially of the urinary tract), constipation, respiratory disorders, congenital or acquired neurologic abnormalities (437), metabolic disease, surgical emergencies (eg, intermittent volvulus, ovarian torsion), cardiac disease, corneal abrasion, bone fractures, hair tourniquet syndrome, tobacco smoke exposure, hunger, abuse, or neglect (438,439). Allergy to cow's milk protein or other formula intolerance may cause infant irritability, distress, and vomiting indistinguishable from GER. In 1 controlled study, an empiric trial of formula made with partially hydrolyzed whey proteins, prebiotic oligosaccharides, and a high β-palmitic acid content significantly decreased colic (440). Data on the efficacy of extensively hydrolyzed formulae in infants with unexplained crying and/or distressed behavior are limited (441,442). An empiric 2- to 4-week trial of an extensively hydrolyzed formula (1 that has been validated as being tolerated by at least 90% of infants with cow's milk protein allergy with 95% confidence) or amino acid–based formula may be indicated in irritable infants after diagnostic evaluations have been performed for other conditions causing irritability. Reflux is an uncommon cause of irritability or unexplained crying in otherwise healthy infants. However, if irritability persists with no explanation other than suspected GERD, expert opinion suggests the following options. The practitioner may continue anticipatory guidance and training of parents in the management of such infants with the expectation of improvement with time. Additional investigations to ascertain the relation between reflux episodes and symptoms or to diagnose reflux or other causes of esophagitis may be indicated (pH monitoring $\pm$ impedance monitoring, endoscopy). A time-limited (2-week) trial of antisecretory therapy may be considered, but there is potential risk of adverse effects, and clinical improvement following empiric therapy may be due to spontaneous symptom resolution or a placebo response. The risk/benefit ratio of these approaches is not clear.

6.1.4. The Child Older Than 18 Months of Age With Chronic Regurgitation or Vomiting

Physiologic regurgitation, episodic vomiting, or regurgitation followed by swallowing of refluxate in the mouth are frequent in infants. Whether of new onset or persisting from infancy, these symptoms are less common in children older than 18 months of age. Although these symptoms are not unique to GERD, evaluation to diagnose possible GERD and to rule out alternative diagnosis is recommended based on expert opinion. Testing may include upper GI endoscopy, and/or esophageal pH/MII, and/or barium upper GI series (Table 4).

6.2. Heartburn

Heartburn or substernal burning pain is a symptom of GERD with or without esophagitis (443). Recent consensus statements suggest that typical heartburn is a reliable indicator for GERD in adolescents and adults if it is the dominant symptom (13,50). One study in adults found that dominant heartburn had a positive predictive value of 81% for GERD determined by pH study (444),

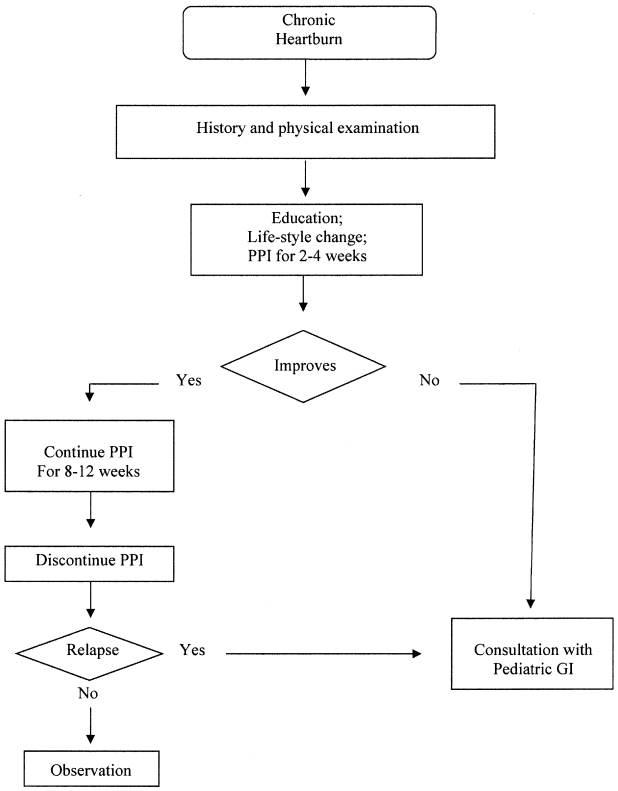

FIG. 3. Approach to the older child or adolescent with heartburn.

but other studies have not confirmed this close association between history and test results (378). Esophageal pH probe results are normal in one third of adults with chronic heartburn, even those whose heartburn is reproduced by esophageal acid perfusion and those who respond favorably to antacids. Some adults with heartburn and normal pH studies have endoscopically proven esophagitis (445). In older children and adolescents the description and localization of heartburn pain is probably reliable. In young children, however, symptom descriptions and localization may be unreliable (56–60,446).

No randomized placebo-controlled studies evaluate lifestyle changes or pharmacologic therapy of heartburn in children or adolescents. Case series have shown that PPI therapy relieves heartburn symptoms in adolescents (55,64,447). Expert opinion suggests using a management approach to heartburn in older children and adolescents similar to that used in adults (Fig. 3). Other causes of heartburn-like chest pain including cardiac, respiratory, musculoskeletal, medication-induced, or infectious etiologies should be considered. If GERD is suspected as the most likely cause of symptoms, lifestyle changes, avoidance of precipitating factors, and a 2- to 4-week trial of PPI are recommended (446,448–450). If there is no improvement following empiric therapy, the older child or adolescent should be referred to a pediatric gastroenterologist for diagnostic evaluation. If improvement follows PPI therapy and lifestyle changes, treatment can be continued for 2 to 3 months. In some patients, abrupt discontinuation of treatment may result in acid rebound that precipitates symptoms; therefore, it is recommended that antisecretory therapy be weaned slowly (451,452). If symptoms recur when therapy is weaned or discontinued, upper endoscopy may be helpful to determine the presence and severity of esophagitis and differentiate reflux-related esophagitis from nonreflux pathologies such as infection or EoE that may present with heartburn (40,453) Because chronic heartburn can have a substantial negative impact on quality of life, long-term therapy with PPIs may be required, even in the absence of esophagitis (454,455). Extrapolation from adult data suggests that in older children and adolescents, on-demand or intermittent therapy with antacids, H2RA, or PPIs may be used for occasional symptoms of heartburn (302,455,456).

6.3. Reflux Esophagitis

In open-label studies of children with erosive esophagitis, PPIs produced healing in 78% to 95% with 8 weeks of therapy and in 94% to 100% with 12 weeks of therapy. Symptoms improved in 70% to 80% of the group treated for 12 weeks (130,312,447). Most patients in these studies had lower grades of erosive esophagitis, and the studies did not include patients with underlying conditions such as NI, repaired tracheoesophageal fistula, chronic lung disease, or HH. PPIs have been shown to heal higher grades of esophagitis (grades 3–4) in children with these underlying conditions, even in some when esophagitis had been refractory to treatment with H2RAs, prokinetic agents, and even antireflux surgery (28,29, 131). However, in these selected cases resistant to standard management, high per-kilogram dose and long duration of therapy (up to 6 months) may be required for healing and symptom control (28,29,131).

In uncontrolled studies of children with erosive and nonerosive disease treated with PPIs, 70% experienced relief of "typical symptoms of GERD," that is, heartburn (312,447). A significant percent of patients remained symptomatic, albeit at lower intensity. Suboptimal symptom relief may be due to large per-kilogram dosing variation. Studies in adults have shown generally poorer therapeutic response to PPI in patients with NERD compared with patients with erosive esophagitis (457,458).

With regard to maintenance therapy, in a prospective study of children whose erosive esophagitis had healed following 3 months of omeprazole therapy, only half maintained the remission of symptoms and endoscopic disease in a maintenance phase during which they received half the healing dose of PPI (316). In another study, patients whose erosive esophagitis healed after

3 months' omeprazole treatment ($1.4\,mg \cdot kg^{-1} \cdot day^{-1}$) underwent double-blind randomization into 3 groups, receiving either maintenance therapy with omeprazole at half the healing dose, ranitidine, or placebo for 6 months (130). In all 3 groups, few patients had a relapse of symptoms or of endoscopic esophagitis during or after maintenance therapy. There were important differences between these 2 studies. Specifically, in the first study, the mean grade of esophagitis was higher, and 41% of patients had an underlying disorder predisposing to GERD. In a retrospective study of 166 children with erosive esophagitis unable to withdraw from PPIs for up to 11 years (median 3.5 years), 79% had at least 1 underlying condition predisposing them to GERD and 39% had HH (28). Thus, patients with lower grades of erosive esophagitis and without an underlying high-risk condition may not require long-term PPI therapy after initial effective treatment. In a recent study of adults with long-term PPI use, 27% were able to discontinue drug without relapse (452).

PPIs are recommended as initial therapy in children with erosive esophagitis. Initial treatment for 3 months is advised. If adequate control of symptoms is not achieved within 4 weeks, the dose of PPI can be increased. Patients who require higher PPI dose to control symptoms and produce healing are those with conditions that predispose to severe-chronic GERD and those with higher grades of esophagitis or BE. In most cases, efficacy of therapy can be monitored by extent of symptom relief without routine endoscopic follow-up. Endoscopic monitoring of treatment efficacy may be useful in patients whose presenting signs and symptoms are atypical, who have persistent symptoms while taking adequate acid-suppressive drugs, or who had higher grades of esophagitis or esophageal stricture at presentation (see also Section 5.2.2). Follow-up endoscopy is not routinely indicated in patients with nonerosive disease, particularly if they are asymptomatic on medication.

Most patients require only 1 daily dose of PPI to obtain symptomatic relief and heal esophagitis (29,131,447, 459). The optimum dosage regimen is to administer a once-daily dose 15 to 30 minutes before the first meal of the day. It is not necessary to make patients achlorhydric to relieve symptoms or heal esophagitis, and, in light of the data on infectious and other complications of acid suppression by H2RAs or PPIs, it is probably not desirable to do so.

Not all reflux esophagitis is chronic or relapsing (130), and therefore trials of reduction of dose and withdrawal of PPI therapy should be performed after the patient has been asymptomatic for some time, that is, after 3 to 6 months on treatment. This approach will minimize the number of children that unnecessarily receive long-term treatment. PPIs should not be stopped abruptly, because rebound acid secretion may cause recurrence of symptoms (451,452). Instead, PPI should be tapered for at least 4 weeks. Recurrence of symptoms and/or esophagitis after repeated trials of PPI withdrawal usually indicates that chronic-relapsing GERD is present, if other causes of esophagitis have been ruled out. At this point, therapeutic options include long-term PPI therapy or antireflux surgery.

6.4. Barrett Esophagus

The prevalence of BE is much lower in children than adults, but it does occur in children with severe-chronic GERD. In 1 group of children with severe-chronic GERD, columnar metaplasia was present in 5% and columnar metaplasia with goblet-cell metaplasia was present in another 5% (28). Accuracy of diagnosis has important implications for longevity and surveillance. The diagnosis of BE is both overlooked and overcalled in children (28,134). Therefore, the primary task of the gastroenterologist is accuracy of diagnosis, especially in light of the proposed new criteria for the diagnosis of BE in children and adults (13,50). If esophagogastric landmarks are obscured by bleeding and exudate, a course of high-dose PPI for at least 12 weeks before making a diagnosis is advised to allow for better visualization of anatomic landmarks and to remove the histologic changes of chronic inflammation that may confuse the diagnosis. After PPI therapy, multiple biopsies should be taken to characterize the type of BE and to rule out dysplasia (134,148).

Dysplasia is managed according to adult guidelines (146,460). If dysplasia is absent, follow-up endoscopy every 3 to 5 years should be performed, until 20 years of age, when adult guidelines for surveillance should be followed (134). The management of nondysplastic BE is the same as that of erosive esophagitis, that is, long-term PPI or antireflux surgery (134,460). BE per se is not an indication for antireflux surgery. In BE, symptoms are often a poor guide to adequacy of treatment, and some advocate more aggressive acid suppression, based on esophageal pH monitoring (460). Although it is unclear whether progression of dysplasia is slowed by acid control, higher doses of PPI may be considered in BE than in esophagitis without metaplasia (461).

6.5. Dysphagia, Odynophagia, and Food Refusal

Dysphagia, or difficulty in swallowing, occurs in association with oral and esophageal anatomic abnormalities, neurologic and motor disorders, oral and esophageal inflammatory diseases, and psychologic stressors or disorders. GERD is commonly cited as a cause of dysphagia or odynophagia, and although it may be causal in some patients, there are no pediatric data demonstrating this relation, nor has symptom improvement in infants and children been demonstrated with antireflux therapy. In a population-based Australian study, 16% of healthy adults reported having ''dysphagia ever'' (462). In this

study, dysphagia correlated with anxiety and depression but also with GERD (odds ratio 2.96) (462). Another study found dysphagia in 11% of healthy adults and 28% of adults with GERD symptoms (463). In a meta-analysis of 11,945 adults with erosive esophagitis, 37% had dysphagia (464). However, in young adults presenting with dysphagia, radiographic evaluation demonstrated conditions other than GERD in 70% that were more likely causes of the symptoms (465). Dysphagia is a prominent symptom in up to 80% of adults and children with EoE (93,450,466).

Odynophagia, or pain caused by swallowing, must be distinguished from heartburn (substernal pain caused by esophageal acid exposure) and dysphagia. Although odynophagia may be a symptom of peptic esophagitis, it is more often associated with other conditions such as oropharyngeal inflammation, esophageal ulcer, EoE, infectious esophagitis (eg, infection with herpes simplex, candida, or cytomegalovirus), and esophageal motor disorders. A patient with odynophagia may in time develop behaviors around eating that resemble dysphagia. There are no pediatric studies on the relation between GERD and odynophagia.

Patients often find it difficult to distinguish between dysphagia and odynophagia. In the majority of patients with dysphagia, the dysphagia is not caused or related to reflux disease. The present literature indicates that dysphagia is frequent among patients with EoE. In those relatively uncommon patients in whom GERD causes dysphagia, esophagitis is often present. Expert opinion suggests that odynophagia may be associated with peptic esophagitis and esophagitis of other causes.

Feeding refusal and feeding difficulty are terms used mainly to describe the following infant symptoms: refusal to eat, uncoordinated sucking and swallowing, gagging, vomiting, and irritability during feeding. A relation between GER or GERD and feeding refusal has not been established. Although older case series suggest that reflux disease caused infant feeding difficulty, no prospective studies have proven causation and none have shown resolution with GERD therapy (467). One retrospective study found a higher incidence of poor intake, decreased feeding readiness, and food refusal in infants with abnormal pH probe tests than in normal case controls (468). Another study found no association between GERD diagnosed by pH probe and feeding difficulty, except in infants who also had excessive regurgitation (61). A double-blind placebo-controlled trial showed no improvement in feeding difficulties following lansoprazole therapy compared with placebo in infants with suspected GERD (9). A recent study found that anorexia or feeding refusal was occasionally a symptom of erosive esophagitis in children 1 to 5 years of age (40).

An upper GI contrast study is useful but not required for the infant with feeding refusal or difficulty or the older child reporting dysphagia. Its major use is to identify a non-GERD disorder such as achalasia or foreign body or to identify esophageal narrowing from a stricture. The upper GI contrast study or a more focused videofluoroscopic swallowing study that evaluates the mechanisms of feeding and swallowing may be helpful to identify nonesophageal causes of feeding difficulties, especially in infants and younger children. In children and adolescents who report dysphagia or odynophagia in combination with esophageal symptoms, endoscopy with biopsy is useful to distinguish among causes of esophagitis.

There is no evidence that supports a causal relation between infant feeding difficulties and GER or GERD. In the infant with feeding refusal, acid suppression without earlier diagnostic evaluation is not recommended. Direct observation focused on neurologic, behavioral, metabolic, and infectious disease is essential for the evaluation and diagnosis of this symptom complex (469). In the older child or adolescent empiric antisecretory therapy is only recommended if there are additional symptoms or findings suggesting GERD.

6.6. The Infant With Apnea or ALTE

The literature on the relation between apnea, respiratory pauses, apparent life-threatening events (ALTEs) or SIDS, and reflux is conflicting, in large part because of the different criteria used to define breath stoppage, the various methods used to measure reflux and respiratory pauses, and the different populations studied.

A recent study combining data from simultaneous esophageal pH/MII and cardiorespiratory monitoring in infants showed a temporal association between 30% of the nonpathologic, short episodes of central apnea and reflux (115). These findings cannot be extrapolated to pathologic infant apnea and may represent a normal protective cessation of breathing during regurgitation. Recent studies using combined pH/MII have generally detected little relation between apneic spells and reflux episodes (470,471). Some studies have found a relation between long episodes of apnea (>30 seconds) and acid reflux in premature infants (472). In 1 older study, short apnea or bradycardia spells were tightly tied to spells of vomiting or regurgitation, whereas the majority of prolonged apnea spells (>20 seconds) were not (473). In highly selected cases, reflux is clearly associated with pathological, central, and obstructive apnea (241). None of these studies has conclusively shown a cause and effect relation between reflux and pathologic apnea.

ALTEs are frightening episodes in infants characterized by a combination of apnea, color change (cyanosis, pallor, and plethora), abnormal muscle tone (limpness and stiffness), choking, and gagging that require intervention by the observer (474). The identification of a behavior as ALTE is observer dependent (475). The first event usually occurs at 1 to 2 months of age and rarely after 8 months. ALTEs may recur (476,477), and infants

with an ALTE are at slightly increased risk for subsequent sudden death (477–482). ALTEs may be associated with infection, child abuse, upper airway obstruction, cardiac, respiratory, metabolic, and neurologic disorders. ALTEs associated with reflux may not be pathologic; some may be an exaggeration of normal protective reflexes that inhibit breathing while the infant retches or while the pharynx is filled with gastric contents.

In older studies, patients with ALTEs had a 60% to 70% prevalence of recurrent regurgitation or emesis (475,477), and abnormal esophageal pH tests were documented in 40% to 80% of patients with ALTEs (483,484). Case reports and series described ALTEs triggered by overt regurgitation into the oropharynx, by aspiration of refluxed gastric contents, and by reflux induced by positional change after feedings (485–488). In selected patients with ALTE, acid perfusion of the esophagus induces obstructive apnea (485) or oxygen desaturation (483), suggesting that 1 mechanism for ALTE is acid stimulation of laryngeal, pharyngeal, or esophageal chemoreceptors with subsequent laryngospasm. In selected infants, a clear temporal relation between apnea and ALTE can be demonstrated. However, large case series have not shown a consistent statistical relation between GER and pathologic apnea or ALTEs (489,490). Larger studies using combined esophageal pH/MII may clarify the extent of these temporal relations.

Poor quality of sleep characterized by irregular breathing patterns is associated with reflux (484,489–496). Although several studies have reported an occasional correlation of GER with short mixed central apneas (5–15 seconds) (492,493,495), all of the patients also had episodes of apnea unrelated to episodes of GER, suggesting a primary impairment in the regulation of respiration.

At present there is no evidence that the characteristics of the ALTE or the polysomnographic record can predict which infants with ALTE are at risk for future life-threatening episodes or sudden death. Although rare, SIDS has been reported to occur in patients with a previous ALTE and documented GER (241,491,497). In none of these patients was a correlation between esophageal acidification and a cardiopulmonary event ever recorded.

The available evidence suggests that in the vast majority of infants, GER is not related to pathologic apnea or to ALTE, although a clear temporal relation based on history, observation or testing occurs in individual infants. Impedance/pH recording in combination with polysomnographic recording is recommended to demonstrate this relation in these infants.

Medical therapy of ALTEs suspected of being GER-related has not been adequately studied. Approaches that decrease the frequency of regurgitation and the volume of reflux such as thickened feeding may theoretically be beneficial. Pharmacotherapy has not been shown to be effective. The occurrence of ALTEs diminishes significantly with age and without therapy in most cases, suggesting that no antireflux therapy is needed. The ALTEs most likely to improve with antireflux therapy are those obviously associated with vomiting or regurgitation, those that occur in the awake infant after feeding, and those characterized by obstructive apnea. Because medical therapy has not been shown to be effective, surgery may be a reasonable approach in the rare infant in whom ALTEs are truly life threatening and are shown to be clearly related to GER.

In some exceptional situations, prone sleeping (with cardiorespiratory monitoring) may be recommended because of a major risk of apnea or aspiration caused by refluxed material.

6.7. Reactive Airways Disease

An etiologic role for reflux in reactive airways disease (asthma) has not been established, although animal and human studies have suggested that reflux may exacerbate existing asthma. Proposed mechanisms by which reflux aggravates asthma are direct production of airway inflammation by aspirated gastric contents, airway hyperresponsiveness triggered by lower airway aspiration of minute amounts of acid, vagally mediated bronchial or laryngeal spasm, and neurally mediated inflammation (498–501). Esophageal acidification in healthy adults has minimal effect on pulmonary function (498); however, esophageal acidification in asthmatic patients can produce airway hyperresponsiveness and airflow obstruction (502).

Few studies have evaluated the impact of asthma on the severity of GERD. Chronic hyperinflation caused by asthma can flatten the diaphragms, alter crural function, and displace the lower esophageal sphincter into the negative atmosphere of the chest, effectively reducing resting LES pressure and causing disappearance of the acute esophagogastric angle of His. Lung hyperinflation and airflow obstruction may produce increased negative intrathoracic pressure, effectively increasing the pressure gradient across the diaphragm and promoting reflux. Although theophylline and β-receptor agonists cause a reduction of resting LES pressure, these drugs have not been linked to the development of GERD in treated asthmatics (503). Oral corticosteroids promote reflux in adults, but the mechanism is unclear (504).

Many studies have demonstrated an association between asthma and measurements of reflux by pH probe or pH/MII. These studies have shown that 60% to 80% of children with asthma have abnormal pH or pH/MII recordings (505). A study of 77 children 3 to 14 years old with difficult-to-control asthma found that 66% had abnormal RI on pH testing (90). In a study of 84 otherwise healthy infants with daily wheezing, 64% had abnormal 24-hour pH studies, and 44% of these had no overt symptoms of GERD (506). Nocturnal wheezing appears particularly related to GERD. One study used combined esophageal pH/MII monitoring and demonstrated a tighter association

between reflux episodes and respiratory symptoms than pH monitoring alone (507), but no studies to date have shown that pH/MII studies are useful in identifying those patients whose asthma may respond to antireflux therapy.

One study found omeprazole treatment to be ineffective in improving asthma symptoms, quality of life, lung function, or use of β_2 agonists in children with asthma and GERD (508). High-dose prolonged PPI therapy in adult asthmatics has shown minimal or no efficacy. In 1 large double-blind placebo-controlled study of esomeprazole in adult asthmatics, no improvement occurred in morning peak expiratory flow, but posthoc analysis indicated mild improvements in FEV_1 among patients with nocturnal asthma symptoms (509). However, patients with known erosive esophagitis or moderate-to-severe GERD symptoms were excluded. Another study showed a 4% decrease in the number of asthma exacerbations and a 14% decrease in the use of oral corticosteroids in adult patients with moderate-to-severe asthma and heartburn treated with lanzoprazole for 24 weeks but no improvement in symptoms, pulmonary functions, or albuterol use (510). One uncontrolled study in children found that children with persistent moderate asthma and reflux who received antireflux treatment including PPI used significantly less medication to control their asthma (511). Another double-blind placebo-controlled study showed no reduction in wheezing among infants treated with lansoprazole versus placebo for 4 weeks, although wheezing was a secondary endpoint and not the primary focus of the study (9). A controlled trial in adults with reflux and asthma evaluated asthma outcomes after 2 years of continuous ranitidine therapy versus antireflux surgery; surgery led to a larger reduction in symptoms and improved overall clinical status, but neither therapy had a clinically meaningful impact on pulmonary function or pulmonary medication use (512). Some uncontrolled case series using nonobjective parameters have shown a dramatic improvement in asthma symptoms in children after antireflux surgery (95).

Although adult studies show only limited, if any, benefit from PPI or surgical therapy, it is possible that selected patients with heartburn, nocturnal asthma, or steroid-dependent, difficult-to-control asthma may derive some benefit. Symptom reporting is less reliable in infants and children than in adults. Therefore, a reasonable approach to evaluation of pediatric patients in whom GERD is suspected of being a contributing or aggravating factor causing wheezing or asthma is shown in Fig. 4. Other causes of wheezing should be ruled out. There is no strong evidence to support empiric PPI therapy in unselected pediatric patients with wheezing or asthma. Finding abnormal esophageal pH exposure by esophageal pH monitoring, with or without impedance, before considering a trial of long-term PPI therapy or surgery may be useful, although the predictive value of these studies for this purpose has not been established.

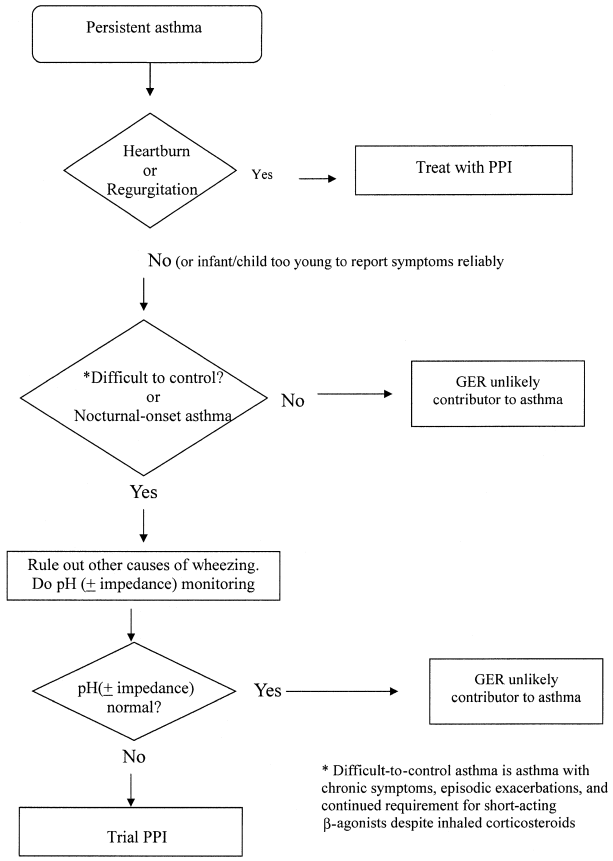

FIG. 4. Approach to the child with asthma that may be worsened by GERD. GERD = gastroesophageal reflux disease.

The relative efficacy of medical versus surgical therapy for GERD in children with asthma is unknown.

6.8. Recurrent Pneumonia

Recurrent pneumonia and interstitial lung disease may be complications of reflux, presumably as a result of the failure of airway protective mechanisms to protect the lungs against aspirated gastric contents (513). Reflux causing recurrent pneumonia has been reported in otherwise healthy infants and children (96,514,515). In a retrospective series reviewing the causes of recurrent pneumonia in a heterogenous group of 238 children, the primary cause was aspiration during swallowing in 48%, immunologic disorders in 14%, congenital heart disease in 9%, asthma in 8%, respiratory tract anatomic abnormalities in 8%, unknown in 8%, and reflux in only 6% (516). Small case series suggest that reflux may cause or exacerbate interstitial lung disorders such as idiopathic pulmonary fibrosis (517,518), cystic fibrosis (CF) (519,520), or lung transplant (520,521).

No test can determine whether reflux is causing recurrent pneumonia. An abnormal esophageal pH test may

increase the probability that reflux is a cause of recurrent pneumonia but is not proof thereof. A normal esophageal pH test cannot exclude reflux as a cause of pneumonia because if airway protection mechanisms are compromised, even brief reflux episodes that are within the normal range, may be associated with aspiration. Aspiration during swallowing is much more common than aspiration of refluxed material (522). Upper esophageal and pharyngeal pH recordings, and combined pH/MII studies have similar limitations and do not improve the ability to predict GER-related pneumonia (523).

Lipid-laden alveolar macrophages have been used as an indicator of aspiration but the sensitivity and specificity as an indicator of GER-related lung disease is poor (187,524–529). Pepsin content of pulmonary lavage fluid has also been used to document aspiration of gastric contents. Pepsin concentration is elevated in pulmonary lavage from patients with reflux (185,186) but there is substantial overlap with controls (187). Nuclear scintigraphy can detect aspirated gastric contents when images are obtained for 24 hours after enteral administration of a labelled meal. One study reporting that 50% of patients with a variety of respiratory symptoms had aspiration on scintigraphy (169) has not been replicated. It is important to recognize that aspiration also occurs in healthy subjects, especially during sleep (171,172) so the threshold for pathologic aspiration of saliva or gastric contents is not established.

No data are available regarding the predictive value of any diagnostic test for determining which patients will respond to either medical or surgical therapy for GERD. Both medical (530) and surgical (97,531) therapy of GERD have been reported to reduce pulmonary symptoms in certain populations of children with recurrent pneumonia. However, in 1 study of children older than 4 years of age, the number of hospitalizations for respiratory related events increased after antireflux surgery (397). Gastrojejunal feeding provides an alternative approach to prevent reflux-related pneumonia in children with severe NI (532). A recent review of children with severe NI and GERD reported that surgical therapy improved several complications but did not alter the risk of pneumonia (533). The potential benefits of antisecretory therapy for neurologically impaired children with recurrent pneumonia must be balanced against the risk that PPI therapy may increase the incidence of community-acquired pneumonia in these patients, as it does in well children (322). A large double-blind placebo-controlled study to determine the role of PPI therapy in the child with NI is lacking.

In many cases the clinician must make management decisions based on inconclusive diagnostic studies with no certainty regarding outcome. In patients with severely impaired lung function, it may be necessary to proceed with antireflux surgery in an attempt to prevent further pulmonary damage, despite lack of definitive proof that reflux is a cause of pulmonary disease. Alternatively, if minimal pulmonary disease is present, consideration of medical therapy with careful follow-up of pulmonary function may be instituted, although the potential benefits versus risks of PPI are unclear. The efficacy of therapies such as lifestyle changes and prokinetics has not been well studied. A trial of nasogastric feeding may be used to exclude aspiration during swallowing as a potential cause of recurrent disease (532). A trial of nasojejunal therapy may help determine whether surgical antireflux therapy is likely to be beneficial.

6.9. Upper Airway Symptoms

The data showing a relation between reflux and upper airway disease are weak, consisting mainly of case descriptions. Airway symptoms attributed to reflux in adults include hoarseness (534), chronic cough (535,536), and the sensation of a lump in the throat (globus sensation) (537,538). Affected adults rarely have typical reflux symptoms. Laryngoscopic findings said to be reflux related include erythema, edema, nodularity, ulceration, granuloma, and cobblestoning (539,540). The sensitivity and specificity of these findings to identify reflux-induced disease are poor (541,542), and a study in children showed poor correlation between laryngeal changes and reflux quantitated by pH probe (543). In a descriptive pediatric study, GERD was more prevalent in children with recurrent laryngotracheitis than in controls (544). In a retrospective study of children undergoing otolaryngologic procedures, an association between esophagitis diagnosed by biopsy and recurrent croup, cough, stridor, laryngomalacia, subglottic stenosis, posterior glottic erythema, and posterior arytenoid erythema was observed (545). Increased frequency of daytime reflux has been described in children with hoarseness (546). One study suggested that reflux contributed to the development of subglottic stenosis in children and to poor outcomes after reparative surgery (547). Increased pharyngeal reflux has been observed in children with laryngomalacia (548,549).

Uncontrolled reports in adults and children showed improved upper airway symptoms after antireflux therapy including fundoplication (193,550–554). However, data from several placebo-controlled studies and careful meta-analyses uniformly have shown no effect of antireflux therapy on upper airway symptoms or signs (555–559). One uncontrolled trial reported a reduction in cough following medical antireflux therapy in children (560). However, a double-blind placebo-controlled study showed no difference in the frequency of symptoms of cough or hoarseness among infants treated with lansoprazole versus those treated with placebo (9).

In summary, descriptive studies report detecting and treating reflux in children with chronic laryngeal signs and symptoms. Upper airway edema, erythema,

cobblestoning, and granulomas are neither sensitive nor specific for the diagnosis of GERD. Criteria used for assessing laryngeal findings are variable as are the criteria for diagnosing GERD in published reports. Laryngoscopy is indicated in some of these children to rule out anatomic abnormalities such as laryngeal cleft and functional abnormalities such as vocal-fold dysfunction. Data are insufficient to allow recommending a standard approach to diagnosis, treatment, and follow-up. Extrapolation from adult studies suggests that PPIs will not benefit most children with upper airway symptoms.

Reflux has been suggested as a factor contributing to recurrent sinus disease, pharyngitis, and otitis media (561,562). One uncontrolled case series of children with chronic sinusitis suggested that antireflux treatment dramatically reduced the need for sinus surgery (563). Another series demonstrated more episodes during which pharyngeal pH was <6.0 in children with recurrent rhinopharyngitis compared with controls (564). Two epidemiologic surveys, however, found no difference in the number of ear and sinus infections in infants with and without reflux (17,565). Otalgia has been associated with reflux in children and reported to improve with treatment of reflux (566). There is no proven mechanism by which reflux should cause sinusitis, pharyngitis, and otitis, although direct irritation by refluxed material causing pharyngeal tissue edema has been suggested. The lack of controlled studies and animal models of mechanism makes these studies difficult to translate to pediatric practice.

6.10. Dental Erosions

Case reports and a recent systematic review report a causative association between GERD and dental erosion (414). The severity of dental erosions seems to be correlated with the presence of GERD symptoms and in adults with the severity of proximal esophageal or oral exposure to an acidic pH. Young children and children with NI appear to be at greatest risk. One study in adolescents showed that reflux was associated with an increased incidence of erosion of enamel on the lingual surfaces of the teeth (567). In contrast, another study reported no increased incidence of dental erosions in adolescents with abnormal esophageal pH monitoring (568). Factors other than reflux may also cause similar dental erosions; these include juice drinking, bulimia, and racial and genetic factors that affect the characteristics of enamel and saliva. The approach to evaluation and therapy—specifically, the choice of diagnostic tests, duration of therapy, and criteria for cessation of therapy—is unclear. Close consultation with a qualified pediatric dentist is required. The inspection of the oral cavity in search for dental erosions is advisable in patients with known GERD.

6.11. Dystonic Head Posturing (Sandifer Syndrome)

Sandifer syndrome (spasmodic torsional dystonia with arching of the back and opisthotonic posturing, mainly involving the neck and back) is an uncommon but specific manifestation of GERD (13,569,570) that must be differentiated from other causes of abnormal movements including seizures, infantile spasms, and dystonia. The mechanisms underlying this disorder are unproven, but the disorder may be a vagally mediated reflex response to esophageal acid exposure. It resolves with antireflux treatment.

7. GROUPS AT INCREASED RISK FOR SEVERE, CHRONIC GERD

Children with certain underlying disorders are at high risk for developing severe-chronic GERD, compared with those who are otherwise healthy. Although the latter do develop GERD, which on occasion may be severe, the prevalence of severe-chronic GERD is much higher in children with certain underlying conditions, such as NI or anatomic abnormalities, such as repaired EA or HH. These children are more likely to require long-term treatment for healing and maintenance (28,372). Complications of severe GERD occur with greatest frequency in children with underlying GERD-provoking conditions (28,31). Performing studies of various GERD therapies in these groups has inherent difficulties because the populations are heterogeneous; many are unable to report symptoms, some have more than 1 condition, and some require medications to be given by feeding tube. These limit the data available to allow evidence-based recommendations on therapy. However, some studies with quantitative endpoints, for example, endoscopic healing, are available (28,29,131).

7.1. Neurologic Impairment

The increased frequency and severity of GERD among infants and children with NI including developmental delay are well documented (397,571,572). For example, children with cerebral palsy are at particularly high risk for GERD (571,573–575). Similarly, children with certain genetic syndromes such as Cornelia de Lange and Down syndrome are prone to GERD (576).

The high incidence of severe, chronic GERD is multifactorial in etiology. It is likely that in each child, factors unique to the specific diagnosis and clinical status are responsible. Contributing factors that increase reflux frequency and delay esophageal clearance are chronic supine positioning, abnormal swallowing, heightened gag reflex, abnormal sensory integration, delayed gastric emptying, constipation, obesity, skeletal abnormalities, abnormal muscle tone, and medication side effects. The severity of GERD may result from poor self-protective

mechanisms and delayed diagnosis caused by difficulties in obtaining an accurate history of symptoms. Treatment should include lifestyle changes tailored to the unique risk factors of the patient. Changes in feeding volume, consistency, and frequency may be helpful, as may positional changes, control of muscular spasticity, and biofeedback. Antisecretory therapy should be optimized. Long-term treatment with PPIs is often effective for symptom control and maintenance of remission of esophagitis (28,577,578). Baclofen may be useful for reduction of vomiting, but care with regard to dosing and side effects is required (346,347). Elemental diet was shown to improve resistant GERD symptoms in 1 small uncontrolled study that did not differentiate EoE from GERD (579).

Descriptive studies suggest that placement of feeding gastrostomy in children with NI, either by open or laparoscopic surgery, increases the risk of subsequent GERD (580,581). Recent surgical studies comparing open and laparoscopic gastrostomy placement suggest that postoperative development of GERD is less common after laparoscopic and percutaneous endoscopic procedures than open surgical procedures (582–584).

Making a clinical diagnosis of GERD in children with NI is hampered by poor communication with the patient and the frequency of atypical presentations such as anxiety, self-injurious behavior, apparent seizures, and dystonia (585). Evaluation of the child with NI requires a high index of suspicion and must not only confirm the diagnosis but also rule out alternative diagnoses. Contrast GI radiographic studies, upper GI endoscopy and biopsy, metabolic and drug toxicity screening, and pH/impedance studies may be required.

Given the morbidity and high failure rates of antireflux surgery in this group, patients whose symptoms are well controlled on medical therapy may not derive additional benefit from antireflux surgery The relative risks versus benefit of antireflux surgery in children with persistent symptoms despite optimized medical therapy have not been clearly defined (397,586). Patients with respiratory complications of GERD appear to benefit most, but a cause-and-effect relation is difficult to establish, and therefore patient selection is difficult (Section 5.3).

7.2. Obesity

Although pediatric data are scarce, in adults, obesity and/or incremental weight gain have been increasingly shown to be associated with a significantly higher prevalence and severity of GERD, BE, and esophageal adenocarcinoma (265–267).

7.3. Esophageal Anatomic Disorders and Achalasia

EA has an incidence of 1 in 3000 live births; thus it is an important cause of chronic-severe GERD in pediatric practice. The esophagus in EA is congenitally dysmotile; it is sometimes foreshortened as a result of surgery or stricture, and a HH is often present (28,29,587), especially in long-gap atresia (588). Significant heart disease, tracheomalacia, or gastric outlet obstruction occurs in up to 18% of these children (587).

Of children and young adults with repaired EA, 50% to 95% have GERD symptoms, including dysphagia and pulmonary symptoms (587,589,590). Esophagitis and BE or some form of metaplasia are prevalent (31,134, 589,590), and esophageal adenocarcinoma and squamous cancer are reported in children and adults (589,591–594). A long-term study of 272 surviving children with EA observed no cases of esophageal cancer (595). However, the authors of that study and others (587,589) recommended that patients with EA undergo regular endoscopy to screen for BE and esophageal cancer, given the relatively normal longevity of most patients with EA. In the pre-PPI era, several case series demonstrated a benefit from antireflux surgery, but failure rates of fundoplication are high in children with repaired EA. Medical therapy with PPIs is highly effective in patients with EA and GERD (28).

Patients with achalasia are at increased risk for chronic GERD, esophagitis, and BE following treatment by either pneumatic dilation or myotomy (596,597). The benefit of antireflux therapy at the time of myotomy remains controversial (598). All of the patients with a history of achalasia or a history of EA repair require follow-up for possible complications of GERD, because even those who underwent antireflux surgery are at risk (596). The potential utility of endoscopic surveillance has not been evaluated in these patients.

7.4. Chronic Respiratory Disorders

A higher prevalence of GERD and its complications has been reported in patients with a variety of respiratory disorders including bronchopulmonary dysplasia, idiopathic interstitial fibrosis, and most commonly, CF (500,599,600). In 1 study, 27% of patients with CF younger than 5 years old reported GI symptoms suggestive of reflux (heartburn or regurgitation), compared with only 6% of their healthy siblings (519). However, intraesophageal pH studies in children with CF detect a much higher prevalence of pathologic GE reflux (500), that is, reflux is silent in the majority. Reflux may be silent because GI symptoms are truly absent, or symptoms may be relatively ignored by patients with CF because of their plethora of other problems. Some children with CF consider upper GI symptoms such as heartburn, chest pain, and occasional vomiting, to be part of CF, and therefore may not report them; this results in delayed diagnosis and presentation with complications of GERD (31). There are no trials formally evaluating the benefits and risks of GERD treatments in children with CF, but the

high incidence of esophagitis and potential risk of adenocarcinoma makes aggressive treatment reasonable. A retrospective review of fundoplication outcome in patients with CF reported that complications requiring repeat surgery occurred in 12%, recurrent GERD symptoms developed in 48%, and only 28% discontinued GERD medications (601).

Bronchopulmonary dysplasia, a chronic lung disease of infancy with varying degrees of alveolar growth arrest, airway branching abnormalities, and peribronchiolar fibrosis, has been associated with GERD (602). However, more recent studies have not confirmed this association (603). Because most of the studies have been cross-sectional or case-control in design, a cause–effect relation remains to be defined.

7.5. Lung Transplantation

Severe GERD is common in patients presenting for transplantation, and a high incidence of GERD occurs following lung transplantation in children and adults (521,604). Complications of GERD are a common source of morbidity in patients with transplantation (521). Pneumonectomy seems to contribute to esophageal and gastric motor dysfunction (605). It has been suggested that in the allograft lung, nonimmune-mediated injury because of reflux contributes to the development of bronchiolitis obliterans syndrome (606).

7.6. The Premature Infant

GERD treatment is frequently administered to premature infants (39,607,608). In a recent study, 25% of infants with birth weights <1000 g were discharged on medications to treat reflux (608). However, the true frequency of peptic esophagitis or pulmonary disease because of GERD is unknown. Most of the physiologic mechanisms that protect against reflux appear to be intact in the preterm infant (609,610). Although some suggest a relation between apnea or bradycardias of prematurity and reflux (472), most studies do not support reflux as a cause of pathologic apnea in premature infants (113,591,611,612). One retrospective study showed that GER-related apnea improved rapidly following commencement of gastrojejunal feeding, suggesting that in some cases reflux may cause apnea (613). Behaviors often interpreted as signs of reflux disease in the preterm infant are nonspecific and not predictive of esophagitis (614). One study in infants with chronic lung disease found that a variety of observed symptoms (respiratory, sensory, and movement) were associated with reflux into the proximal esophagus (610), but the clinical significance of these symptoms is not clear.

Although reflux episodes may be more common in infants with bronchopulmonary dysplasia, there is no evidence that GERD therapy affects the clinical course or outcome (603,615). GERD is frequently diagnosed by inadequate criteria in the preterm infant. The relative risks, benefits, and indications for GERD therapy are unclear in premature infants. The long-term risk of GERD in premature infants during adulthood is controversial.

One study (616) reported a greater than 11-fold increase in the incidence of esophageal adenocarcinoma in adults who were born preterm or small-for-gestational age. However, a subsequent nested case-control study did not confirm a strong association between risk of esophageal cancer and birth weight (617).

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APPENDICES

Appendix A. Summary of Recommendations for Diagnostic Approaches and the Quality of the Evidence

Section	Recommendation	Vote Mean (range*)	Quality of Evidence†
4.1	4.1.1 In infants and toddlers, there is no symptom or group of symptoms that can reliably diagnose GERD or predict treatment response.	5.9 (5–7)	B
	4.1.2 In older children and adolescents a history and physical examination are generally sufficient to reliably diagnose GERD and initiate management.	5.3 (4–6)	C
4.2	Esophageal pH monitoring is a valid and reliable measure of esophageal acid exposure only.	6.5 (6–7)	B
4.3	Combined multiple esophageal impedance-pH recording is superior to pH monitoring alone for evaluation of GER-related symptom association.	6.5 (6–7)	B

Continued

Appendix A. *Continued*

Section	Recommendation	Vote Mean (range*)	Quality of Evidence†
4.5	4.5.1. Reflux-induced esophageal damage is defined endoscopically as visible breaks of the distal esophageal mucosa.	6.2 (5–7)	C
	4.5.2. Endoscopic biopsy cannot determine whether esophagitis, if present, is due to reflux.	6.4 (5–7)	B
	4.5.3. Absence of histological changes does not rule out reflux disease.	6.8 (6–7)	B
	4.5.4. When endoscopy is performed, esophageal biopsies are recommended for diagnosis of Barrett's esophagus and causes of esophagitis other than GER.	6.0 (5–7)	C
4.6	The upper GI series is not useful for the diagnosis of GERD, but is useful for the diagnosis of anatomic abnormalities.	6.8 (6–7)	B
4.7	There may be a role for nuclear scintigraphy to diagnose aspiration in patients with chronic refractory respiratory symptoms, but the technique is not recommended in patients with other potentially GER-related symptoms.	6.3 (5–7)	B
4.9	The presence of pepsin in broncho-alveolar lavage fluid is an indicator of GER-related aspiration, but its clinical utility remains to be established.	6.2 (5–7)	B
	Lipid-laden macrophages lack specificity and sensitivity for diagnosing GER-related aspiration.		B
4.10	4.10.1 There is no evidence to support an empiric trial of pharmacologic treatment in infants and young children with symptoms suggestive of GERD.	6.5 (6–7)	B
	4.10.2 In older children and adolescents with heartburn and chest pain, a time-limited trial of acid-suppressive treatment may be useful to determine whether GER is causing the symptoms.	6.4 (5–7)	C

Level B: Consistent Retrospective Cohort, Exploratory Cohort, Ecological Study, Outcomes Research, case-control study; or extrapolations from level A studies. Level C: Case-series study or extrapolations from level B studies. GERD = gastroesophageal reflux disease; GER = gastroesophageal reflux; GI = gastrointestinal.

* Vote values were from 1 (least agreement) to 7 (most agreement).

† Categories of the quality of evidence (11).

Appendix B. Summary of Recommendations for Treatment Options and the Quality of the Evidence

Section	Recommendation	Vote Mean (range*)	Quality of Evidence†
5.1.1	5.1.1.1 There is evidence to support a trial of an extensively hydrolyzed protein formula for a 2- to 4-week trial in formula-fed infants with vomiting.	6.4 (6–7)	B
	5.1.1.2 Thickening of formula results in decreased visible reflux (regurgitation).	6.9 (6–7)	A
5.1.2	Prone and lateral positioning is associated with a higher rate of SIDS. In infants from birth to 12 months of age, the risk of SIDS outweighs the potential benefits of prone sleeping. Therefore, supine positioning during sleep is generally recommended.	6.8 (6–7)	A
5.1.3	5.1.3.1 In older children and adolescents, there is no evidence to support specific dietary restrictions to decrease symptoms of GER. In adults, obesity and late-night eating are associated with GER.	6.6 (5–7)	A
	5.1.3.2 In adolescents with GERD, left-side sleeping positioning and elevation of the head of the bed may decrease symptoms and GER.	6.0 (5–7)	B
5.2.1	H2RAs produce relief of symptoms and mucosal healing.	6.2 (5–7)	A
5.2.2	PPIs are superior to H2RAs in relieving symptoms and healing esophagitis.	6.2 (5–7)	A
5.2.3	Potential side effects of each currently available prokinetic agent outweigh the potential benefits. There is insufficient support to justify the routine use of metoclopramide, erythromycin, bethanechol, or domperidone for GERD.	6.4 (6–7)	C
5.2.4	Because more effective alternatives (H2RAs and PPIs) are available, chronic therapy with buffering agents, alginates, and sucralfate is not recommended for GERD.	6.5 (6–7)	A
5.3	Antireflux surgery should be considered only in children with GERD and failure of optimized medical therapy, *or* long-term dependence on medical therapy where compliance or patient preference preclude ongoing use, *or* life-threatening complications.	6.4 (5–7)	C

Level A: Consistent Randomized Controlled Clinical Trial, cohort study, all or none (see note below), clinical decision rule validated in different populations. Level B: Consistent Retrospective Cohort, Exploratory Cohort, Ecological Study, Outcomes Research, case-control study; or extrapolations from level A studies. Level C: Case-series study or extrapolations from level B studies. GERD = gastroesophageal reflux disease; GER = gastroesophageal reflux; H2RAs = histamine-2 receptor antagonists; PPIs = proton pump inhibitors; SIDS = sudden infant death syndrome.

* Vote values were from 1 (least agreement) to 7 (most agreement).

† Categories of the quality of evidence (11).

Appendix C. Summary of Recommendations for the Evaluation and Management of Infants and Children With Suspected GERD and the Quality of the Evidence

Section	Recommendation	Vote Mean (range*)	Quality of Evidence†
6.1.1.	6.1.1 In the infant with recurrent regurgitation, a thorough history and physical examination with attention to warning signs are generally sufficient to allow the clinician to establish a diagnosis of uncomplicated GER.	6.7 (6–7)	C
	6.1.2.1 In the infant with uncomplicated regurgitation, parental education, reassurance, and anticipatory guidance are recommended.	6.7 (6–7)	C
	6.1.2.2 Thickening of formula can be considered in addition to parental education, reassurance, and anticipatory guidance. In general, no other intervention is necessary. If symptoms worsen or do not resolve by 12 to 18 months of age or ''warning signs'' develop, referral to a pediatric gastroenterologist is recommended.	7 (7–7)	A
6.1.2	In the regurgitating/vomiting infant with poor weight gain despite adequate energy intake, urinalysis, CBC, electrolytes, urea/creatinine, and celiac screening are recommended; UGI series should be considered. Recommended dietary management includes a 2-week trial of extensively hydrolyzed/amino acid formula, thickened formula, or increased energy density. If dietary managements fails and/or if the investigations reveal no abnormalities, referral to a pediatric GI is recommended.	6.2 (6–7)	D
6.1.3	In otherwise healthy infants with unexplained crying, irritability, or distressed behavior, there is no evidence to support acid suppression.	7.0 (7–7)	A
6.2	6.2.1 For the treatment of chronic heartburn in older children or adolescents, lifestyle changes with a 4-week PPI trial are recommended.	6.4 (6–7)	A
	6.2.2 If symptoms resolve, continue PPIs for 3 months. If chronic heartburn persists or recurs after treatment, it is recommended that the patient be referred to a pediatric gastroenterologist.	6.4 (6–7)	D
6.3	In the infant or child with reflux esophagitis, initial treatment consists of lifestyle changes and PPI therapy. In most cases, efficacy of therapy can be monitored by the degree of symptom relief.	6.3 (5–7)	A
6.5	6.5.1 In the infant with feeding refusal, acid suppression without earlier diagnostic evaluation is not recommended.	6.5 (5–7)	D
	6.5.2 In the child with dysphagia or odynophagia, a barium esophagram is recommended, generally followed by an upper endoscopy. Acid suppression without earlier diagnostic evaluation is not recommended.	6.1 (5–7)	D
6.6	In the vast majority of infants, reflux is not related to pathologic apnea or to apparent life-threatening event, although a clear temporal relation exists in individual infants. In infants in whom this relation is suspected or if symptoms recur, impedance/pH recording in combination with polysomnographic recording may aid in establishing cause and effect.	5.6 (5–6)	B
6.7	Patients with asthma and heartburn should be treated for the heartburn. Despite a high frequency of abnormal reflux studies in asthmatic patients, only a select group with nocturnal asthma symptoms or with steroid-dependent, difficult-to-control asthma may benefit from long-term medical or surgical antireflux therapy.	6.1 (5–7)	B

Level A: Consistent Randomised Controlled Clinical Trial, cohort study, all or none (see note below), clinical decision rule validated in different populations. Level B: Consistent Retrospective Cohort, Exploratory Cohort, Ecological Study, Outcomes Research, case-control study; or extrapolations from level A studies. Level C: Case-series study or extrapolations from level B studies. Level D: Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles. CBC = complete blood count; GER = gastroesophageal reflux; GI = gastrointestinal; PPIs = proton pump inhibitors; UGI = upper gastrointestinal.

* Vote values were from 1 (least agreement) to 7 (most agreement).

† Categories of the quality of evidence (11).

Appendix D. Conflict of Interest Statements

Members without any relationships with potential conflict of interest from 1 year before the committee proceedings beginning (October 17, 2006) to the present time:

Greg Liptak, Lynnette Mazur, Colin Rudolph, Judith Sondheimer

Members with relationships with potential conflict of interest from 1 year before the committee proceedings beginning October 17, 2006 to May 1, 2009:

Carlo Di Lorenzo: AstraZeneca—consultant and research support; Takeda—consultant; Sucampo—research support; Braintree—speaker and research support.

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Yvan Vandenplas: AstraZeneca, Mead Johnson Nutritionals—speaker; Biocodex, Orafti, SHS, United Pharmaceuticals—consultant and speaker; Movetis—consultant; Nestle, Nutricia (Danone)—speaker.
Gigi Veereman-Wauters: Danone—scientific advisory board; Orafti—speaker; Centocor—consultant; Schering Plough NV Belgium—consultant; Schering Plough US—consultant; Movetis—consultant; Abbott Nutrition—consultant; UCB group—travel support; Nestle—travel support; Biocodex—travel support.
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