Abstract

Gastroesophageal reflux (GER), defined as passage of gastric contents into the esophagus, and GER disease (GERD), defined as symptoms or complications of GER, are common pediatric problems encountered by both primary and specialty medical providers. Clinical manifestations of GERD in children include vomiting, poor weight gain, dysphagia, abdominal or substernal pain, esophagitis and respiratory disorders. The GER Guideline Committee of the North American Society for Pediatric Gastroenterology and Nutrition has formulated a clinical practice guideline for the management of pediatric GER. The GER Guideline Committee, consisting of a primary care pediatrician, two clinical epidemiologists (who also practice primary care pediatrics) and five pediatric gastroenterologists, based its recommendations on an integration of a comprehensive and systematic review of the medical literature combined with expert opinion. Consensus was achieved through Nominal Group Technique, a structured quantitative method.

The Committee examined the value of diagnostic tests and treatment modalities commonly used for the management of GERD, and how those interventions can be applied to clinical situations in the infant and older child. The guideline provides recommendations for management by the primary care provider, including evaluation, initial treatment, follow-up management and indications for consultation by a specialist. The guideline also provides recommendations for management by the pediatric gastroenterologist.

This document represents the official recommendations of the North American Society for Pediatric Gastroenterology and Nutrition on the evaluation and treatment of gastroesophageal reflux in infants and children. The American Academy of Pediatrics has also endorsed these recommendations. The recommendations are summarized in a synopsis within the article. This review and recommendations are a general guideline and are not intended as a substitute for clinical judgment or as a protocol for the management of all patients with this problem.

SYNOPSIS

This clinical practice guideline was developed to assist the primary and specialist medical provider in the evaluation and management of gastroesophageal reflux in infants and children. Recommendations are based on an integration of a comprehensive and systematic review of the medical literature combined with expert opinion. The guideline is not intended for the management of neonates less than 72 hours old, premature infants or infants and children with either neurologic impairments or anatomic disorders of the upper gastrointestinal tract. The recommendations are a general guideline and are not intended as a substitute for clinical judgment or as a protocol for the management of all patients with this problem.

Gastroesophageal reflux (GER), defined as the passage of gastric contents into the esophagus, and GER disease (GERD), defined as symptoms or complications of GER, are common pediatric problems. Clinical manifestations of GERD in children include vomiting, poor weight gain, dysphagia, abdominal or substernal pain, esophagitis and respiratory disorders. The following section summarizes the conclusions and recommendations of the GER Guideline Committee of the North American Society for Pediatric Gastroenterology and Nutrition on the value of diagnostic tests and treatment modalities commonly used for the management of GERD, and how those interventions can be applied to clinical situations in the infant and older child.

Diagnostic Approaches

History and Physical Examination. In most infants with vomiting, and in most older children with regurgitation and heartburn, a history and physical examination are sufficient to reliably diagnose GER, recognize complications, and initiate management.

Upper GI Series. The upper gastrointestinal (GI) series is neither sensitive nor specific for the diagnosis of GER, but is useful for the evaluation of the presence of anatomic abnormalities, such as pyloric stenosis, malrotation and annular pancreas in the vomiting infant, as well as hiatal hernia and esophageal stricture in the older child.

Esophageal pH Monitoring. Esophageal pH monitoring is a valid and reliable measure of acid reflux. Esophageal pH monitoring is useful to establish the presence of abnormal acid reflux, to determine if there is a temporal association between acid reflux and frequently occurring symptoms, and to assess the adequacy of therapy in patients who do not respond to treatment with acid suppression. Esophageal pH monitoring may be normal in some patients with GERD, particularly those with respiratory complications.

Endoscopy and Biopsy. Endoscopy with biopsy can assess the presence and severity of esophagitis, strictures and Barrett's esophagus, as well as exclude other disorders, such as Crohn's disease and eosinophilic or infectious esophagitis. A normal appearance of the esophagus during endoscopy does not exclude histopathological esophagitis; subtle mucosal changes such as erythema and pallor may be observed in the absence of esophagitis. Esophageal biopsy is recommended when endoscopy is performed to detect microscopic esophagitis and to exclude causes of esophagitis other than GER.

Empiric Medical Therapy. A trial of time-limited medical therapy for GER is useful for determining if GER is causing a specific symptom.

Treatment Options

Diet Changes in the Infant. There is evidence to support a one- to two-week trial of a hypoallergenic formula in formula fed infants with vomiting. Milk-thickening agents do not improve reflux index scores but do decrease the number of episodes of vomiting.

Positioning in the Infant. Esophageal pH monitoring has demonstrated that infants have significantly less GER when placed in the prone position than in the supine position. However, prone positioning is associated with a higher rate of the sudden infant death syndrome (SIDS). In infants from birth to 12 months of age with GERD, the risk of SIDS generally outweighs the potential benefits of prone sleeping. Therefore, non-prone positioning during sleep is generally recommended. Supine positioning confers the lowest risk for SIDS and is preferred. Prone positioning during sleep is only considered in unusual cases where the risk of death from complications of GER outweighs the potential increased risk of SIDS. When prone positioning is necessary, it is particularly important that parents be advised not to use soft bedding, which increases the risk of SIDS in infants placed prone.

Positioning in the Child & Adolescent. In children older than one year it is likely that there is a benefit to left side positioning during sleep and elevation of the head of the bed.

Lifestyle Changes in the Child & Adolescent. It is recommended that children and adolescents with GERD avoid caffeine, chocolate and spicy foods that provoke symptoms. Obesity, exposure to tobacco smoke and alcohol are also associated with GER. It is not known whether lifestyle changes have an additive benefit in patients receiving pharmacological therapy.

Acid-suppressant Therapy. Histamine-$_2$ receptor antagonists (H_2RAs) produce relief of symptoms and mucosal healing. Proton pump inhibitors (PPIs), the most effective acid suppressant medications, are superior to H_2RAs in relieving symptoms and healing esophagitis. Chronic antacid therapy is generally not recommended since more convenient and safe alternatives (H_2RAs and PPIs) are available.

Prokinetic Therapy. Cisapride is available in the USA only through a limited-access program. Cisapride reduces the frequency of symptoms, including regurgitation and vomiting. However, because of concerns about the potential for serious cardiac arrhythmias in patients receiving cisapride, appropriate patient selection and monitoring as well as proper use, including correct dosage (0.2 mg/kg/dose QID) and avoidance of co-administration of contraindicated medications, are important. Other prokinetic agents have not been shown to be effective in the treatment of GERD in children.

Surgical Therapy. Case series indicate that surgical therapy generally results in favorable outcomes. The potential risks, benefits and costs of successful prolonged medical therapy versus fundoplication have not been well studied in infants or children in various symptom presentations.

Evaluation and Management of Infants and Children with Suspected GERD

The approach to the evaluation and management of infants and children with GERD depends upon the presenting symptoms or signs. Below is a summary of conclusions and recommendations derived from an integration of the research evidence with clinical experience for various clinical presentations. Where there are no

randomized studies, the recommendations are based on the consensus opinion of the GER Guideline Committee.

The Infant with Recurrent Vomiting. In the infant with recurrent vomiting, a thorough history and physical examination, with attention to warning signals, is generally sufficient to allow the clinician to establish a diagnosis of uncomplicated GER (the "happy spitter"). An upper GI series is not required unless there are signs of gastrointestinal obstruction. Other diagnostic tests may be indicated if there are symptoms of poor weight gain, excessive crying, irritability, disturbed sleep, feeding or respiratory problems. In the infant who has uncomplicated GER, parental education, reassurance and anticipatory guidance are recommended. Generally no other intervention is necessary. Thickening of formula and a brief trial of a hypoallergenic formula are other treatment options. If symptoms worsen or do not improve by 18 to 24 months of age, re-evaluation for complications of GER is recommended. Generally this includes an upper GI series and consultation with a pediatric gastroenterologist.

The Infant with Recurrent Vomiting and Poor Weight Gain. In the infant with vomiting and poor weight gain it is recommended that the adequacy of calories and the effectiveness of swallowing be assessed. If there is poor weight gain despite adequate caloric intake, a diagnostic evaluation to uncover other causes of vomiting or weight loss is generally indicated. Tests may include a complete blood count, electrolytes, bicarbonate, urea nitrogen, creatinine, alanine aminotransferase, ammonia, glucose, urinalysis, urine ketones and reducing substances, and a review of newborn screening tests. An upper GI series to evaluate anatomy is also recommended. Treatment options include thickening of formula, a trial of a hypoallergenic formula, increasing the caloric density of the formula, acid suppression therapy, prokinetic therapy and, in selected cases, prone positioning. Further management options include endoscopy with biopsy, hospitalization, tube feedings and rarely surgical therapy. Careful follow-up is necessary to assure adequate weight gain.

The Infant with Recurrent Vomiting and Irritability. Normal infants typically fuss or cry intermittently for an average of two hours daily, which may be perceived as excessive by some parents. A symptom diary may be useful to determine the extent to which the infant is irritable and has disturbed sleep. As in all infants with vomiting, other causes of vomiting need to be excluded. Expert opinion suggests two diagnostic and treatment strategies. Empiric treatment with either a sequential or simultaneous two-week trial of a hypoallergenic formula and acid suppression may be initiated. If there is no improvement, either esophageal pH monitoring to determine the adequacy of therapy or upper endoscopy with biopsy to diagnose esophagitis may be performed. If there is no response to therapy and these studies are normal, it is unlikely that GER is contributing to symptoms. Alternatively, evaluation could begin with esophageal pH monitoring to determine if episodes of irritability and sleep disturbance are temporally associated with acid reflux.

The Child or Adolescent with Recurrent Vomiting or Regurgitation. In otherwise normal children who have recurrent vomiting or regurgitation after the age of 2 years, management options include an upper GI series, upper endoscopy with biopsy, and prokinetic therapy.

Heartburn in the Child or Adolescent. For the treatment of heartburn in children or adolescents, lifestyle changes accompanied by a two- to four-week therapeutic trial of an H_2RA or PPI are recommended. If symptoms persist or recur, the child can be referred to a pediatric gastroenterologist for upper endoscopy with biopsy and in some cases long-term therapy.

Esophagitis. In the infant or child with esophagitis, initial treatment consists of lifestyle changes and H_2RA or PPI therapy. In patients with only histopathological esophagitis, the efficacy of therapy can be monitored by the degree of symptom relief. In patients with erosive esophagitis, repeat endoscopy is recommended to assure healing.

Dysphagia or Odynophagia. In the child with dysphagia (difficulty swallowing) or odynophagia (painful swallowing), a barium esophagram is recommended. If the initial history is suggestive of esophagitis, upper endoscopy may be performed as the initial diagnostic test. Treatment without prior diagnostic evaluation is not recommended. In the infant with feeding refusal, because a large variety of disorders may contribute to infant feeding difficulties, empiric therapy for GER is generally not recommended. However, if there are other signs or symptoms suggestive of GERD then a time-limited course of medical therapy can be considered.

Apnea or Apparent Life-threatening Events (ALTE). In patients with ALTEs recurrent regurgitation or emesis is common. However, investigations in unselected patients with ALTE have not demonstrated a convincing temporal relationship between esophageal acidification and apnea or bradycardia. There are no randomized studies to evaluate the usefulness of esophageal pH monitoring in infants with ALTE. In patients with frequent ALTE in which the role of GER is uncertain, esophageal pH monitoring may be useful to determine if there is a temporal association of acid reflux with ALTE. The evidence suggests that infants with ALTE and GER may be more likely to respond to anti-reflux therapy when there is gross emesis or oral regurgitation at the time of the ALTE, when episodes occur in the awake infant, and when the ALTE is characterized by obstructive apnea. Therapeutic options include thickened feedings and prokinetic and acid suppressant therapy. Since most infants improve with medical management, surgery is considered only in severe cases.

Asthma. In patients where symptoms of asthma and GER coexist, and in infants and toddlers with chronic vomiting or regurgitation and recurrent episodes of cough and wheezing, a three-month trial of vigorous acid suppressant therapy of GER is recommended. In patients with persistent asthma without symptoms of GER, esophageal pH monitoring is recommended in selected patients who are more likely to benefit from GER therapy. These include patients with radiographic evidence of recurrent pneumonia; patients with nocturnal asthma more than once a week; and patients requiring either continuous oral corticosteroids, high-dose inhaled corticosteroids, more than two bursts per year of oral corticosteroids or those with persistent asthma unable to wean medical management. If esophageal pH monitoring demonstrates an increased frequency or duration of esophageal acid exposure, a trial of prolonged medical therapy for GER is recommended.

Recurrent Pneumonia. GER can cause recurrent pneumonia in the absence of esophagitis or when esophageal pH monitoring is normal. There is insufficient evidence to provide recommendations for a uniform approach to diagnosis and treatment. Diagnostic evaluation may include flexible bronchoscopy with pulmonary lavage for lipid-laden macrophages, nuclear scintigraphy and assessment of airway protective mechanisms during swallowing.

Upper Airway Symptoms. Hoarseness, chronic cough, stridor and globus sensation can be associated with GER in infants and children. There is insufficient evidence to provide recommendations for diagnosis and treatment.

1. Background

Gastroesophageal reflux (GER), defined as passage of gastric contents into the esophagus, is a normal physiologic process that occurs throughout the day in healthy infants, children, and adults (1–4). Most episodes of reflux are brief and asymptomatic, not extending above the distal esophagus. Regurgitation is defined as passage of refluxed gastric contents into the oral pharynx. Vomiting is defined as expulsion of the refluxed gastric contents from the mouth. GER occurs during episodes of transient relaxation of the lower esophageal sphincter or inadequate adaptation of the sphincter tone to changes in abdominal pressure (5,6). The strength of the lower esophageal sphincter, the primary antireflux barrier, is normal in the vast majority of children with GER (5,6).

Gastroesophageal reflux disease (GERD) occurs when gastric contents reflux into the esophagus or oropharynx and produce symptoms (Table 1). The pathogenesis of GERD is multifactorial and complex, involving the frequency of reflux, gastric acidity, gastric emptying, esophageal clearing mechanisms, the esophageal mucosal barrier, visceral hypersensitivity, and airway responsiveness. To date no medical treatment targets the primary mechanism of GER, transient relaxation of the lower esophageal sphincter. The primary goals of therapy are to relieve the patient's symptoms, promote normal weight gain and growth, heal inflammation caused by refluxed gastric contents (esophagitis), and prevent respiratory and other complications associated with chronic reflux of gastric contents.

During infancy GER is common and is most often manifest as vomiting. Recurrent vomiting occurs in 50% of infants in the first three months of life, in 67% of four month old infants, and in 5% of 10 to 12 month old infants (7). Vomiting resolves spontaneously in nearly all of these infants (8). Parents do not usually perceive vomiting as a problem when it occurs no more often than once daily, but they are more likely to be concerned when vomiting is more frequent, the volume of vomitus is large, or when the infant cries frequently or with vomiting.

TABLE 1. *Complications of gastroesophageal reflux*

Symptoms
Recurrent vomiting
Weight loss or poor weight gain
Irritability in infants
Regurgitation
Heartburn or chest pain
Hematemesis
Dysphagia or feeding refusal
Apnea or ALTE
Wheezing or stridor
Hoarseness
Cough
Abnormal neck posturing (Sandifer syndrome)
Findings
Esophagitis
Esophageal stricture
Barrett's esophagus
Laryngitis
Recurrent pneumonia
Hypoproteinemia
Anemia

A small minority of infants develop GERD with symptoms including anorexia, dysphagia (difficulty swallowing), odynophagia (painful swallowing), arching of the back during feedings, irritability, hematemesis, anemia or failure to thrive. GER is one of the causes of apparent life-threatening events (ALTE) in infants and has been associated with chronic respiratory disorders including reactive airways disease, recurrent stridor, chronic cough and recurrent pneumonia in infants.

In preschool age children GER may manifest as intermittent vomiting. Older children are more likely to have the adult-type pattern of chronic heartburn or regurgitation with reswallowing. Esophagitis in older children may present as dysphagia or food impaction. Rarely, esophageal pain causes stereotypical, repetitive stretching and arching movements that are mistaken for atypical seizures or dystonia (Sandifer syndrome) (9,10). More severe inflammation may cause chronic blood loss with anemia, hematemesis, hypoproteinemia or melena (11). If the inflammation is untreated, circumferential scarring or strictures may form. Chronic inflammation may also result in replacement of distal esophageal mucosa with a metaplastic potentially malignant specialized epithelium known as a Barrett's mucosa (12). GER is common in children with asthma, but recurrent aspiration pneumonia due to GER is uncommon except in the neurologically impaired child. Hoarseness has also been associated with GER in children.

Little is known about the prevalence or natural history of GERD in children and adolescents. Numerous disorders can present with the same symptoms and signs as GER or GERD. Diagnostic and therapeutic approaches vary with the age of the patient and the presenting sign or symptom. Although GER is a common pediatric problem, no evidence-based guidelines for its evaluation and treatment currently exist. Therefore, the GER Guideline Committee was formed by the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN) to develop a clinical practice guideline for the management of GER and GERD in infants and children.

The GER Guideline Committee consists of a primary care pediatrician, two clinical epidemiologists who are also primary care pediatricians and five pediatric gastroenterologists. This clinical practice guideline is designed to assist primary care providers, pediatric gastroenterologists, pediatric surgeons, pediatric pulmonologists and pediatric otolaryngologists in the management of children with GER in both inpatient and outpatient settings. The guideline is not intended for the management of neonates less than 72 hours old, premature infants or infants and children with either neurologic impairments

or anatomic disorders of the upper gastrointestinal tract. The management of infants less than two years of age was considered separately from the management of children and adolescents two to 18 years of age. The desirable outcome of optimal management was defined as improvement or resolution of the presenting symptoms and complications of GER, with interventions that have few or no adverse effects, and with resultant resumption of functional health. Cost effectiveness was not considered because of a lack of information in pediatric patients.

This document represents the official recommendations of the North American Society for Pediatric Gastroenterology and Nutrition on the evaluation and treatment of gastroesophageal reflux in infants and children. The American Academy of Pediatrics has also endorsed these recommendations. This review and recommendations are a general guideline and are not intended as a substitute for clinical judgment or as a protocol for the management of all patients with this problem.

2. Methods

In order to develop an evidence-based guideline the following search strategy was used. Articles on diagnosis, treatment, and complications were searched separately. Articles published in English between January 1966 and March 1999 on GER in children were searched using Ovid and PubMed. Letters, abstracts, editorials, case reports, reviews, and articles related to premature infants and children with neurological impairments were excluded. The search strategies for diagnosis yielded 169 articles, 129 articles after exclusion criteria were applied, while the search strategy for treatment yielded 770 articles. After exclusion criteria were applied, there were 23 articles related to non-pharmacological treatment (positioning and dietary changes), 42 to pharmacological treatment (prokinetics and acid-suppressants) and 70 to surgical treatment (fundoplication). Searches on specific complications of GER yielded the following: 140 before and 20 after application of exclusion criteria for apnea and apparent life-threatening events; 91 before and 27 after exclusion criteria for asthma; 18 before and 9 after exclusion criteria for eosinophilic esophagitis; and 83 before and 34 after exclusion criteria for pulmonary disease. Subsequently, additional articles were identified and reviewed. When the pediatric literature was insufficient, the adult literature was also considered.

Articles were evaluated using published criteria (13,14). To evaluate inter-rater reliability, both clinical epidemiologists independently reviewed twenty-nine of the therapy articles on respiratory complications. Concordance using the criteria was 48% with all differences attributable to case series (Level IIa) and descriptive studies (Level III) evidence. If case series and large case reports were considered equivalent, the concordance was 100%. The Committee based its recommendations on integration of the literature review with expert opinion. Consensus was achieved through Nominal Group Technique, a structured, quantitative method (15). Using the methods of the Canadian Preventive Services Task Force (16), the quality of evidence of each of the recommendations made by the GER Guideline Committee was determined and is summarized in the Appendix.

In the following sections we examine the effectiveness of diagnostic tests and treatment modalities commonly utilized for the management of GERD. Subsequent sections indicate how those interventions can be applied to various clinical situations in the infant and older child.

3. Diagnostic Approaches

Although many tests have been used for the diagnosis of GER, few objective studies compare the various diagnostic approaches. More importantly, it is not known whether tests can predict when an individual patient will improve with either medical or surgical therapy for GERD. A test may be useful to document the occurrence of GER, to detect complications of GER, to establish a causal relationship between GER and symptoms, to evaluate therapy or to exclude other causes of symptoms. Since each test is designed to answer a particular question, it is valuable only when used in the appropriate clinical situation.

3.1 History and Physical Examination

A review of the medical literature found no reports comparing the history and physical examination to diagnostic tests. In two pediatric studies of persistent GER there was no relationship between symptoms and the presence of esophagitis (17,18). Nonetheless, based upon expert opinion, in most infants with vomiting and most older children with regurgitation and heartburn, a history and physical examination are sufficient to reliably diagnose GER, recognize complications, and initiate management.

3.2 Barium Contrast Radiography

The upper gastrointestinal (GI) series is useful to detect anatomic abnormalities, such as pyloric stenosis, malrotation, hiatal hernia and esophageal stricture. When compared to esophageal pH monitoring, the upper GI series is neither sensitive nor specific for the diagnosis of GER. The sensitivity, specificity and positive predictive value of the upper GI series range from 31% to 86%, 21% to 83%, and 80% to 82% respectively when compared to esophageal pH monitoring (19–24). The brief duration of the upper GI series results in false negative results, while the frequent occurrence of non-pathological reflux results in false positive results. Thus, the upper GI series is not a useful test to reliably determine the presence or absence of GER.

3.3 Esophageal pH Monitoring

Esophageal pH monitoring, used widely as an index of esophageal acid exposure, measures the frequency and duration of episodes of acid reflux (25). The test is performed by the transnasal placement of a microelectrode into the lower esophagus, which measures and records intraesophageal pH. Most clinicians utilize computerized devices that record intraesophageal pH every 4 to 8 seconds (26,27). Computerized analysis calculates the number and duration of reflux episodes (28). An episode of acid reflux is usually defined as esophageal pH <4 for a specified minimum duration, usually 15 to 30 seconds (29).

The recording device, diet, position and activity during the study affect the measurement of esophageal pH. Location of the probe sensor also affects the results; the distal esophagus is normally exposed to more acid than the proximal esophagus. There is technical and biological variability on sequential 24-hour pH monitoring studies, but this variability appears to affect the interpretation of results in only a small number of patients (30–32). Abbreviated studies of fewer than 12 hours are less reproducible than longer studies (33,34).

Asymptomatic episodes of acid reflux occur in normal infants, children, adolescents and adults. In a study of 509 normal infants, 0 to 11 months of age, there were 31 ± 21 episodes of acid reflux per day; the upper limit of normal was 73 episodes daily (2). In three studies of 48 children, 0 to 9 years of age, the mean upper limit of normal was 25 daily (29,35,36) and in 50 normal adults it was 45 daily (37). The mean upper limit of normal for the number of episodes of acid reflux lasting 5 minutes or longer was 9.7 in infants, 6.8 in children and 3.2 in adults. The percentage of the total time that the esophageal pH is <4, also called the reflux index, is considered the most valid measure of reflux because it reflects the cumulative exposure of the esophagus to acid. The mean upper limit of normal of the reflux index was 11.7% in infants 0 to 11 months (2), 5.4% in children 0 to 9 years old (29,35,36), and approximately 6% in 432 normal adults (38). These studies indicate that acid reflux is a physiologic process that is more common in normal infants in the first year of life than it is in normal older children and adults. Based on the above studies, it is recommended that the upper limit of normal of the reflux index be defined as up to 12% in the first year of life and up to 6% thereafter.

The presence of endoscopic and histopathological esophagitis is strongly associated with abnormal esophageal pH monitoring. In pediatric patients with endoscopic esophagitis (ulcerations or erosions) or biopsy proven esophagitis, approximately 95% will have an abnormal reflux index (39–41). However, not all patients with GER have esophagitis. In the selected populations of patients reported, esophagitis is present in 50% of patients with positive esophageal pH monitoring studies (39–41) and the severity of esophagitis does not correlate with the reflux index (42). Proximal esophageal and pharyngeal pH monitoring have not been proven to be more useful than lower esophageal pH monitoring alone for determining which patients are at risk for upper airway complications of GER (3,43,44).

Esophageal pH monitoring can be used to detect abnormal acid reflux in selected clinical situations. Esophageal pH monitoring can determine if a patient's symptom is temporally associated with acid reflux by calculating the symptom index. The symptom index is the ratio of the number of episodes of a symptom (e.g., heartburn) that occur concurrent with acid reflux divided by the total number of episodes of that symptom. In adults, symptom index scores ≥0.5 suggest a relationship between heartburn and gastroesophageal reflux; in these cases, symptoms have successfully been controlled with acid suppression therapy (45). One study using the symptom index in infants compared behavior with episodes of acid reflux (46). Esophageal pH monitoring is also useful to assess the adequacy of the dosage of acid suppression therapy in children being treated with a proton pump inhibitor (47) and may be useful to determine if a patient may be at increased risk for airway complications of GER. For example, approximately 60% of children with asthma, poorly responsive to conventional treatment, had abnormal esophageal pH monitoring studies (48–50).

Esophageal pH monitoring does not detect non-acidic reflux episodes such as occur post-prandially in infants. In some patients, esophageal pH monitoring may be within the range of normal but brief episodes of GER may cause complications such as ALTE, cough or aspiration pneumonia.

In summary, esophageal pH monitoring is a valid and reliable measure of acid reflux. Esophageal pH monitoring establishes the presence of abnormal acid reflux, to determine if there is a temporal association between acid reflux and frequently occurring symptoms, and to assess the adequacy of therapy in patients who do not respond to treatment with acid suppressants

3.4 Endoscopy and Biopsy

Endoscopy enables both visualization and biopsy of the esophageal epithelium. Endoscopy and biopsy can determine the presence and severity of esophagitis, strictures and Barrett's esophagus, as well as exclude other disorders, such as Crohn's disease, webs and eosinophilic or infectious esophagitis. A normal appearance of the esophagus during endoscopy does not exclude histopathological esophagitis. The subtle mucosal changes of erythema and pallor may be observed in the absence of esophagitis (18,42,51). Endoscopic visualization of esophageal erosions or ulceration correlates with histopathological esophagitis, but the severity of endoscopic and histopathological changes may not correlate since the lesion can be patchy and biopsies sample only a small

portion of the mucosal surface. Endoscopic grading systems for the severity of erosive esophagitis, such as the Los Angeles criteria (52), have not yet been validated in pediatric patients but may provide more uniform definitions of severity, if applied. Other findings, such as the presence of vertical lines (53) also correlate with histopathological esophagitis in children. Because there is a poor correlation between endoscopic appearance and histopathology, esophageal biopsy is recommended when diagnostic endoscopy is performed.

In normal infants and children, eosinophils and neutrophils are not present in the esophageal epithelium (40,54). Basal zone hyperplasia (>20% to 25% of total epithelial thickness) and increased papillary length (>50% to 75% of epithelial thickness) have been found to correlate with increased acid exposure (40,55). The available pediatric data suggest that intraepithelial eosinophils or neutrophils as well as morphometric measures of basal cell layer thickness and papillary height are valid indicators of reflux esophagitis. It has been proposed that a high number of eosinophils in the esophageal epithelium (>7 to 24 per high power field) suggest the diagnosis of eosinophilic esophagitis (56,57).

3.5 Scintigraphy

A nuclear scintiscan is performed by the oral ingestion or instillation of technetium-labeled formula or food into the stomach. The areas of interest, the stomach, esophagus and lungs, are scanned for evidence of GER and aspiration. Unlike esophageal pH monitoring, the nuclear scan can demonstrate reflux of non-acidic gastric contents. Scintigraphy also provides information about gastric emptying, which may be delayed in children with GERD (58–60). However, a lack of standardized techniques and the absence of age-specific normative data limit the value of this test. Episodes of aspiration may be detected during a one-hour study or on images obtained up to 24 hours after the feeding is administered (61). A negative test does not exclude the possibility of infrequently occurring aspiration (62).

The reported sensitivity and specificity of the nuclear scan for the diagnosis of GER are 15% to 59% and 83% to 100%, respectively, when compared to esophageal pH monitoring (19,63–65). This lack of correlation most likely reflects the difference in techniques of the two tests. Scintigraphy measures both acid and non-acid reflux in the initial postprandial period, whereas esophageal pH monitoring measures acid reflux for prolonged periods up to 24 hours and protocols used for analysis often exclude the postprandial recording times (64,66). The role of nuclear scintigraphy in the diagnosis and management of GERD in infants and children is unclear.

3.6 Empiric Therapy

A trial of time-limited medical therapy for GER is useful for determining if GER is causing a specific symptom. Empiric therapy is widely used (67) but has not been validated for any symptom presentation in pediatric patients. Empiric treatment trials with omeprazole have been reported for cough (68,69), heartburn (70,71), non-cardiac chest pain (72) and dyspepsia (73) in adult patients.

4. Treatment Options

Treatment options are classified as lifestyle changes and pharmacological or surgical therapies. Lifestyle changes for infants include alterations in formula composition and sleep positioning. Lifestyle changes in adolescents include dietary modifications, altered sleep position, weight reduction and smoking cessation (74). Medications buffer gastric acid, reduce gastric acid secretion or alter gastrointestinal motility. Surgical therapy includes operative techniques that reduce or eliminate GER.

4.1 Lifestyle Changes

4.1.1 Feeding Changes in Infants. In most infants, symptoms of GER do not decrease when there is a change from one milk formula to another. However, a subset of infants with vomiting has cow's milk protein allergy (75). In these infants, elimination of cow's milk protein from the diet resulted in decreased vomiting within 24 hours. Two successive, blind challenges corroborated the diagnosis of cow's milk protein allergy-induced vomiting in infants (76,77). A similar study found that IgG anti-ß-lactoglobulin, a major antigenic determinant in cow's milk, was present in infants allergic to cow's milk protein with symptom reduction following the elimination of cow's milk (78,79). There is, therefore, evidence to support a one to two week trial of a hypoallergenic formula in formula fed infants with vomiting. There are no studies that evaluate the therapeutic value of a soy-protein formula for this indication, nor are there studies that evaluate whether sensitization to soy proteins causes vomiting. Similarly, there are no studies that examine whether sensitization to maternal dietary proteins passed into human breast milk leads to vomiting in breast fed infants. The role of breast feeding versus formula feeding in the treatment of GERD is uncertain. One study (80) measured esophageal acidification in breast-fed and formula-fed healthy term neonates aged 2 to 8 days during various sleep states. During active sleep, but not other sleep states, formula fed infants had an increased number of reflux episodes and increased esophageal acid exposure compared to breast fed infants.

Milk-thickening agents do not improve reflux index scores (81,82) but do decrease the number of episodes of vomiting (81–83). In the United States of America (USA), thickening is usually achieved with the addition of rice cereal to formula (83). When thickening an infant formula with a caloric density of 20 kcal per ounce, the

addition of one tablespoonful of rice cereal per ounce of formula increases the caloric density to approximately 34 kcal per ounce, whereas the addition of one tablespoonful of rice cereal per two ounces of formula increases the caloric density to approximately 27 kcal per ounce. When formula is thickened it is necessary to cross-cut the nipple to allow for adequate flow. Thickened formula may increase coughing during feedings (84). Newer formulas that contain carob flour or locust bean gum as thickening agents are now available in Europe. These formulas have been reported to decrease vomiting and esophageal acid exposure when compared with unthickened formula (85) and formula thickened with rice cereal (86). A formula with added rice starch is now available in the USA and Canada but there are no published studies regarding its efficacy for the treatment of GERD in infants.

Infants who are underweight due to GERD may gain weight when the caloric density of their feedings is increased. Some infants require more aggressive intervention such as overnight nasogastric tube feeding to promote weight gain (87). Rarely, patients require nasojejunal tube feeding to promote growth and prevent vomiting or aspiration. Although these approaches to therapy of GERD are widely utilized, there are no controlled studies comparing these treatment approaches to pharmacological or surgical treatments.

4.1.2 Positioning Therapy for Infants. Esophageal pH monitoring has demonstrated that infants have significantly less GER when placed in the prone position than in the supine position. In a study of 79 infants and children (11.6 ± 27 months old) with symptomatic GER, the reflux index during sleep was 24% in the supine position and 8% in the prone position (88). In a study of 60 asymptomatic newborns (1 to 10 days old) kept in one position for 17 hours, the reflux index was 5% when supine and 1% when prone (89). In a randomized crossover design study of 24 infants <5 months of age, each infant was evaluated in each of four positions (prone, supine, left, right) in both horizontal and 30 degree upright positions. The reflux index was significantly higher in the supine (15%) than in the prone (7%) position (90). There is conflicting evidence whether there is less reflux in infants placed prone at a 30-degree angle compared to prone flat (88–91). The amount of reflux is similar in the supine 30-degree angle and in the supine flat positions (88,90). The prone position is superior to semi-supine positioning in an infant seat, which exacerbates GER (92).

One sudy of 60 asymptomatic newborns showed similar reflux in the left, right and supine positions, which was more reflux than in the prone position (89). In contrast, in a study of 24 infants <5 months old, the left side position was similar to the prone position and led to less reflux than the right side and supine positions (90). In adults reflux occurs less often in the left lateral decubitus (left side down) than in the right lateral decubitus (right side down) position (93,94).

Prone positioning has been recommended for the treatment and prevention of GER in infants. However, this advice conflicts with the recent recognition that prone positioning is associated with a higher rate of the sudden infant death syndrome (SIDS). The Nordic epidemiological SIDS study demonstrated that the odds ratio of SIDS mortality was 13.9 for the prone position and 3.5 for the side position when compared to the supine position (95). Another study demonstrated that the SIDS mortality per 1000 live births was 4.4 in the prone position and <0.1 for the non-prone position (96). In California the SIDS rate declined from 1.2 to 0.7 per 1000 live births after a public health campaign to promote back sleeping (97). Evidence suggests that universal use of the supine position would likely markedly reduce SIDS (98). The side position appears to be unstable, because infants turn during sleep from side to prone. Prone sleeping results in longer uninterrupted sleep periods, and supine sleeping in more arousability, frequent awakening and crying during the night.

In view of the recent evidence describing the successful prevention of SIDS with supine positioning, it is now appropriate to modify the earlier advocacy of prone positioning for GERD. In infants from birth to 12 months with GERD, the risk of SIDS generally outweighs the potential benefits of prone sleeping. Therefore, consistent with the new recommendations of the American Academy of Pediatrics, non-prone positioning during sleep is recommended (99). Supine positioning confers the lowest risk for SIDS and is preferred. Prone positioning is acceptable while the infant is awake, particularly in the postprandial period. Prone positioning during sleep is only considered in unusual cases where the risk of death from complications of GER outweighs the potential increased risk of SIDS. When prone positioning is necessary, it is particularly important that parents be advised not to use soft bedding, which increases the risk of SIDS in infants placed prone (odds ratio 1.7) (100,101).

The efficacy of positioning therapy in children older than one year has not been studied. It is likely that there is a benefit to left side positioning and elevation of the head of the bed, as in adults (102–104).

4.1.3 Lifestyle Changes in Children and Adolescents. Lifestyle changes are often recommended to adults with gastroesophageal reflux. These include dietary modification, avoidance of alcohol, weight loss, and cessation of smoking. Most of the studies investigating these factors have been performed in adults; thus, their applicability to children remains indeterminate. A review of the pediatric and adult literature may be summarized as follows. The current evidence does not support a recommendation to decrease fat intake to treat GER (105–112). However, the limited evidence available supports the recommendation that children and adolescents with GERD avoid caffeine, chocolate and spicy

foods that provoke symptoms (113–124). Similarly there is evidence that obesity, exposure to tobacco smoke and alcohol are associated with GER (125–148). It is not known whether lifestyle changes have an additive benefit in patients receiving pharmacological therapy.

4.2 Pharmacological Therapies

The purpose of the two major pharmacological treatments for GERD, acid suppressants and prokinetic agents, is to reduce the amount of acid refluxate to which the esophagus or respiratory tract is exposed, thereby preventing symptoms and promoting healing. The aim of acid suppressants is to reduce esophageal acid exposure by either neutralizing gastric acid or decreasing secretion. The aim of prokinetic agents is to reduce the amount of refluxate by improving contractility of the body of the esophagus, increasing pressure in the lower esophageal sphincter, decreasing the frequency of transient lower esophageal sphincter relaxations and accelerating gastric emptying.

Studies of pharmacological therapies for the treatment of GERD in children are difficult to compare because of heterogeneous patient populations, variable drug doses and duration of therapy, and a lack of standard outcome variables. The majority of studies published to date have used two outcome assessments: symptom responses and change in results of esophageal pH monitoring. Many studies are confounded by multiple treatments including lifestyle changes and other drugs. For purposes of this guideline, double blind single drug studies or randomized comparison studies of pharmacological therapies were reviewed. When no such studies were available, other studies were considered. Recommended drug doses and the common adverse effects of these medications are listed in Table 2.

4.2.1 Acid Suppressants. Acid suppressants act to decrease esophageal acid exposure by reducing the quantity of gastric acid. The antisecretory agents, histamine-2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs), reduce the secretion of gastric acid, whereas antacids neutralize gastric acid. Because of their superior efficacy and convenience, antisecretory agents have largely superceded antacids and surface agents in the treatment of GERD. Generally PPIs produce a greater reduction in acid secretion and have a longer duration of action than H_2RAs.

4.2.1.1 Histamine-2 Receptor Antagonists. H_2RAs act to decrease acid secretion by inhibiting the histamine-$_2$ receptor on the gastric parietal cell. In one study in infants ranitidine treatment, 2 mg per kg per dose BID, reduced by 44% the duration that gastric pH was <4, and with TID dosing the reduction was 90% (149). Ranitidine 5 mg/kg per dose orally has been shown to increase gastric pH for 9 to 10 hours in infants (150). Tolerance to intravenous ranitidine and escape from its acid inhibitory effect within six weeks has been observed (151).

Numerous randomized controlled trials in adults have demonstrated that cimetidine, ranitidine and famotidine

TABLE 2. *Drugs demonstrated to be effective in gastroesophageal reflux disease*

Type of medication	Recommended oral dosage	Adverse effects/precautions
Histamine$_2$ receptor antagonists		
Cimetidine	40mg/kg/day divided TID or QID (adult dose: 800–1200 mg/dose BID or TID)	rash, bradycardia, dizziness, nausea, vomiting, hypotension, gynecomastia, reduces hepatic metabolism of theophylline and other medications, neutropenia, thrombocytopenia, agranulocytosis, doses should be decreased with renal insufficiency
Nizatidine	10 mg/kg/day divided BID. (adult dose: 150 mg BID or 300 mg qhs)	headaches, dizziness, constipation, diarrhea, nausea, anemia, urticaria, doses should be decreased with renal insufficiency
Ranitidine	5 to 10 mg/kg/day divided TID (Adult dose: 300mg BID)	headache, dizziness, fatigue, irritability, rash, constipation, diarrhea, thrombocytopenia, elevated transaminases, doses should be decreased with renal insufficiency
Famotidine	1 mg/kg/day divided BID (adult dose: 20 mg BID)	headaches, dizziness, constipation, diarrhea, nausea, doses should be decreased with renal insufficiency
Proton pump inhibitors		
Omeprazole	1.0 mg/kg/day divided qd or BID (adult dose 20 mg qd)	headache, diarrhea, abdominal pain, nausea, rash, constipation, vitamin B12 deficiency
Lanzoprazole	No pediatric dose available (adult dose: 15–30 mg qd)	headache, diarrhea, abdominal pain, nausea, elevated transaminase, proteinuria, angina, hypotension
Pantoprazole	No pediatric dose available. (adult dose: 40 mg qd)	headache, diarrhea, abdominal pain, nausea
Rabeprazole	No pediatric dose available (adult dose: 20 mg qd)	headache, diarrhea, abdominal pain, nausea
Prokinetic		
Cisapride	0.8 mg/kg/day divided QID. (adult dose: 10–20 mg QID)	rare cases of serious cardiac arrhythmia (FDA recommends ECG before administration) beware of drug interactions do not use in patients with liver, cardiac or electrolyte abnormalities (FDA recommends K+, Ca++, Mg++ and creatinine before administration)

are superior to placebo for relief of symptoms and healing of esophageal mucosa (152–154). However, the efficacy of H_2RAs is much greater for mild esophagitis than for severe esophagitis (155). One randomized placebo-controlled trial in infants and children with erosive esophagitis demonstrated the efficacy of H_2RA therapy (156) in 32 children who received either cimetidine 30–40 mg/kg per day or placebo. The cimetidine treated group had significant improvement in clinical and histopathology scores, but there was no improvement in the placebo group. Another randomized placebo controlled study in 24 children with mild to moderate esophagitis demonstrated that nizatidine 10 mg/kg per day was more effective than placebo for the healing of esophagitis and symptom relief (157). There are case series that provide additional support for the efficacy of H_2RAs in infants and children (158–161). Although no randomized controlled studies in children demonstrate the efficacy of ranitidine or famotidine for the treatment of esophagitis, expert opinion is that these agents appear to be as effective as cimetidine and nizatidine.

4.2.1.2 Proton Pump Inhibitors. Proton pump inhibitors (PPIs), the most effective acid suppressant medications, covalently bond and deactivate the H+, K+ –ATPase pumps (162). To be activated PPIs require acid in the parietal cell canaliculus, and they are most effective when the parietal cell is stimulated by a meal following a fast (162). Optimal effectiveness is achieved when the PPI is administered one–half hour before breakfast so that peak plasma concentrations coincide with the mealtime. If given twice daily, the second dose is best administered one–half hour before the evening meal. Concomittant administration of H_2RAs can inhibit efficacy. A steady state of acid suppression is not achieved for several days. There are limited data on the pharmacology of PPIs in infants and children. In one study, doses of omeprazole of 10 to 60 mg (0.7 to 3.3 mg/kg) daily were required to normalize esophageal pH monitoring, and a starting dose of 0.7 mg/kg per day was recommended (47). In other case series reporting successful omeprazole treatment of esophagitis, doses of 0.5 or 0.6 mg/kg daily were administered for 6 to 13 weeks (163–166).

Numerous randomized controlled trials in adults have demonstrated that PPIs are superior to H_2RAs in relieving symptoms and healing esophagitis (152). PPIs are effective in patients with esophagitis refractory to high–dose H_2RA therapy (167,168), and are more effective than H_2RAs in maintaining remission of erosive esophagitis (169). There are currently no reported placebo controlled trials of PPIs in infants or children. However, one randomized controlled trial of 25 infants and children with reflux esophagitis found comparable effectiveness of omeprazole (40 mg per 1.73 m^2 surface area) and very high dose ranitidine (20 mg/kg/day) in reducing symptoms and improving histopathology and esophageal pH monitoring (170). In addition, in multiple case series of pediatric patients refractory to previous treatment regimens including H_2RAs, omeprazole appeared to be highly effective in the treatment of severe esophagitis, resulting in both symptomatic and endoscopic improvement while on treatment (47,163–166). Other proton pump inhibitors, lansoprazole, pantoprazole and rabeprazole, have been introduced recently but studies of their efficacy in infants and children have not yet been reported. Esophageal pH monitoring can be performed to assess the adequacy of the dosage but target values for either esophageal acid exposure or gastric pH that assure therapeutic efficacy are not known. Long term safety studies in adults treated with omeprazole for a mean of 6.5 years (range 1.4 to 11.2 years) show omeprazole is highly effective and safe for the control of reflux esophagitis in adults (171). Despite omeprazole therapy, 12% of the patients who did not have Barrett's esophagus at baseline developed Barrett's metaplasia during follow–up. Similar studies of the efficacy and safety of long term treatment have not been performed in pediatric patients.

One approach to acid reducing therapy, called *step-up* therapy, is to begin treatment with an H_2RA at standard dosage, following with a PPI at standard dosage and then a PPI at higher dosage if necessary to achieve improvement (47). An alternative approach, called *step-down* therapy, is to begin treatment with a PPI at higher dosage to achieve improvement, following with a PPI at standard dosage and then an H_2RA to maintain improvement. Studies in adults indicate that the step-down approach may be more cost effective (171) and has been recommended in a recently published evidence-based guideline for adult patients (172), but there are no published studies comparing these two strategies in children.

The current evidence supports the recommendation to use antisecretory therapy for the treatment of reflux esophagitis. The effectiveness of acid reducing therapy for other manifestations of GERD is not well documented in children. However, since these agents reduce esophageal acid exposure they are likely to be a useful treatment of GER-related respiratory disorders (see sections 5.5 to 5.9).

4.2.1.3 Antacids. The aim of antacids, which act by neutralizing gastric acid, is to reduce esophageal acid exposure and thereby reduce symptoms of heartburn, alleviate esophagitis and prevent acid-triggered respiratory symptoms. Intensive high-dose antacid therapy (magnesium hydroxide and aluminum hydroxide; 700 mmol/1.73 m2/day) has been shown to be as effective as cimetidine for the treatment of peptic esophagitis in children aged 2 to 42 months (173,174). However, treatment with aluminum-containing antacids significantly increases plasma aluminum levels in infants (175,176). Plasma aluminum levels measured in infants receiving these agents approach levels previously noted to cause osteopenia, microcytic anemia, and neurotoxicity in pediatric patients (177–179). There are no published studies evaluating the efficacy or safety of commercially

available antacids containing either magnesium hydroxide alone or calcium carbonate. Antacid therapy is commonly used for the short-term relief of intermittent symptoms of GER in children and adolescents. Although there appears to be little risk to this approach, it has not been formally studied. Because more convenient and safe alternatives are available, chronic antacid therapy is generally not recommended.

4.2.2 Prokinetic Therapy. Transient lower esophageal sphincter relaxations, which are prolonged relaxations unaccompanied by a swallow, are considered the most important pathophysiological mechanism of GER. Other mechanisms are free reflux and strain-induced reflux, when abdominal pressure exceeds the pressure of the lower esophageal sphincter. Although prokinetic agents appear to increase lower esophageal sphincter pressure, a number of studies have failed to demonstrate that prokinetic agents reduce the frequency of episodes of acid reflux, suggesting that they do not reduce the frequency of transient relaxations of the lower esophageal sphincter. The rationale for prokinetic therapy in the treatment of GERD is based on evidence it enhances esophageal peristalsis and accelerates gastric emptying.

Since regurgitation and vomiting are common symptoms in infants and children with reflux, even in the absence of erosive esophagitis, prokinetic agents may have a special role in the treatment of GER in infants and children with conditions where acid suppressants are unlikely to be helpful. Double blind single drug studies and randomized comparison studies of cisapride, metoclopramide, bethanecol and domperidone have been performed in infants and children with GER. Cisapride appears to be a marginally effective prokinetic agent for the treatment of GERD, whereas the effectiveness in children of other prokinetic agents is unproven.

Cisapride is a mixed serotonergic agent that facilitates the release of acetylcholine at synapses of the myenteric plexus. Six randomized controlled trials of cisapride therapy in infants less than two years of age have demonstrated improvement in symptoms or esophageal pH monitoring or both when compared to placebo (180–185). Modest improvement in clinical symptoms, with a reduction in the frequency and volume of vomiting, has been reported in four of five studies where duration of therapy was at least four weeks (180–182,184,186). Improvement occurred more often in infants who regurgitated or vomited after every meal or more than six times daily (182,184,186). One study reported complete resolution of vomiting in less than 20 percent of treated infants (182). In all studies a significant percentage of patients receiving placebo also improved, and in one study vomiting resolved in 14 percent of placebo-treated patients (182).

Randomized controlled trials using prolonged esophageal pH monitoring have demonstrated that cisapride therapy is superior to placebo in reducing esophageal acid exposure and enhancing esophageal acid clearance following reflux. All studies reported statistically significant improvement compared to baseline measurements of one or more of the following parameters: reflux index (percentage of the time that esophageal pH was less than 4), mean duration of reflux episodes, and number of episodes longer than 5 minutes (180–187). Cisapride improved symptom scores, esophageal histopathology, and pulmonary function in patients with reflux esophagitis and respiratory complications (50,180,181). This may be due to reduced esophageal acid exposure and enhanced esophageal acid clearance.

Metoclopramide is an antidopaminergic agent with cholinomimetic and mixed serotonergic effects. In adults the effects of metoclopramide on esophageal motility and clinical efficacy have been equivocal (188) and the addition of metoclopramide to ranitidine therapy for treatment of GERD resulted in no better efficacy and increased the number of adverse events (189). Four randomized controlled studies of at least two weeks duration on the efficacy of metoclopramide in the treatment of GER in children have been reported. Two of four studies reported a decrease in the frequency and volume of vomiting (190,191), whereas in two other studies metoclopramide was no better or worse than placebo (192,193). The reported effects on esophageal pH monitoring of acute and steady-state dosing of metoclopramide have also been contradictory, with both positive (187,194,195) and negative results (192,193,196). Adverse effects of metoclopramide, which are not uncommon, include central nervous system complications such as parkinsonian reactions and tardive dyskinesia, which may be irreversible (197).

Bethanechol, a direct cholinergic agonist, has been studied in two controlled trials of 6 weeks duration. In one study bethanechol was superior to placebo in reducing the frequency and volume of vomiting, but prolonged esophageal pH monitoring was not performed (198). The other study, which compared bethanechol to antacids, found no difference between the two treatments in clinical outcome or esophageal pH monitoring (199). Of three reports regarding domperidone therapy, one study found improvement in both clinical symptoms and pH score following two weeks of therapy (191), while two studies reported no improvement in either outcome measure following four and eight weeks of therapy (200,201).

In conclusion, there is evidence to support the use of cisapride when a prokinetic is indicated for the treatment of GERD in infants and children. However, because of concerns about the potential for serious cardiac arrhythmias in patients receiving cisapride, appropriate patient selection and monitoring as well as proper use, including correct dosage and avoidance of co-administration of contraindicated medications, are important (202). Despite these concerns, the use of cisapride can be considered for the treatment of selected infants with vomiting and poor weight gain, ALTE or asthma who have failed lifestyle and antisecretory therapy. In some children over

2 years of age with asthma or with recurrent vomiting that is adversely affecting lifestyle cisapride therapy may also be considered. Cisapride recently was withdrawn from the USA market due to these safety concerns and therefore in order to receive cisapride patients must be enrolled in a limited access protocol that requires repeated venipuncture and electrocardiograms, making the use of cisapride a less practical option. There is insufficient evidence that other prokinetic agents are effective in the treatment of GERD in infants and children.

4.2.3 Surface Agents. Sodium alginate forms a surface gel that decreases the regurgitation of gastric contents into the esophagus and protects the esophageal mucosa. Randomized comparison studies have demonstrated conflicting outcomes for both symptoms (203,204) and esophageal pH monitoring (205,206). The formulation utilized for most published studies is not available in the USA.

Sucralfate gel acts by adhering to peptic lesions, and protects the esophageal mucosal surface. In adults sucralfate (1 g po QID) decreases symptoms and promotes healing in patients with non-erosive esophagitis (207). The only randomized comparison study in children demonstrated that sucralfate is as effective as cimetidine for treatment of esophagitis (208). Sucralfate is an aluminum complex, and the potential adverse effects of aluminum in infants and children need to be considered. The available data are inadequate for determining the safety or efficacy of sucralfate in the treatment of GERD in children.

4.3 Surgical Treatment for GERD

Surgery is often considered for the child with GERD who has persistence of symptoms following medical management or who is unable to be weaned from medical therapy. The Nissen fundoplication is the most popular of the many surgical procedures that have been used. Recently experience with laparoscopic procedures has been reported. Results and complication rates do not appear to vary by procedure.

The literature concerning surgical treatment of GERD in children consists of a large number of descriptive papers composed of case series (209–221). The methodology for patient selection and outcome was not always well defined. Patients usually had surgery for failed medical management. There are no published randomized controlled trials. Because most series extended over many years, medical management in earlier patients was often limited to life style changes such as positional therapy and thickened feedings. Some patients received H_2RAs but few if any patients received PPIs. Most did not receive a prokinetic agent and those that did often received metoclopramide. Thus many of the patients did not receive optimal medical therapy by today's standards. Outcome measures were often vague or unspecified. The groups were heterogeneous without adjustment for co-morbid conditions. Many (if not most) of the surgically treated patients were neurologically impaired. A variety of surgical procedures were used. The addition of a pyloroplasty was variable. The outcome was sometimes defined by symptoms and at other times by postoperative tests.

Success rates (complete relief of symptoms) from 57% to 92% have been reported. Mortality related to operation in large series has ranged from 0% to 4.7%. Unrelated death rates from co-morbid conditions were 0% to 21%. The reported overall complication rates have varied between 2.2% and 45%. The most commonly reported complications include breakdown of the wrap (0.9% to 13%), small bowel obstruction (1.3% to 11%), gas bloat syndrome (1.9% to 8%), infection (1.2% to 9%), atelectasis or pneumonia (4.3% to 13%), perforation (2% to 4.3%), persistent esophageal stricture (1.4% to 9%) and esophageal obstruction (1.4% to 9%). Other complications not reported in enough detail to estimate complication rates include dumping syndrome (222,223), incisional hernia and gastroparesis. Reoperation rates were 3% to 18.9%. The results of pediatric series of laparoscopic fundoplications suggest that the results and complication rates are similar to those of the open procedure, but hospitalization is shortened (224,225).

These case series indicate overall favorable outcomes. The potential risks, benefits and costs of successful prolonged medical therapy versus surgical therapy have not been well-studied in infants or children with various symptom presentations. If chronic esophagitis is the primary indication for possible GERD surgery, an upper endoscopy with biopsy and prolonged esophageal pH monitoring study is recommended to demonstrate conclusively that esophagitis is due to GER, rather than other etiologies, such as eosinophilic esophagitis. If airway symptoms are the primary indication for surgery, review of diagnostic studies including radiographic studies, bronchoalveolar lavage, esophageal pH monitoring studies and swallowing studies may all impact on the decision to proceed with surgery, which may be beneficial in some patients even when esophageal pH monitoring is normal (226).

5. Evaluation and Management of Infants and Children with Suspected GERD

The approach to evaluation and management of infants and children with GERD depends upon the presenting symptoms or signs. The following sections discuss the evidence that supports a relationship between a particular clinical disorder and GER in pediatric patients. The approach to determining if GER is causing disease in a patient and the management of pediatric patients with specific symptom presentations is then reviewed. Recommendations are based upon the available evidence

and the consensus opinion of the GER Guidelines Guideline Committee.

5.1 Recurrent Vomiting

The diagnostic challenge for the practitioner is to distinguish between vomiting due to GER and vomiting caused by other disorders. Numerous disorders can present with recurrent vomiting that mimics GERD (see Table 3). Laboratory and radiographic investigation may be necessary to exclude other causes of vomiting. The infant with recurrent vomiting is discussed separately from the older child with recurrent vomiting.

5.1.1 The Infant with Recurrent Vomiting. In the infant with recurrent vomiting, a thorough history and physical examination (Table 4), with attention to warning signals that suggest other diagnosis (Table 5), is generally sufficient to allow the clinician to establish a diagnosis of uncomplicated GER (Figure 1). An upper GI series or other diagnostic test is not required unless gastrointestinal obstruction is suspected. Other diagnostic tests may be indicated if there are symptoms of poor weight gain, excessive crying, irritability, disturbed sleep, feeding or respiratory problems.

5.1.2 The Infant with Uncomplicated GER (Figure 1). The classical presentation of uncomplicated GER in infants is effortless, painless vomiting in a well appearing child with normal growth, often referred to as the "happy spitter'. Generally, only parental education, reassurance and anticipatory guidance are necessary for management of the infant who has uncomplicated GER. Parents are advised about potential complications, including poor weight gain, excessive crying, and feeding or respiratory problems. Some infants with cow milk allergy have symptoms that are indistinguishable from GER. Therefore, a one to two week trial of a hypoallergenic formula may be reasonable (section 4.1.1). Thickening of formula may also be considered as an option for therapy. Continuation of supine positioning is recommended. There is no evidence that pharmacological therapy affects the natural history of uncomplicated GER in infants.

Recurrent vomiting due to GER generally decreases in frequency over the first year of life and resolves by 12 months of age (8). If symptoms worsen or do not improve by 18 to 24 months of age, further evaluation is recommended, including an upper GI series and consultation with a pediatric gastroenterologist is recommended (see section 5.1.5).

5.1.3 The Infant with Recurrent Vomiting and Poor Weight Gain (Figure 2). The infant with recurrent vomiting and poor weight gain is a distinct clinical entity that is not to be confused with the happy spitter. While the history and physical examination, as well as the detection of warning signals, is identical to that described for the infant with recurrent vomiting (section 5.1.1), the finding of growth failure is a crucial factor that alters clinical management. No well-controlled studies of diagnostic or therapeutic strategies for these infants are available, and the following approach is based on expert opinion. Other causes of poor weight gain are first considered. It is recommended that the adequacy of calories being offered and ingested be assessed, by careful evaluation of the dietary history, approach to formula preparation and effectiveness of swallowing. If problems are

TABLE 3. *Differential diagnosis of vomiting in infants and children*

Gastrointestinal obstruction
pyloric stenosis
malrotation with intermittent volvulus
intermittent intussusception
intestinal duplication
Hirschsprung disease
antral/duodenal web
foreign body
incarcerated hernia
Gastrointestinal disorders
achalasia
gastroparesis
gastroenteritis
peptic ulcer disease
gastroesophageal reflux
eosinophilic esophagitis/ gastroenteritis
food allergy or intolerance
inflammatory bowel disease
pancreatitis
appendicitis
Neurologic
hydrocephalus
subdural hematoma
intracranial hemorrhage
mass lesion
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
maple syrup urine disease
Renal
obstructive uropathy
renal insufficiency
Toxic
lead
iron
Vitamin A or D
medications (ipecac, digoxin, theophylline, etc.)
Cardiac
congestive heart failure

TABLE 4. *History in the child with suspected gastroesophageal reflux disease*

Feeding history
Amount/frequency (overfeeding)
Type (preparation errors)
Changes
Position/burping
Behavior during feedings
choking, gagging, coughing, arching
discomfort, feeding refusal
Pattern of vomiting
Frequency/amount
Painful
Forceful
Hematemesis
Association with fever, lethargy, diarrhea
Past medical history
Prematurity
Growth and development (MR/CP/Dev Delay)
Surgery
Hospitalization
Newborn screen (galactosemia, maple sugar urine disease, congenital adrenal hyperplasia)
Recurrent illness (croup/stridor, pneumonia, wheeze, hoarseness, excessive fussiness/crying, hiccups)
Apnea
Inadequate weight gain
Psycho-social history
Stress
Family history
Significant Illness
GI (familial pattern to obstructive disorders, celiac)
Other (metabolic, allergy)
Growth chart
Length, weight
Head circumference
Warning signs (see Table 5)

identified, these are addressed such that adequate caloric intake is assured. Parents may need to be instructed to not limit formula intake. If problems are identified and ameliorated, close follow-up will determine if further evaluation is indicated. See section 5.4 regarding the infant who is unable or refuses to ingest formula.

TABLE 5. *Warning signals in the vomiting infant*

Bilious vomiting
GI bleeding: hematemesis, hematochezia
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, distention
Genetic disorders (eg: Trisomy 21)
Other chronic disorders (eg: HIV)

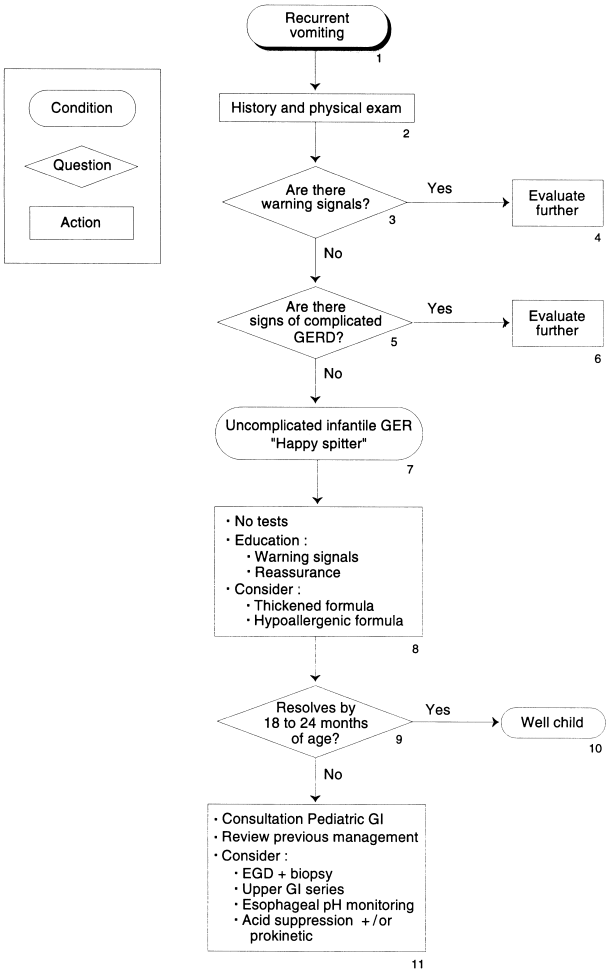

FIG. 1. An algorithm for the management of an infant with uncomplicated GER (the "happy spitter"). (Pediatric GI = pediatric gastroenterologist; EGD = esophagogastroduodenoscopy; UGI = upper gastrointestinal series radiography).

If an infant with vomiting is not gaining weight despite ingesting adequate calories then further diagnostic evaluation is necessary. Tests to uncover other causes of vomiting (such as a complete blood count, electrolytes, bicarbonate, urea nitrogen, creatinine, alanine aminotransferase, ammonia, glucose, urinalysis, urine ketones and reducing substances, and review of newborn screening for galactosemia and maple sugar urine disease) are considered. An upper GI series to evaluate anatomy is also recommended.

When no abnormalities are found, management options include medical therapy, observation in the hospital and endoscopy with biopsy. Initial medical therapeutic options include thickening of the formula, a trial of a hypoallergenic formula, acid suppression therapy, prokinetic therapy and consideration of prone positioning. Hospitalization to observe the parent-child interaction

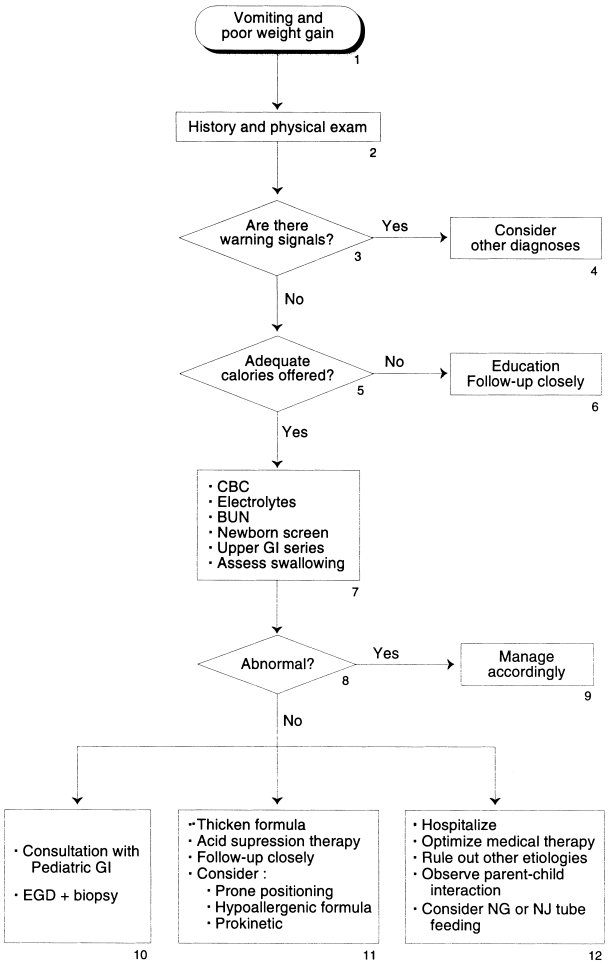

FIG. 2. An algorithm for the management of an infant with vomiting and poor weight gain. (CBC = complete blood count; BUN = blood urea nitrogen; NG = nasogastric; NJ = nasojejunal).

and to optimize medical management may be indicated in more severe cases. Endoscopy with biopsy may be useful to determine if esophagitis is present and to delineate other causes of vomiting or poor weight gain. Other options to improve caloric intake in the infant with vomiting include increasing the caloric density of the formula, and nasogastric or transpyloric tube feedings (87). Rarely surgical therapy may be indicated. Careful follow-up is necessary to assure adequate weight gain (85). If weight gain is sustained, the patient can be expected to have decreasing requirements for interventions as the amount of vomiting and regurgitation decrease with age.

5.1.4 The Infant with Recurrent Vomiting and Irritability. Vomiting, irritability and disturbed sleep in a child less than one year of age may be due to GERD. These non-specific symptoms also occur in normal infants and are associated with a wide range of conditions. Although crying is a quantifiable measure of irritability, normal infants typically fuss or cry intermittently for an average of two hours daily. Substantial individual variation occurs; some infants cry as much as six hours per day. The duration of crying typically peaks at six weeks of age (227). One parent may consider crying to be normal while another would describe the same behavior as extreme irritability. Similarly, the sleeping patterns of infants show individual and maturational variation as does the parental perceptions of normal infant sleep patterns (228).

Evidence supporting the theory that reflux causes esophageal pain and hence irritability or sleep disturbance in infancy is largely extrapolated from studies in adults (45,229,230). Very few pediatric studies address this issue. Using simultaneous video and esophageal pH monitoring, one study (46) showed an association between grimacing and reflux episodes. However, another pediatric study showed no correlation between excessive crying and esophagitis (18) and another noted no increase in irritability or back arching in infants with pathologic reflux (231). In two small studies, an association between excessive irritability and sleep disturbance in infants with abnormal pH probe studies was observed. One study found more nighttime waking, delayed onset of sleeping and greater daytime sleeping in infants with GER as compared to population norms but not when compared to a control group of infants with normal pH probe findings (232). Another study demonstrated no increase in sleep disturbances in those infants with pathologic reflux (231). One study of five infants with colic and esophagitis showed that treatment with cimetidine decreased crying from 3.7 to 1.2 hours after a week of treatment, which was significantly different from 13 children with colic who did not have esophagitis and who were not treated (233).

No studies address the best approach to evaluation of infants with vomiting and irritability or disturbed sleep. As in all infants with vomiting, other causes of vomiting need to be excluded (section 5.1.1 and Table 3). A symptom diary (234) may be useful to determine the extent to which the infant is irritable and has disturbed sleep. In addition, it is important to assure that the infant is receiving adequate feedings, since hunger may also result in irritability. Expert opinion suggests two diagnostic and treatment strategies, neither of which has been validated. The first approach is to empirically treat potential etiologies, beginning with a simultaneous or sequential two-week trial of a hypoallergenic formula and/or acid suppression (Section 5.1). If neither therapy succeeds in reducing symptoms, either esophageal pH monitoring to determine the adequacy of acid suppression (see section 3.3) or upper endoscopy with biopsy to diagnose esophagitis (see section 3.4) may be performed. If these studies are normal, and no response to empiric therapy has occurred, it is unlikely that GER is contributing to the symptoms. An alternative approach is to perform esophageal pH monitoring to determine if episodes of irritability or sleep disturbance are temporally associated with

acid reflux by calculating a symptom index (see section 3.3). One study suggested that simultaneous video monitoring was helpful (46). Time limited therapy can be initiated if episodes of GER provoke symptoms.

5.1.5 Management of the Child Over 2 Years of Age with Recurrent Regurgitation or Vomiting. No published studies describe the management of a group of otherwise normal children who have recurrent regurgitation or vomiting after the age of 2 years. These children usually vomit, or regurgitate and reswallow, between once a day and once a week. The vomiting is not associated with pain or discomfort, is not posttussive, and is non-bloody and non-bilious. Often the vomiting occurs postprandially or with exertion. This type of vomiting can be a nuisance or in some instances may disrupt a child's normal participation in childhood activities. Expert opinion suggests that in most patients an upper GI series be performed to exclude an anatomic abnormality. Some experts also recommend upper endoscopy with biopsy, although in many cases there will be no abnormalities. If vomiting persists and the child remains otherwise asymptomatic, a therapeutic trial of a prokinetic agent may be considered. If a good response to the prokinetic agent occurs, long-term therapy is an option. The small risks must be balanced with the potential improved quality of life in the individual and the family. In very unusual circumstances where the vomiting does not improve with pharmacological therapy and produces serious adverse effects on the patient's lifestyle, surgical therapy is a consideration.

5.2 Management of the Child with Heartburn or Chest Pain (Figure 3)

Heartburn or substernal burning pain may be caused by GER in the presence or absence of esophagitis (235). Other causes of chest pain include cardiac, respiratory, musculoskeletal, medication induced or infectious etiologies. In older children and adolescents the description and localization of esophageal pain is similar to adults, but in younger children symptom description and localization may be atypical. Regurgitation of sour fluid into the mouth may be present. No randomized, placebo-controlled studies evaluating the efficacy of either lifestyle or pharmacological therapy for the treatment of heartburn in children or adolescents have been published. Expert opinion suggests the use of management approaches similar to those described in adult patients. Initial interventions of lifestyle changes, avoidance of precipitating factors, accompanied by a two to four week therapeutic trial of an H_2RA or PPI are recommended (172,236–238). If no improvement occurs, the child can be referred to a pediatric gastroenterologist for upper endoscopy with biopsy. If the child improves, therapy can be administered for two to three months. If symptoms recur as therapy is discontinued, referral for upper endoscopy to determine the presence and severity of esophagitis is recommended. Because persistent symptoms of heartburn may have a substantial negative impact on a patient's quality of life, long-term therapy can be continued with either a PPI or H_2RA to provide relief from symptoms even in the absence of esophagitis (70,239). Episodic meal-induced heartburn in older children may be treated with antacids or an H_2RA, as in adults (240).

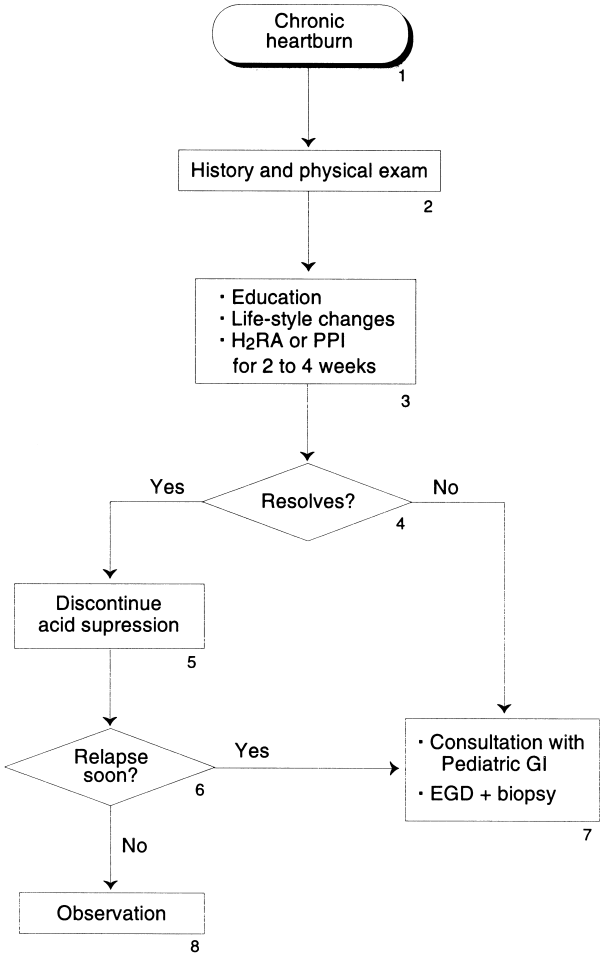

FIG. 3. An algorithm for the management of a child or adolescent with chronic heartburn. (H_2RA = histamine-$_2$ receptor antagonist; PPI = proton pump inhibitor).

5.3 The Infant or Child with Esophagitis (Figure 4)

The typical features of reflux esophagitis are described in section 3.5. Initial treatment consists of lifestyle changes and H_2RA or PPI therapy Initialtherapy. Initial treatment with a PPI results in a more rapid rate of symptom relief and healing compared to treatment with an H_2RA (152). If patients have previously been treated for GERD, medical therapy can be optimized by either the

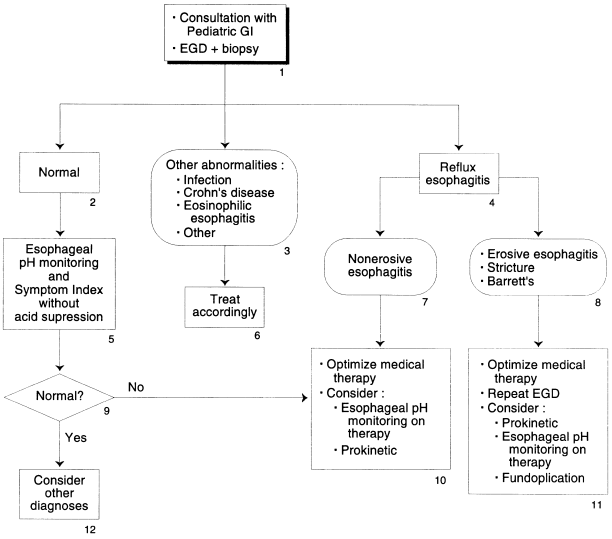

FIG. 4. An algorithm for the continued management of a child or adolescent with esophagitis.

addition of a PPI or a higher dose of PPI (47,241). In one pediatric study, cisapride alone was effective for treatment of histologic esophagitis (181). However, in adults a comparison of the efficacy of a PPI alone versus a combination of a PPI and cisapride did not show a statistically significant difference (169).

Expert opinion suggests that in infants and children with only histologic esophagitis, the efficacy of therapy can be monitored by the degree of symptom relief, whereas in patients with erosive esophagitis, repeat endoscopy is recommended to assure healing. Complete healing may prevent complications including esophageal stricture, Barrett's esophagus or esophageal adenocarcinoma, although no data are available to support this contention. High dose, long-term PPI therapy or surgical therapy may be considered when Barrett's esophagus or esophageal stricture is also present.

If patients do not respond to therapy there are two potential explanations to explore: either the diagnosis is incorrect or treatment is inadequate. The possibility of another diagnosis, such as eosinophilic esophagitis may be considered (56,57). If the clinical presentation and histopathology are consistent with a diagnosis of reflux esophagitis, then the evaluation of adherence to and adequacy of therapy is recommended. Esophageal pH monitoring while the patient is *on therapy* will determine if higher doses of acid reducing medications are needed. If the diagnosis is uncertain, esophageal pH monitoring while the patient is *off therapy* may be useful since a normal study would suggest that esophagitis is less likely to be due to GER.

When surgical therapy is considered, the potential complications of anti-reflux surgery are balanced with the nuisance, risks, effectiveness and cost of long-term pharmacological therapy. There are no studies comparing long term outcomes of medical versus surgical therapy in infants and children since the introduction of PPIs.

5.4 The Infant with Feeding Refusal or the Child with Dysphagia

Esophagitis may cause discomfort or pain (odynophagia) or difficulty (dysphagia) with eating in infants, children and adults. The older child or adult is able to describe sensations that aid in discriminating between oropharyngeal disorders and esophageal disorders. Mouth or pharyngeal pain, poor coordination of bolus formation, coughing or apnea during feeding suggests oropharyngeal anatomical or functional problems. Complaints of chest pain or food being stuck in the chest generally indicate that there is an esophageal disorder, although the sensory discrimination of the site of obstruction is often inaccurate. Reflux esophagitis appears to be one of the more common causes of these symptoms in children, being diagnosed in 12 of 16 children reported in one retrospective series (242).

In the older child or adolescent with symptoms suggestive of an esophageal cause of dysphagia or odynophagia, diagnostic evaluation usually begins with a radiographic contrast study (barium esophagram) to identify anatomic abnormalities, such as strictures or vascular rings, and motility disorders, such as achalasia. Upper endoscopy with biopsy is also usually performed. If esophagitis is present, treatment of the underlying cause of esophagitis (e.g., reflux esophagitis, pill esophagitis or eosinophilic esophagitis) generally leads to symptom resolution. There are no studies evaluating this proposed diagnostic approach in older children or adolescents; however, in a study of young adults (243), the barium esophagram revealed a cause of symptoms in 70% of patients. If the initial history is suggestive of esophagitis, upper endoscopy may be performed as the initial diagnostic test. Treatment without prior diagnostic evaluation is generally not recommended.

In infants, although case series have described an association of feeding difficulties with signs and symptoms of GER (244–246), none has demonstrated that GER is causally related to the feeding difficulties or that feeding improves following treatment. Because a large variety of disorders may contribute to infant feeding difficulties (247), empiric therapy for GER is generally not recommended in children with feeding difficulties. However, if there are other signs or symptoms suggestive of GERD (section 5.1.1) then a time-limited course of medical therapy can be considered.

5.5 The Infant with Apnea or ALTE

An apparent life-threatening event (ALTE) is defined as an episode occurring in an infant that is frightening to

the observer and characterized by a combination of apnea, change in color (cyanosis, pallor, rubor, plethora), change in muscle tone (limpness, stiffness), or choking and gagging that requires intervention by the caretaker (248). The first event usually occurs between one and two months, and rarely after 8 months of age (249,250). There is evidence that ALTEs can recur (250–252), and that infants with an ALTE are at risk for a subsequent sudden death (252–258). ALTEs can be caused by intentional suffocation, cardiac, central nervous system and infectious disorders, and can be due to upper airway obstruction or central apnea as well as GER.

In patients with ALTEs the prevalence of recurrent regurgitation or emesis is 60% to 70% (249,252), and 40% to 80% of patients have abnormal esophageal pH monitoring (259–261). Case reports have described ALTEs triggered by overt regurgitation into the oropharynx or by aspiration of refluxed gastric contents (262–264). Gross emesis or oral regurgitation has been correlated with either prolonged apnea (>20 seconds), or with shorter apnea and bradycardia, but the majority of prolonged apnea episodes in these patients were not associated with regurgitation (265). The first report of simultaneous recordings of esophageal pH, heart rate, chest wall movement and nasal airflow demonstrated that reflux could precede apnea (262). In selected patients with a history of ALTE, esophageal acid infusion has been shown to induce obstructive apnea (262) or oxygen desaturation (259), suggesting that one mechanism by which GER may trigger an ALTE is acid stimulation of laryngeal, pharyngeal, or esophageal chemoreceptors with resultant laryngospasm.

Despite these early reports and the demonstrated potential for GER to cause apnea, subsequent investigations in unselected patients with ALTE have not demonstrated a convincing temporal relationship between esophageal acidification and apnea or bradycadia (260, 261, 266-272). Although several studies reported an occasional correlation of GER with short mixed central apneas (5 to 15 sec) (266,269,271), all of the patients reported also had episodes of apnea which were unrelated to episodes of GER, suggesting a primary impairment in the regulation of respiration. The most convincing relationship between GER and episodes of obstructive or mixed apnea has been in infants in whom the episodes occurred while the patient was awake, supine and within one hour of a feeding. One study performed simultaneous recording of esophageal pH, heart rate, chest wall movement and nasal airflow to demonstrate a relationship between GER and obstructive or mixed apnea in 8 of 15 such patients (273).

At present there is no evidence that the characteristics of an ALTE or polysomnographic diagnostic study can predict which infants are at risk for future life-threatening episodes or sudden death. In one study of 182 infants with ALTE followed for two months, the coexistence of GER and ALTE did not predict the risk for a subsequent episode of prolonged apnea or bradycardia. SIDS has rarely been reported to occur in patients with a previous ALTE and documented GER (261,274); in none of these patients was a previous correlation between esophageal acidification and a cardiopulmonary event recorded.

Similarly there are no randomized studies to evaluate the usefulness of esophageal pH monitoring in infants with ALTE. In patients with frequent ALTE in which the role of GER is uncertain, esophageal pH monitoring may be useful to determine if there is a temporal association of acid reflux with ALTE. For adequate interpretation of esophageal pH monitoring in this situation, simultaneous recording of heart rate, chest wall impedance, nasal airflow and oxygen saturation is necessary to detect obstructive apnea.

The evidence suggests that infants with ALTE and GER may be more likely to respond to anti-reflux therapy when there is gross emesis or oral regurgitation at the time of the ALTE, when episodes occur in the awake infant, and when the ALTE is characterized by obstructive apnea. The effectiveness of medical therapy of GER-associated ALTEs has not been adequately studied. To reduce overt emesis and inhibit acid reflux, therapeutic options include thickened feedings and prokinetic and acid suppressant therapy. Surgical therapy has been reported to be effective in preventing recurrent ALTE and death in heterogeneous groups of patients (263,274), but there are no studies comparing surgery to medical management. Since most infants improve with medical management, surgery is considered only in severe cases. Caution should be exercised when diagnosing and treating GER as a presumptive cause of ALTE. Antireflux surgery has been performed for GER in infants with ALTE that was subsequently determined to be due to repetitive intentional suffocation (275).

5.6 The Infant or Child with Asthma (Figure 5)

Asthma affects an estimated 4.8 million children (276), 5% of whom have persistent asthma, defined as a frequency greater than 2 or 3 times weekly. Although a direct causal relationship between GER and asthma is rare, a number of animal and human studies have suggested that GER may contribute to asthma severity. Proposed pathogenetic mechanisms include direct aggravation of airway inflammation by aspiration of gastric contents, or airway hyperresponsiveness triggered by aspiration of minute amounts of acid into the lower airway (277–279). Esophageal acidification as an independent variable has minimal effect on pulmonary function (277). However, esophageal acid exposure in asthmatic patients may contribute to airway hyperresponsiveness and variable airflow obstruction (280).

Symptoms of GER are common in children with asthma (281). A high percentage of children with persis-

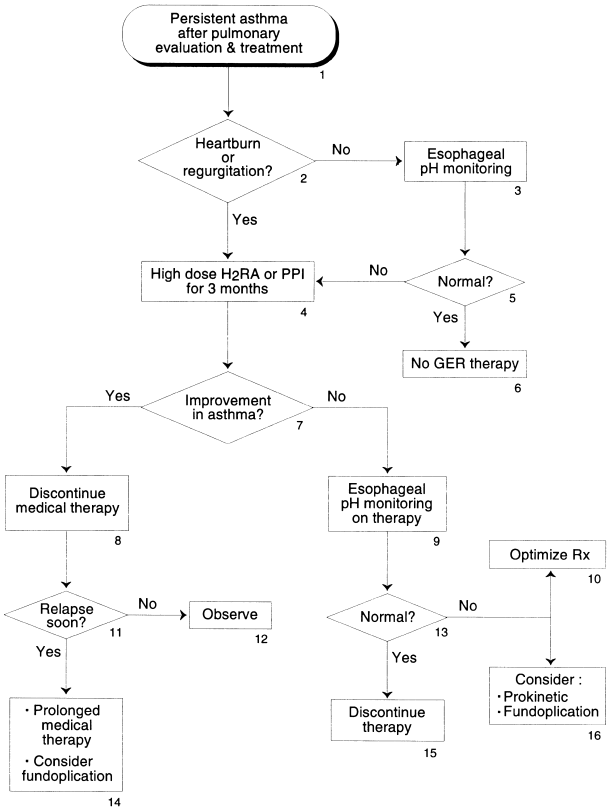

FIG. 5. An algorithm for the management of a child or adolescent with persistent asthma and suspected GER. See also Figure 3. (Rx = therapy).

tent asthma have gastroesophageal reflux detectable by abnormal esophageal pH monitoring. The reported prevalence ranges from 25% to 75%. Of 668 patients studied in 13 series, 407 or 61% were reported to have abnormal pH studies utilizing a variety of scoring techniques (48–50,65,282–290). There was a similar prevalence of GER (53%) in three studies of infants less than 2 years of age (49,282,283). Approximately 50% of patients with persistent asthma and abnormal esophageal pH monitoring have no or minimal clinical symptoms of GER, such as vomiting, regurgitation, or heartburn (48, 50,282,284,288). There is no consistent evidence that specific asthma symptoms or response to asthma therapy correlates with abnormal esophageal pH monitoring.

A number of cohort comparisons have been performed in patients with GER symptoms or positive esophageal pH probe monitoring. These studies demonstrate that prolonged medical treatment of GER improves clinical symptoms of persistent asthma and reduces required doses of bronchodilator and anti-inflammatory medications. From four case series reporting on a total of 168 patients, 63% had clinical improvement or reduced dosages of bronchodilator and anti-inflammatory medications following a variety of medical approaches (50,284, 288,291). Improvement of respiratory variables has been described in infants less than one year of age (291) and older children with or without atopy (50). Reported successful therapies have included positional therapy and thickened formula without medication (284,288), cisapride (50), and H_2RA (292). There are no studies of combined prokinetic and antisecretory therapy to treat GER in patients with asthma. Adult studies suggest that duration of therapy is very important, and aggressive acid suppression for at least 3 months may be necessary to reduce respiratory symptoms (68) (293,294). No studies address the empiric treatment of asthma in patients without GER symptoms or with normal esophageal pH monitoring.

More striking results have been reported following antireflux surgery. Eighty-five percent of 258 patients reported in 6 case series improved clinically as assessed by decreased frequency and severity of asthmatic attacks and reduced dosages of bronchodilator and anti-inflammatory medications (213,284,288,291,295,296). Although details were often not provided, it appears that all the patients had severe persistent asthma requiring frequent oral steroids or high dose inhaled steroid prior to surgery. The diagnosis of GER was most often confirmed by esophageal pH monitoring. Indications for antireflux surgery included evidence of recurrent pneumonia, failed time-limited medical antireflux management, dependence on aggressive medical management, and non-respiratory complications (persistent vomiting, vomiting with growth retardation, severe esophagitis). Subjective improvement in asthma after fundoplication was correlated with a clear history of reflux symptoms preceding the onset of asthma symptoms, a positive response to medical therapy prior to surgery, a history of recurrent pneumonia, and nocturnal attacks of asthma. Failure of medical antireflux management did not preclude a favorable response to surgical antireflux management. Adult surgical series have shown similar improvements in symptoms and reductions of medication use following surgery but without dramatic improvement in pulmonary function tests (297).

Thus there is substantial published evidence that GER is a potential contributor to symptoms of persistent asthma. The true incidence of GER in children with asthma is not known, as the reported data is from selected referred groups of patients with persistent asthma. The available evidence does not support therapy of GER in all patients with persistent asthma who fail to respond to standard asthma therapy. However, a trial of vigorous, prolonged medical therapy of GER is recommended for children when symptoms of asthma and GERD (e.g., heartburn, regurgitation) co-exist, and in infants and toddlers with chronic vomiting or regurgitation and recurrent episodes of cough and wheezing.

If a patient with persistent asthma does not have symptoms of GER, esophageal pH monitoring is recommended in selected patients who are more likely to benefit from GER therapy. This includes patients with ra-

diographic evidence of recurrent pneumonia; patients with nocturnal asthma more than once a week; and patients requiring either continuous oral corticosteroids, high-dose inhaled corticosteroids, more than two bursts per year of oral corticosteroids or those with persistent asthma unable to wean medical management. If esophageal pH monitoring demonstrates an increased frequency or duration of esophageal acid exposure, a trial of prolonged medical therapy for GER is recommended.

Currently there is insufficient pediatric evidence to establish the optimal medical therapy for GER in patients with asthma. It is recommended that a three month trial of vigorous antisecretory therapy and possibly cisapride be considered. It is recommended that outcome variables be determined prior to initiating therapy and be monitored during therapy. Outcome variables include heartburn and regurgitation; frequency of asthma symptoms (coughing, dyspnea, wheezing, and chest tightness); frequency and severity of acute exacerbations; frequency of nocturnal symptoms and breathlessness; symptom scores; quick-relief beta2-agonist use; changes in spirometry measurements (FEV1, FVC, FEV1/FVC) in older children; and subjective measures of quality of life. Antireflux surgery is considered in patients with persistent asthma and recurrent pneumonia, patients requiring prolonged medical therapy and patients with nonrespiratory complications of GER such as persistent vomiting, vomiting with growth retardation and severe esophagitis.

5.7 Recurrent Pneumonia and GER

GER-related aspiration pneumonia may arise in the absence of esophagitis. The incidence of GER and recurrent pneumonia in otherwise normal infants and children (288,290) (298) is difficult to establish due to the heterogeneity of the patients in reported studies, which include a large number of children with neurological disabilities and anatomic disorders of the upper intestinal tract. Several reports show that pediatric patients with recurrent pneumonia and GER improve after receiving medical or surgical GER therapy (296,299). In addition, many patients with idiopathic pulmonary fibrosis have GER (300), suggesting that repeated small episodes of aspiration of gastric contents can eventually cause severe compromise of pulmonary function. These clinical reports as well as clinical experience indicate that GER can cause recurrent pneumonia and chronic pulmonary fibrosis.

Before considering GER as a potential cause of recurrent pneumonia, it is important to exclude other causes, such as an anatomic abnormality, aspiration during swallowing, foreign body, cystic fibrosis or immunodeficiency (301). Determining whether GER is causing recurrent pneumonia in an individual patient is difficult but certain patient populations are prone to aspiration. The presence of neuromuscular disease (302) or a history of esophageal or laryngeal anatomic abnormalities increases the risk of aspiration during swallowing and following episodes of GER. The incidence of GER-related recurrent aspiration in otherwise normal infants and children is unknown but it appears to be rare.

Normal esophageal pH monitoring does not exclude GER as a cause of aspiration pneumonia. The addition of an upper esophageal or pharyngeal pH recording does not improve the ability of pH monitoring to determine which patients are at risk for aspiration as a complication of GER (43). Presumably, patients with even rare episodes of reflux of gastric contents into the pharynx are at risk for aspiration if airway protective reflexes are abnormal. A variety of tests may be useful to evaluate these protective mechanisms.

Flexible bronchoscopy with pulmonary lavage for lipid laden alveolar macrophages has been utilized to detect aspiration (303,304). However, lipid-laden macrophages may be present in normal individuals so their presence in pulmonary lavage lacks sensitivity and specificity for determining if the cause of pulmonary disease is aspiration. Recent efforts to improve the sensitivity and specificity utilize careful protocols that score the lipid content of over 100 macrophages, but considerable overlap exists between normal controls, patients with other causes of pulmonary disease and those with a history consistent with aspiration (305–308). If bronchoscopy with pulmonary lavage demonstrates a large percentage of lipid-laden macrophages, aspiration is more likely, but this test does not discriminate between aspiration that occurs during swallowing and that following GER. The lack of specificity of the test requires that the results be interpreted in the context of other clinical findings.

Nuclear scintigraphy can detect episodes of aspiration when follow-up images are obtained up to 24 hours after the feeding is administered. A positive test demonstrates that aspiration occurred but a negative test does not exclude the possibility that GER with aspiration occurs infrequently (section 3.5). Despite the potential utility of scintigraphy, no data are available regarding its predictive value in management of children or adults with suspected aspiration pneumonia.

Evaluation of airway protection mechanisms during feeding may also be helpful since patients who aspirate during feedings are also likely to aspirate refluxate. One study in neurologically disabled children showed that recurrent pneumonia was more likely in those with an abnormal swallowing study (309). Thus, a videofluoroscopic swallowing study (VSS) or fiberendoscopic swallowing evaluation (FEEST), particularly with neurosensory testing, may help identify at risk patients (310–313).

Often the clinician must make management decisions based on inconclusive information. If the patient has severely impaired lung function, it may be necessary to proceed with antireflux surgery in an attempt to prevent

further pulmonary damage, despite a lack of definitive proof that GER is causing pulmonary disease in the individual patient. The potential benefits of surgery are balanced with the recognition of potential complications (section 4.3). Alternatively, if minimal pulmonary disease is present, consideration of medical therapy with careful follow-up of pulmonary function can be considered. No controlled studies demonstrate the benefits of any medical therapy in preventing progression of chronic pulmonary disease caused by GER in children, but lifestyle and pharmacological agents are options.

5.8 The Infant or Child with Upper Airway Symptoms or Signs

Airway symptoms of hoarseness (314), chronic cough (315,316) and globus sensation (the sensation of a lump in the throat) (317,318) have been associated with GER in adult patients. Characteristic reflux-induced findings of airway erythema, edema, nodularity, ulceration, granuloma and cobblestoning have been described (319,320). The sensitivity and specificity of descriptive laryngoscopic findings for the identification of GER-induced disease are unknown in both pediatric and adult patients. These symptoms or signs usually occur in the absence of classical symptoms of GER such as heartburn or chest pain. In adult GER patients, increased acid exposure in the proximal esophagus (321) and pharynx (322) has been observed in those with airway symptoms of cough or frequent throat clearing. Gastropharyngeal reflux was more prevalent in a small study of children with recurrent laryngotracheitis compared to control patients (323). An increased frequency of episodes of awake GER in children with hoarseness has been suggested in one pediatric case series (324). One case report documents a temporal association of GER episodes and cough in an infant (325). Another case series suggests that GER may contribute to either the pathogenesis of subglottic stenosis or may compromise surgical results (326), while another notes increased pharyngeal reflux in children with laryngomalacia (44).

Several uncontrolled treatment studies in adults have demonstrated improvements in laryngeal symptoms and findings following aggressive medical therapy for GER, with recurrence of symptoms when treatment was discontinued (68,69,320,327,328). Improvement in symptoms of hoarseness after GER therapy was reported in one child (329). Another uncontrolled case series describes improvement in a variety of upper airway symptoms in pediatric patients following treatment of GER with a variety of therapies (330). One study demonstrates a marked reduction in cough symptoms in adults with GER following laparoscopic fundoplication (331). There are no randomized placebo controlled treatment trials evaluating the efficacy of GER therapy of laryngeal symptoms in adults or children. Adult data suggest that if a therapeutic trial is considered, it must be prolonged (longer than three months) to adequately assess efficacy (68). If there is clinical improvement, followed by a recurrence off therapy, it is reasonable to suspect a role for GER in the pathogenesis of symptoms in an individual patient.

In summary, several studies describe the presence of GER in children with either chronic or recurrent laryngeal symptoms. The evaluation of suspected GER-associated laryngeal symptoms is complicated by a lack of a uniform interpretation of laryngeal findings. Nonetheless laryngoscopy is generally indicated to rule out potential anatomic abnormalities of airway protection such as a laryngeal cleft. At this time, there is insufficient evidence and experience in children to provide recommendations for a uniform approach to diagnosis and treatment.

5.9 Other Disorders Potentially Associated with GER

Multiple case reports suggest an association between GER and a variety of other disorders. One study suggested that adolescents with GER had an increased incidence of erosion of enamel on the lingual surfaces of their teeth (332). However, another study showed no increased incidence of dental erosions in adolescents with abnormal esophageal pH monitoring (333).

GER has been suggested as a potential contributing factor in recurrent sinus disease, pharyngitis and otitis media. One uncontrolled case series of children with chronic sinusitis suggested that treatment of GER dramatically reduced the need for sinus surgery in children (334). Another demonstrated that in children with recurrent rhinopharyngitis, there was an increased number of episodes with the pharyngeal pH falling to below 6 in affected patients compared to controls (335). However, the occurrences of ear and sinus infections were similar in infants with or without GER (8). No data demonstrate an association of otitis media and GER. However, otalgia has been associated with GER in children and was reported to improve with treatment of GER (336).

Authors

Colin D. Rudolph, MD, PhD
Cincinnati, OH

Lynnette J. Mazur, MD
Houston, TX

Gregory S. Liptak, MD
Rochester, NY

Robert D. Baker, MD, PhD
Buffalo, NY

John T. Boyle, MD
Greenville, SC

Richard B. Colletti, MD
Burlington, VT

William T. Gerson, MD
Burlington, VT

Steven L. Werlin, MD
Milwaukee, WI

REFERENCES

1. Vandenplas Y, Sacre-Smits L. Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0-15 months old. *J Pediatr Gastroenterol Nutr* 1987;6:220–4.
2. Vandenplas Y, Goyvaerts H, Helven R, et al. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. *Pediatrics* 1991;88:834–40.
3. Gustafsson PM, Tibbling L. 24-hour oesophageal two-level pH monitoring in healthy children and adolescents. *Scand J Gastroenterol* 1988;23:91–4.
4. Nelson SP, Chen EH, Syniar GM, et al. Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med* 2000;154:150–4.
5. Werlin SL, Dodds WJ, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in children. *J Pediatr* 1980;97:244–9.
6. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children [see comments]. *Gastroenterology* 1997;113:399–408.
7. Nelson SP, Chen EH, Syniar GM, et al. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med* 1997;151:569–72.
8. Nelson SP, Chen EH, Syniar GM, et al. One-year follow-up of symptoms of gastroesophageal reflux during infancy. Pediatric Practice Research Group. *Pediatrics* 1998;102:E67.
9. Werlin SL, D'Souza BJ, Hogan WJ, et al. Sandifer syndrome: an unappreciated clinical entity. *Dev Med Child Neurol* 1980;22: 374–8.
10. Gorrotxategi P, Reguilon MJ, Arana J, et al. Gastroesophageal reflux in association with the Sandifer syndrome. *Eur J Pediatr Surg* 1995;5:203–5.
11. Herbst JJ, Johnson DG, Oliveros MA. Gastroesophageal reflux with protein-losing enteropathy and finger clubbing. *Am J Dis Child* 1976;130:1256–8.
12. Hassall E. Barrett's esophagus: new definitions and approaches in children. *J Pediatr Gastroenterol Nutr* 1993;16:345–64.
13. Sackett DL, Richardson WS, Rosenberg W, et al. Evidence-based Medicine: How to Practice and Teach EBM. 1998, Edinburgh: Churchill Livingston.
14. Sackett DL, Haynes B, Tugwell P. Clinical Epidemiology: A Basic Science for Clinical Medicine. 2nd ed. 1991, Boston: Little Brown.
15. McMurray AR. Three decision-making aids: brainstorming, nominal group, and Delphi technique. J Nurs Staff Dev 1994;10: 62–5.
16. Examination CTFotPH, The periodic health examination. *Can Med Assoc J* 1979;121:119.
17. Hyams JS, Ricci A, Jr, Leichtner AM. Clinical and laboratory correlates of esophagitis in young children. *J Pediatr Gastroenterol Nutr* 1988;7:52–6.
18. Chadwick LM, Kurinczuk JJ, Hallam LA, et al. Clinical and endoscopic predictors of histological oesophagitis in infants. *J Paediatr Child Health* 1997;33:388–93.
19. Seibert JJ, Byrne WJ, Euler AR, et al. Gastroesophageal reflux–the acid test: scintigraphy or the pH probe? *AJR Am J Roentgenol* 1983;140:1087–90.
20. Stephen TC, Younoszai MK, Massey MP, et al. Diagnosis of gastroesophageal reflux in pediatrics. *J Ky Med Assoc* 1994; 92: 188–91.
21. Meyers WF, Roberts CC, Johnson DG, et al. Value of tests for evaluation of gastroesophageal reflux in children. *J Pediatr Surg* 1985;20:515–20.
22. Thompson JK, Koehler RE, Richter JE. Detection of gastroesophageal reflux: value of barium studies compared with 24-hr pH monitoring [see comments]. *AJR Am J Roentgenol* 1994;162: 621–6.
23. Gupta JP, Kumar A, Jain AK, et al. Gastro-esophageal reflux disease (GERD): an appraisal of different tests for diagnosis. *J Assoc Physicians India* 1990;38 Suppl 1:699–702.
24. Chen MY, Ott DJ, Sinclair JW, Wu WC, et al. Gastroesophageal reflux disease: correlation of esophageal pH testing and radiographic findings. *Radiology* 1992;185:483–6.
25. Colletti RB, Christie DL, Orenstein SR. Statement of the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN). Indications for pediatric esophageal pH monitoring. *J Pediatr Gastroenterol Nutr* 1995;21:253–62.
26. Newman LJ, Berezin S, San Filippo JA, et al. A new ambulatory system for extended esophageal pH monitoring. *J Pediatr Gastroenterol Nutr* 1985;4:707–10.
27. A standardized protocol for the methodology of esophageal pH monitoring and interpretation of the data for the diagnosis of gastroesophageal reflux. Working Group of the European Society of Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 1992;14:467–71.
28. Tappin DM, King C, Paton JY. Lower oesophageal pH monitoring–a useful clinical tool. *Arch Dis Chil* 1992;67:146–8.
29. Euler AR , Byrne WJ. Twenty-four-hour esophageal intraluminal pH probe testing: a comparative analysis. *Gastroenterology* 198;80:957–61.
30. Mahajan L, Wyllie R, Oliva L, et al. Reproducibility of 24-hour intraesophageal pH monitoring in pediatric patients. *Pediatrics* 1998;101:260–3.
31. Hampton FJ, MacFadyen UM, Simpson H. Reproducibility of 24 hour oesophageal pH studies in infants. *Arch Dis Child* 1990;65: 1249–54.
32. Vandenplas Y, Helven R, Goyvaerts H, et al. Reproducibility of continuous 24 hour oesophageal pH monitoring in infants and children [see comments]. *Gut* 1990;31:374–7.
33. Friesen CA, Hodge C, Roberts CC. Accuracy and reproducibility of 12-h esophageal pH monitoring. *J Pediatr Gastroenterol Nutr* 1991;12:166–8.
34. Barabino A, Costantini M, Ciccone MO, et al. Reliability of short-term esophageal pH monitoring versus 24-hour study [see comments]. *J Pediatr Gastroenterol Nut,* 1995;21:87–90.
35. Sondheimer JM. Continuous monitoring of distal esophageal pH: a diagnostic test for gastroesophageal reflux in infants. *J Pediatr* 1980;96:804–7.
36. Boix-Ochoa J, Lafuenta JM, Gil-Vernet JM. Twenty-four hour exophageal pH monitoring in gastroesophageal reflux. *J Pediatr Surg* 1980;15:74–8.
37. Jamieson JR, Stein HJ, DeMeester TR, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility [see comments]. *Am J Gastroenterol* 1992;87:1102–11.
38. Quigley EM. 24-h pH monitoring for gastroesophageal reflux disease: already standard but not yet gold? [editorial]. *Am J Gastroenterol* 1992;87:1071–5.
39. Vandenplas Y, Franckx-Goossens A, Pipeleers-Marichal M, et al. Area under pH 4: advantages of a new parameter in the interpre-

tation of esophageal pH monitoring data in infants. *J Pediatr Gastroenterol Nutr* 1989;9:34–9.
40. Black DD, Haggitt RC, Orenstein SR, et al. Esophagitis in infants. Morphometric histological diagnosis and correlation with measures of gastroesophageal reflux. *Gastroenterology* 1990; 98: 1408–14.
41. Cucchiara S, Staiano A, Gobio Casali L, et al. Value of the 24 hour intraoesophageal pH monitoring in children. *Gut* 1990;31: 129–33.
42. Biller JA, Winter HS, Grand RJ, et al. Are endoscopic changes predictive of histologic esophagitis in children? *J Pediatr* 1983; 103:215–8.
43. Cucchiara S, Santamaria F, Minella R, et al. Simultaneous prolonged recordings of proximal and distal intraesophageal pH in children with gastroesophageal reflux disease and respiratory symptoms. *Am J Gastroenterol* 1995;90:1791–6.
44. Matthews BL, Little JP, McGuirt WJ, et al. Reflux in infants with laryngomalacia: results of 24-hour double-probe pH monitoring. *Otolaryngol Head Neck Surg* 1999;120:860–4.
45. Katzka DA, Paoletti V, Leite L, et al. Prolonged ambulatory pH monitoring in patients with persistent gastroesophageal reflux disease symptoms: testing while on therapy identifies the need for more aggressive anti-reflux therapy [see comments]. *Am J Gastroenterol* 1996;91:2110–3.
46. Feranchak AP, Orenstein SR, Cohn JF. Behaviors associated with onset of gastroesophageal reflux episodes in infants. Prospective study using split-screen video and pH probe. *Clin Pediatr (Phila)* 1994;33:654–62.
47. Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children [see comments]. *J Pediatr* 1993;123:148–54.
48. Buts JP, Barudi C, Moulin D, Claus D, et al. Prevalence and treatment of silent gastro-oesophageal reflux in children with recurrent respiratory disorders. *Eur J Pediatr* 1986;145:396–400.
49. Malfroot A, Vandenplas Y, Verlinden M, et al. Gastroesophageal reflux and unexplained chronic respiratory disease in infants and children. *Pediatr Pulmonol* 1987;3:208–13.
50. Tucci F, Resti M, Fontana R, et al. Gastroesophageal reflux and bronchial asthma: prevalence and effect of cisapride therapy [see comments]. *J Pediatr Gastroenterol Nutr* 1993;17:265–70.
51. Leape LL, Ramenofsky ML. Surgical treatment of gastroesophageal reflux in children. Results of Nissen's fundoplication in 100 children. *Am J Dis Child* 1980;134:935–8.
52. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172–80.
53. Gupta SK, Fitzgerald JF, Chong SK, et al. Vertical lines in distal esophageal mucosa (VLEM): a true endoscopic manifestation of esophagitis in children? *Gastrointest Endosc* 1997;45:485–9.
54. Shub MD, Ulshen MH, Hargrove CB, et al. Esophagitis: a frequent consequence of gastroesophageal reflux in infancy. *J Pediatr* 1985;107:881–4.
55. Winter HS, Madara JL, Stafford RJ, et al. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. *Gastroenterology* 1982.83:818–23.
56. Liacouras CA, Wenner WJ, Brown K, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids [see comments]. *J Pediatr Gastroenterol Nutr* 1998;26: 380–5.
57. Ruchelli E, Wenner W, Voytek T, et al. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. *Pediatr Dev Pathol* 1999;2:15–8.
58. Di Lorenzo C, Piepsz A, Ham H, et al. Gastric emptying with gastro-oesophageal reflux. *Arch Dis Child* 1987;62:449–53.
59. Papaila JG, Wilmot D, Grosfeld JL, et al. Increased incidence of delayed gastric emptying in children with gastroesophageal reflux. A prospective evaluation. *Arch Surg* 1989;124:933–6.
60. Hillemeier AC, Lange R, McCallum R, et al. Delayed gastric emptying in infants with gastroesophageal reflux. *J Pediatr* 1981; 98:190–3.
61. McVeagh P, Howman-Giles R, Kemp A. Pulmonary aspiration studied by radionuclide milk scanning and barium swallow roentgenography. *Am J Dis Child* 1987;141:917–21.
62. Fawcett HD, Hayden CK, Adams JC, et al. How useful is gastroesophageal reflux scintigraphy in suspected childhood aspiration? *Pediatr Radiol* 1988;18:311–3.
63. Arasu TS, Wyllie R, Fitzgerald JF, et al. Gastroesophageal reflux in infants and children comparative accuracy of diagnostic methods. *J Pediatr* 1980;96:798–803.
64. Tolia V, Kauffman RE. Comparison of evaluation of gastroesophageal reflux in infants using different feedings during intraesophageal pH monitoring. *J Pediatr Gastroenterol Nutr* 1990; 10:426–9.
65. Balson BM, Kravitz EK, McGeady SJ. Diagnosis and treatment of gastroesophageal reflux in children and adolescents with severe asthma. *Ann Allergy Asthma Immunol* 1998;81:159–64.
66. Orenstein SR, Klein HA, Rosenthal MS. Scintigraphy versus pH probe for quantification of pediatric gastroesophageal reflux: a study using concurrent multiplexed data and acid feedings. *J Nucl Med* 1993;34:1228–34.
67. van Pinxteren B, Numans ME, Bonis PA, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* 2000;2.
68. Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough [see comments]. *Am J Gastroenterol* 1999;94:3131–8.
69. Wo JM, Grist WJ, Gussack G, et al. Empiric trial of high-dose omeprazole in patients with posterior laryngitis: a prospective study [see comments]. *Am J Gastroenterol* 1997;92:2160–5.
70. Havelund T, Lind T, Wiklund I, et al. Quality of life in patients with heartburn but without esophagitis: effects of treatment with omeprazole [see comments]. *Am J Gastroenterol* 1999;94: 1782–9.
71. Lind T, Havelund T, Lundell L, et al. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis–a placebo-controlled randomized trial. *Ailment Pharmacol Ther* 1999;13:907–14.
72. Fass R, Fennerty MB, Ofman JJ, et al. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain [see comments . *Gastroenterology* 1998;115:42–9.
73. Johnsson F, Weywadt L, Solhaug JH, et al. One-week omeprazole treatment in the diagnosis of gastro-oesophageal reflux disease. *Scand J Gastroenterol* 1998;33:15–20.
74. Oliveria SA, Christos PJ, Talley NJ, et al. Heartburn risk factors, knowledge, and prevention strategies: a population-based survey of individuals with heartburn. *Arch Intern Med* 1999;159:1592–8.
75. Forget P, Arends JW. Cow's milk protein allergy and gastro-oesophageal reflux. *Eur J Pediatr* 1985;144:298–300.
76. Iacono G, Carroccio A, Cavataio F, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. *J Allergy Clin Immunol* 1996;97:822–7.
77. Hill DJ, Cameron DJ, Francis DE, et al. Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance. *J Allergy Clin Immunol* 1995;96:386–94.
78. Cavataio F, Iacono G, Montalto G, et al. Gastroesophageal reflux associated with cow's milk allergy in infants: which diagnostic examinations are useful? *Am J Gastroenterol* 1996;91:1215–20.
79. Cavataio F, Iacono G, Montalto G, et al. Clinical and pH-metric characteristics of gastro-oesophageal reflux secondary to cows' milk protein allergy [see comments]. *Arch Dis Child* 1996;75: 51–6.
80. Heacock HJ, Jeffery HE, Baker JL, et al. Influence of breast versus formula milk on physiological gastroesophageal reflux in

healthy, newborn infants. *J Pediatr Gastroenterol Nutr* 1992;14: 41–6.
81. Vandenplas Y, Sacre L. Milk-thickening agents as a treatment for gastroesophageal reflux [published erratum appears in *Clin Pediatr (Phila)* 1987 Mar;26(3):148]. *Clin Pediatr (Phila)* 1987;26: 66–8.
82. Bailey DJ, Andres JM, Danek GD, et al. Lack of efficacy of thickened feeding as treatment for gastroesophageal reflux. *J Pediatr* 1987;110:187–9.
83. Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. *J Pediatr* 1987;110: 181–6.
84. Orenstein SR, Shalaby TM, Putnam PE. Thickened feedings as a cause of increased coughing when used as therapy for gastroesophageal reflux in infants. *J Pediatr* 1992;121:913–5.
85. Vandenplas Y, Hachimi-Idrissi S, Casteels A, et al. A clinical trial with an "anti-regurgitation" formula. *Eur J Pediatr* 1994;153: 419–23.
86. Borrelli O, Salvia G, Campanozzi A, et al. Use of a new thickened formula for treatment of symptomatic gastrooesophageal reflux in infants. *Ital J Gastroenterol Hepatol* 1997;29:237–42.
87. Ferry GD, Selby M, Pietro TJ. Clinical response to short-term nasogastric feeding in infants with gastroesophageal reflux and growth failure. *J Pediatr Gastroenterol Nutr* 1983;2:57–61.
88. Meyers WF, Herbst JJ. Effectiveness of positioning therapy for gastroesophageal reflux. *Pediatrics* 1982;69:768–72.
89. Vandenplas Y, Sacre-Smits L. Seventeen-hour continuous esophageal pH monitoring in the newborn: evaluation of the influence of position in asymptomatic and symptomatic babies. *J Pediatr Gastroenterol Nutr* 1985;4:356–61.
90. Tobin JM, McCloud P, Cameron DJ. Posture and gastro-oesophageal reflux: a case for left lateral positioning. *Arch Dis Child* 1997;76:254–8.
91. Orenstein SR. Prone positioning in infant gastroesophageal reflux: is elevation of the head worth the trouble? *J Pediatr* 1990; 117:184–7.
92. Orenstein SR, Whitington PF, Orenstein DM. The infant seat as treatment for gastroesophageal reflux. *N Engl J Med* 1983;309: 760–3.
93. Katz LC, Just R, Castell DO. Body position affects recumbent postprandial reflux. J Clin Gastroenterol 1994;18:280–3.
94. Khoury RM, Camacho-Lobato L, Katz PO, et al. Influence of spontaneous sleep positions on nighttime recumbent reflux in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 1999;94:2069–73.
95. Oyen N, Markestad T, Skaerven R, et al. Combined effects of sleeping position and prenatal risk factors in sudden infant death syndrome: the Nordic Epidemiological SIDS Study. *Pediatrics* 1997;100:613–21.
96. Skadberg BT, Morild I, and Markestad T. Abandoning prone sleeping: effect on the risk of sudden infant death syndrome [see comments]. *J Pediatr* 1998;132:340–3.
97. Adams EJ, Chavez GF, Steen D, et al. Changes in the epidemiologic profile of sudden infant death syndrome as rates decline among California infants:1990–1995. *Pediatrics* 1998;102:1445–51.
98. Jeffery HE, Megevand A, Page M. Why the prone position is a risk factor for sudden infant death syndrome. *Pediatr* 1999;104: 263–269.
99. Changing concepts of sudden infant death syndrome: implications for infant sleeping environment and sleep position. American Academy of Pediatrics. Task Force on Infant Sleep Position and Sudden Infant Death Syndrome. *Pediatrics* 2000;105:650–6.
100. Mitchell EA, Thompson JM, Ford RP, et al. Sheepskin bedding and the sudden infant death syndrome. New Zealand Cot Death Study Group. *J Pediatr* 1998;133:701–4.
101. Mitchell EA, Thompson JMD, Ford RPK, et al. Softness and potential to cause rebreathing: differences in bedding used by infants at high risk for sudden infant death syndrome. *J Pediatr* 1998;133:701–4.
102. Stanciu C, Bennett JR. Effects of posture on gastro-oesophageal reflux. *Digestion* 1977;15:104–9.
103. Johnson LF, DeMeester TR Evaluation of elevation of the head of the bed, bethanechol, and antacid form tablets on gastroesophageal reflux. *Dig Dis Sci* 1981;26:673–80.
104. Hamilton JW, Boisen RJ, Yamamoto DT, et al. Sleeping on a wedge diminishes exposure of the esophagus to refluxed acid. *Dig Dis Sci* 1988;33:518–22.
105. Vandenplas Y, Sacre L, Loeb H. Effects of formula feeding on gastric acidity time and oesophageal pH monitoring data. *Eur J Pediatr* 1988;148:152–4.
106. Casaubon PR, Dahlstrom KA, Vargas J, et al. Intravenous fat emulsion (intralipid) delays gastric emptying, but does not cause gastroesophageal reflux in healthy volunteers. *J Parenter Enteral Nutr* 1989;13:246–8.
107. Becker DJ, Sinclair J, Castell DO, et al. A comparison of high and low fat meals on postprandial esophageal acid exposure. *Am J Gastroenterol* 1989;84:782–6.
108. Iwakiri K, Kobayashi M, Kotoyori M, et al. Relationship between postprandial esophageal acid exposure and meal volume and fat content. *Dig Dis Sci* 1996;41:926–30.
109. Noeser A, Gelineck J, Funch-Jensen P, et al. The incidence of gastro-oesophageal reflux after solid and semi-solid meal. *Rontgenblatter* 1989;42:530–1.
110. Penagini R, Mangano M, Bianchi PA. Effect of increasing the fat content but not the energy load of a meal on gastro-oesophageal reflux and lower oesophageal sphincter motor function [see comments]. *Gut* 1998; 42:330–3.
111. Pehl C, Waizenhoefer A, Wendl B, et al. Effect of low and high fat meals on lower esophageal sphincter motility and gastro-esophageal reflux in healthy subjects. *Am J Gastroenterol* 1999; 94:1192–6.
112. Ruhl CE, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I Epidemiologic Followup Study. First National Health and Nutrition Examination Survey. *Ann Epidemiol* 1999; 9:424–35.
113. Vandenplas Y, De Wolf D, Sacre L. Influence of xanthines on gastroesophageal reflux in infants at risk for sudden infant death syndrome. *Pediatrics* 1986;77:807–10.
114. Pehl C, Pfeiffer A, Wendl B, et al. The effect of decaffeination of coffee on gastro-oesophageal reflux in patients with reflux disease. *Aliment Pharmacol Ther* 1997;11:483–6.
115. Wendl B, Pfeiffer A, Pehl C, et al. Effect of decaffeination of coffee or tea on gastro-oesophageal reflux. *Aliment Pharmacol Ther* 1994;8:283–7.
116. Brazer SR, Onken JE, Dalton CB, et al. Effect of different coffees on esophageal acid contact time and symptoms in coffee-sensitive subjects. *Physiol Behav* 1995;57:563–7.
117. Chang CS, Poon SK, Lien HC, et al. The incidence of reflux esophagitis among the Chinese. *Am J Gastroenterol* 1997;92: 668–71.
118. Castiglione F, Emde C, Armstrong D, et al. Oesophageal pH-metry: should meals be standardized? *Scand J Gastroenterol* 1992;27:350–4.
119. Murphy DW, Castell DO. Chocolate and heartburn: evidence of increased esophageal acid exposure after chocolate ingestion. *Am J Gastroenterol* 1988;83:633–6.
120. Wright LE, Castell DO. The adverse effect of chocolate on lower esophageal sphincter pressure. *Am J Dig Dis* 1975;20:703–7.
121. Bartlett DW, Evans DF, Smith BG. Oral regurgitation after reflux provoking meals: a possible cause of dental erosion? *J Oral Rehabil* 1997;24:102–8.
122. Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. *Am J Dig Dis* 1976;21:953–6.
123. Allen ML, Mellow MH, Robinson MG, et al. The effect of raw

onions on acid reflux and reflux symptoms [see comments]. *Am J Gastroenterol* 1990;85:377–80.
124. Bulat R, Fachnie E, Chauhan U, et al. Lack of effect of spearmint on lower oesophageal sphincter function and acid reflux in healthy volunteers. *Aliment Pharmacol Ther* 1999;13:805–12.
125. Fisher BL, Pennathur A, Mutnick JL, et al. Obesity correlates with gastroesophageal reflux. *Dig Dis Sci* 1999;44:2290–4.
126. Wilson LJ, Ma W, Hirschowitz BI. Association of obesity with hiatal hernia and esophagitis. Am J *Gastroenterol* 1999;94: 2840–4.
127. Fraser-Moodie CA, Norton B, Gornall C, et al. Weight loss has an independent beneficial effect on symptoms of gastro-oesophageal reflux in patients who are overweight. *Scand J Gastroenterol* 1999;34:337–40.
128. Kjellin A, Ramel S, Rossner S, et al. Gastroesophageal reflux in obese patients is not reduced by weight reduction. *Scand J Gastroenterol* 1996;31:1047–51.
129. Mathus-Vliegen LM, Tytgat GN. Twenty-four-hour pH measurements in morbid obesity: effects of massive overweight, weight loss and gastric distension [see comments]. *Eur J Gastroenterol Hepatol* 1996;8:635–40.
130. Alaswad B, Toubas PL, Grunow JE. Environmental tobacco smoke exposure and gastroesophageal reflux in infants with apparent life-threatening events. *J Okla State Med Assoc* 1996;89: 233–7.
131. Blecker U, de Pont SM, Hauser B, et al. The role of "occult" gastroesophageal reflux in chronic pulmonary disease in children. *Acta Gastroenterol Belg* 1995;58:348–52.
132. Trudgill NJ, Smith LF, Kershaw J, et al. Impact of smoking cessation on salivary function in healthy volunteers. *Scand J Gastroenterol* 1998;33:568–71.
133. Kahrilas PJ, Gupta RR. The effect of cigarette smoking on salivation and esophageal acid clearance. *J Lab Clin Med* 1989;114: 431–8.
134. Chattopadhyay DK, Greaney MG, Irvin TT. Effect of cigarette smoking on the lower oesophageal sphincter. *Gut* 1977;18:833–5.
135. Locke GR, Talley NJ, Fett SL, et al. Risk factors associated with symptoms of gastroesophageal reflux. *Am J Med* 1999;106: 642–9.
136. Romero Y, Cameron AJ, Locke GR, et al. Familial aggregation of gastroesophageal reflux in patients with Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterology* 1997;113:1449–56.
137. Kadakia SC, Kikendall JW, Maydonovitch C, et al. Effect of cigarette smoking on gastroesophageal reflux measured by 24-h ambulatory esophageal pH monitoring. *Am J Gastroenterol* 1995; 90:1785–90.
138. Schindlbeck NE, Heinrich C, Dendorfer A, et al. Influence of smoking and esophageal intubation on esophageal pH-metry. *Gastroenterology* 1987;92:1994–7.
139. Waring JP, Eastwood TF, Austin JM, et al. The immediate effects of cessation of cigarette smoking on gastroesophageal reflux. *Am J Gastroenterol* 1989;84:1076–8.
140. Pehl C, Pfeiffer A, Wendl B, et al. Effect of smoking on the results of esophageal pH measurement in clinical routine. *J Clin Gastroenterol* 1997;25:503–6.
141. Rahal PS, Wright RA. Transdermal nicotine and gastroesophageal reflux. *Am J Gastroenterol* 1995;90:919–21.
142. Environmental tobacco smoke: a hazard to children. American Academy of Pediatrics Committee on Environmental Health [see comments]. *Pediatrics* 1997;99:639–42.
143. Dybing E , Sanner T. Passive smoking, sudden infant death syndrome (SIDS) and childhood infections. *Hum Exp Toxicol* 1999; 18:202–5.
144. Cook DG, Strachan DP, Health effects of passive smoking-10: Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999;54:357–66.
145. Banciu T, Sorian E. Gastroesophageal reflux in chronic alcoholics. Endoesophageal pH determinations using Heidelberg telemetring capsule. *Med Interne* 1989;27:279–82.
146. Vitale GC, Cheadle WG, Patel B, et al. The effect of alcohol on nocturnal gastroesophageal reflux. *Jama* 1987;258:2077–9.
147. Pehl C, Pfeiffer A, Wendl B, et al. Different effects of white and red wine on lower esophageal sphincter pressure and gastroesophageal reflux. *Scand J Gastroenterol* 1998;33:118–22.
148. Pehl C, Wendl B, Pfeiffer A, et al. Low-proof alcoholic beverages and gastroesophageal reflux. *Dig Dis Sci* 1993;38:93–6.
149. Sutphen JL, Dillard VL. Effect of ranitidine on twenty-four-hour gastric acidity in infants. *J Pediatr* 1989;114:472–4.
150. Mallet E, Mouterde O, Dubois F, et al. Use of ranitidine in young infants with gastro-oesophageal reflux. *Eur J Clin Pharmacol* 1989;36:641–2.
151. Hyman PE, Garvey TQd, Abrams CE. Tolerance to intravenous ranitidine. *J Pediatr* 1987;110:794–6.
152. Chiba N, De Gara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. *Gastroenterology* 1997;112:1798–810.
153. McCarty-Dawson D, Sue SO, Morrill B, et al. Ranitidine versus cimetidine in the healing of erosive esophagitis. *Clin Ther* 1996; 18:1150–60.
154. Stacey JH, Miocevich ML, Sacks GE The effect of ranitidine (as effervescent tablets) on the quality of life of GORD patients. *Br J Clin Pract* 1996;50:190-4,196.
155. Sabesin SM, Berlin RG, Humphries TJ, et al. Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations. Results of a multicenter, placebo-controlled, dose-ranging study. USA Merck Gastroesophageal Reflux Disease Study Group [see comments]. *Arch Intern Med* 1991;151: 2394–400.
156. Cucchiara S, Gobio-Casali L, Balli F, et al. Cimetidine treatment of reflux esophagitis in children: an Italian multicentric study. *J Pediatr Gastroenterol Nutr* 1989;8:150–6.
157. Simeone D, Caria MC, Miele E, et al. Treatment of childhood peptic esophagitis: a double-blind placebo-controlled trial of nizatidine. *J Pediatr Gastroenterol Nutr* 1997;25:51–5.
158. Kelly DA. Do H2 receptor antagonists have a therapeutic role in childhood? [see comments]. *J Pediatr Gastroenterol Nutr* 1994; 19:270–6.
159. Berezin S, Medow MS, Glassman M, et al. Use of the intraesophageal acid perfusion test in provoking nonspecific chest pain in children. *J Pediatr* 1989;115:709–12.
160. Minella R, Basile P, Stalano A, et al. Ranitidine treatment in pediatry. Med Univ, 1989.2:1–5.
161. DeAngelis G and Banchini G, Ranitidine in paediatric patients, a personal experience. *Clin Trials J* 1989;26:370–5.
162. Wolfe MM, Sachs G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 2000;118 (suppl 1):S9-S31.
163. Kato S, Ebina K, Fujii K, et al. Effect of omeprazole in the treatment of refractory acid-related diseases in childhood: endoscopic healing and twenty-four-hour intragastric acidity. *J Pediatr* 1996;128:415–21.
164. De Giacomo C, Bawa P, Franceschi M, et al. Omeprazole for severe reflux esophagitis in children. *J Pediatr Gastroenterol Nutr* 1997;24:528–32.
165. Alliet P, Raes M, Bruneel E, et al. Omeprazole in infants with cimetidine-resistant peptic esophagitis. *J Pediatr* 1998;132: 352–4.
166. Strauss RS, Calenda KA, Dayal Y, et al. Histological esophagitis: clinical and histological response to omeprazole in children. *Dig Dis Sci* 1999;44:134–9.
167. Klinkenberg-Knol EC, Jansen JM, Festen HP, et al. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *Lancet* 1987;1:349–51.
168. Sontag SJ. The medical management of reflux esophagitis. Role

of antacids and acid inhibition. *Gastroenterol Clin North Am* 1990;19:683–712.
169. Vigneri S, Termini R, Leandro G, et al. A comparison of five maintenance therapies for reflux esophagitis [see comments]. *N Engl J Med* 1995;333:1106–10.
170. Cucchiara S, Minella R, Iervolino MR, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. *Arch Dis Child* 1993;69:655–9.
171. Klinkenberg-Knol EC, Nelis F, Dent J, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa [see comments]. *Gastroenterology* 2000;118:661–9.
172. Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management– the Genval workshop report. *Gut* 1999;44(suppl 2):S1-S16.
173. Cucchiara S, Staiano A, Romaniello G, et al. Antacids and cimetidine treatment for gastro-oesophageal reflux and peptic oesophagitis. *Arch Dis Child* 1984;59:842–7.
174. Iacono G, Carroccio A, Montalto G, et al. Magnesium hydroxide and aluminum hydroxide in the treatment of gastroesophageal reflux. *Minerva Pediatr* 1991;43:797–800.
175. Tsou VM, Young RM, Hart MH, et al. Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. *Pediatrics* 1991;87:148–51.
176. Woodard-Knight L, Fudge A, Teubner J, et al. Aluminium absorption and antacid therapy in infancy. *J Paediatr Child Health* 1992;28:257–9.
177. Sedman A. Aluminum toxicity in childhood. *Pediatr Nephrol* 1992;6:383–93.
178. Aluminum toxicity in infants and children. American Academy of Pediatrics, Committee on Nutrition. Pediatrics 1996;97:413–6.
179. Klein GL. Metabolic bone disease of total parenteral nutrition. *Nutrition* 1998;14:149–52.
180. Cucchiara S, Staiano A, Boccieri A, et al. Effects of cisapride on parameters of oesophageal motility and on the prolonged intraoesophageal pH test in infants with gastro-oesophageal reflux disease. *Gut* 1990;31:21–5.
181. Cucchiara S, Staiano A, Capozzi C, et al. Cisapride for gastro-oesophageal reflux and peptic oesophagitis. *Arch Dis Child* 1987; 62:454–7.
182. Vandenplas Y, de Roy C, Sacre L. Cisapride decreases prolonged episodes of reflux in infants. *J Pediatr Gastroenterol Nutr* 1991; 12:44–7.
183. Saye ZN, Forget PP, Geubelle F. Effect of cisapride on gastroesophageal reflux in children with chronic bronchopulmonary disease: a double-blind cross-over pH-monitoring study. *Pediatr Pulmonol* 1987;3:8–12.
184. Scott RB, Ferreira C, Smith L, et al. Cisapride in pediatric gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 1997;25:499–506.
185. Cohen RC, O'Loughlin EV, Davidson GP, et al. Cisapride in the control of symptoms in infants with gastroesophageal reflux: a randomized, double-blind, placebo-controlled trial [see comments]. *J Pediatr* 1999;134:287–92.
186. Van Eygen M, Van Ravensteyn H. Effect of cisapride on excessive regurgitation in infants. *Clin Ther* 1989;11:669–77.
187. Rode H, Stunden RJ, Millar AJ, et al. Esophageal pH assessment of gastroesophageal reflux in 18 patients and the effect of two prokinetic agents: cisapride and metoclopramide. *J Pediatr Surg* 1987;22:931–4.
188. Grande L, Lacima G, Ros E, et al. Lack of effect of metoclopramide and domperidone on esophageal peristalsis and esophageal acid clearance in reflux esophagitis. A randomized, double-blind study. *Dig Dis Sci* 1992;37:583–8.
189. Richter JE, Sabesin SM, Kogut DG, et al. Omeprazole versus ranitidine or ranitidine/metoclopramide in poorly responsive symptomatic gastroesophageal reflux disease. *Am J Gastroenterol* 1996;91:1766–72.
190. Leung C, Lai W. Use of metoclopramide for the treatment of gastroesophageal reflux in infants and children. *Curr Ther Res* 1984;36:911–15.
191. De Loore I, Van Ravensteyn H, Ameryckx L Domperidone drops in the symptomatic treatment of chronic paediatric vomiting and regurgitation. A comparison with metoclopramide. *Postgrad Med J* 1979;55:40–2.
192. Machida HM, Forbes DA, Gall DG, et al. Metoclopramide in gastroesophageal reflux of infancy. *J Pediatr* 1988;112:483–7.
193. Bellissant E, Duhamel JF, Guillot M, et al. The triangular test to assess the efficacy of metoclopramide in gastroesophageal reflux. *Clin Pharmacol Ther* 1997;61:377–84.
194. Kearns GL, Butler HL, Lane JK, Carchman SH, and Wright GJ, Metoclopramide pharmacokinetics and pharmacodynamics in infants with gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 1988;7:823–9.
195. Tolia V, Calhoun J, Kuhns L, et al. Randomized, prospective double-blind trial of metoclopramide and placebo for gastroesophageal reflux in infants [see comments]. *J Pediatr* 1989;115: 141–5.
196. Pons G, Duhamel JF, Guillot M, et al. Dose-response study of metoclopramide in gastroesophageal reflux in infancy. *Fundam Clin Pharmacol* 1993;7:161–6.
197. Putnam PE, Orenstein SR, Wessel HB, et al. Tardive dyskinesia associated with use of metoclopramide in a child. *J Pediatr* 1992; 121:983–5.
198. Euler AR. Use of bethanechol for the treatment of gastroesophageal reflux. *J Pediatr* 1980;96:321–4.
199. Levi P, Marmo F, Saluzzo C, et al. Bethanechol versus antiacids in the treatment of gastroesophageal reflux. *Helv Paediatr Acta* 1985;40:349–59.
200. Bines JE, Quinlan JE, Treves S, et al. Efficacy of domperidone in infants and children with gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 1992;14:400–5.
201. Carroccio A, Iacono G, Montalto G, et al. Domperidone plus magnesium hydroxide and aluminum hydroxide: a valid therapy in children with gastroesophageal reflux. A double-blind randomized study versus placebo. *Scand J Gastroenterol* 1994;29:300–4.
202. Shulman RJ, Boyle JT, Colletti RB, et al. The use of cisapride in children. The North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 1999;28:529–33.
203. Poynard T, Vernisse B, Agostini H. Randomized, multicentre comparison of sodium alginate and cisapride in the symptomatic treatment of uncomplicated gastro-oesophageal reflux. *Aliment Pharmacol Ther* 1998;12:159–65.
204. Greally P, Hampton FJ, MacFadyen UM, et al. Gaviscon and Carobel compared with cisapride in gastro-oesophageal reflux. *Arch Dis Child* 1992;67:618–21.
205. Buts JP, Barudi C, Otte JB. Double-blind controlled study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants and children. *Eur J Pediatr* 1987;146:156–8.
206. Forbes D, Hodgson M, Hill R. The effects of gaviscon and metoclopramide in gastroesophageal reflux in children. *J Pediatr Gastroenterol Nutr* 1986;5:556–9.
207. Simon B, Ravelli GP, Goffin H. Sucralfate gel versus placebo in patients with non-erosive gastro- oesophageal reflux disease. *Aliment Pharmacol Ther* 1996;10:441–6.
208. Arguelles-Martin F, Gonzalez-Fernandez F, Gentles MG. Sucralfate versus cimetidine in the treatment of reflux esophagitis in children. *Am J Med* 1989;86:73–6.
209. Dalla Vecchia LK, Grosfeld JL, West KW, et al. Reoperation after Nissen fundoplication in children with gastroesophageal reflux: experience with 130 patients. *Ann Surg* 1997;226:315-21;discussion 321-3.
210. Veit F, Schwagten K, Auldist AW, et al. Trends in the use of fundoplication in children with gastro-oesophageal reflux. *J Paediatr Child Health* 1995;31:121–6.
211. Randolph J. Experience with the Nissen fundoplication for cor-

rection of gastroesophageal reflux in infants. *Ann Surg* 1983;198: 579–84.
212. Bensoussan AL, Yazbeck S, Carceller-Blanchard A. Results and complications of Toupet partial posterior wrap: 10 years' experience. *J Pediatr Surg* 1994;29:1215–7.
213. Ahrens P, Heller K, Beyer P, et al. Antireflux surgery in children suffering from reflux-associated respiratory diseases. *Pediatr Pulmonol* 1999;28:89–93.
214. Bergmeijer JH, Harbers JS, Molenaar JC. Function of pediatric Nissen-Rossetti fundoplication followed up into adolescence and adulthood. *J Am Coll Surg* 1997;184:259–61.
215. Blane CE, Turnage RH, Oldham KT, et al. Long-term radiographic follow-up of the Nissen fundoplication in children. *Pediatr Radiol* 1989;19:523–6.
216. Bliss D, Hirschl R, Oldham K, et al. Efficacy of anterior gastric fundoplication in the treatment of gastroesophageal reflux in infants and children. *J Pediatr Surg* 1994;29:1071-4;discussion 1074-5.
217. Caniano DA, Ginn-Pease ME, et al. The failed antireflux procedure: analysis of risk factors and morbidity. *J Pediatr Surg* 1990; 25:1022-5;discussion 1025-6.
218. Fonkalsrud EW, Ashcraft KW, Coran AG, et al. Surgical treatment of gastroesophageal reflux in children: a combined hospital study of 7467 patients [see comments]. *Pediatrics* 1998;101:419–22.
219. Fonkalsrud EW, Bustorff-Silva J, Perez CA, et al. Antireflux surgery in children under 3 months of age. *J Pediatr Surg* 1999; 34:527–31.
220. Weber TR. Toupet fundoplication for gastroesophageal reflux in childhood. *Arch Surg* 1999;134:717-20; discussion 720-1.
221. Spillane AJ, Currie B, Shi E. Fundoplication in children: experience with 106 cases. *Aust N Z J Surg* 1996; 66:753–6.
222. Samuk I, Afriat R, Horne T, et al. Dumping syndrome following Nissen fundoplication, diagnosis, and treatment. *J Pediatr Gastroenterol Nutr* 1996;23:235–40.
223. Khoshoo V, Roberts PL, Loe WA, et al. Nutritional management of dumping syndrome associated with antireflux surgery. *J Pediatr Surg* 1994;29:1452–4.
224. Tovar JA, Olivares P, Diaz M, et al. Functional results of laparoscopic fundoplication in children. *J Pediatr Gastroenterol Nutr* 1998;26:429–31.
225. Rothenberg SS. Experience with 220 consecutive laparoscopic Nissen fundoplications in infants and children. *J Pediatr Surg* 1998;33:274–8.
226. Tovar JA, Angulo JA, Gorostiaga L, et al. Surgery for gastroesophageal reflux in children with normal pH studies. *J Pediatr Surg* 1991;26:541–5.
227. Hunziker UA, Barr RG. Increased carrying reduces infant crying: a randomized controlled trial. *Pediatrics* 1986;77:641–8.
228. Armstrong KL, Quinn RA, Dadds MR. The sleep patterns of normal children. *Med J Aust* 1994;161:202–6.
229. Singh S, Richter JE, Bradley LA, et al. The symptom index. Differential usefulness in suspected acid-related complaints of heartburn and chest pain [see comments]. *Dig Dis Sci* 1993;38: 1402–8.
230. Wiener GJ, Richter JE, Copper JB, et al. The symptom index: a clinically important parameter of ambulatory 24- hour esophageal pH monitoring. *Am J Gastroenterol* 1988;83:358–61.
231. Heine RG, Jaquiery A, Lubitz L, et al. Role of gastro-oesophageal reflux in infant irritability. *Arch Dis Child* 1995;73:121–5.
232. Ghaem M, Armstrong KL, Trocki O, et al. The sleep patterns of infants and young children with gastro- oesophageal reflux. *J Paediatr Child Health* 1998;34:160–3.
233. Berezin S, Glassman MS, Bostwick H, et al. Esophagitis as a cause of infant colic. *Clin Pediatr (Phila)* 1995;34:158–9.
234. Barr RG, Rotman A, Yaremko J, et al. The crying of infants with colic: a controlled empirical description. *Pediatrics* 1992;90:14–21.
235. Castell DO. A practical approach to heartburn [In Process Citation]. *Hosp Pract (Off Ed)* 1999;34:89-94, 97-8.
236. Richter JE, Kovacs TO, Greski-Rose PA, et al. Lansoprazole in the treatment of heartburn in patients without erosive oesophagitis. *Aliment Pharmacol Ther* 1999;13:795–804.
237. Venables TL, Newland RD, Patel AC, et al. Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. *Scand J Gastroenterol* 1997;32:965–73.
238. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999;94:1434–42.
239. Revicki DA, Crawley JA, Zodet MW, et al. Complete resolution of heartburn symptoms and health-related quality of life in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1999;13:1621–30.
240. Pappa KA, Williams BO, Payne JE, et al. A double-blind, placebo-controlled study of the efficacy and safety of non-prescription ranitidine 75 mg in the prevention of meal-induced heartburn. *Aliment Pharmacol Ther* 1999;13:467–73.
241. Holloway RH, Dent J, Narielvala F, et al. Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis [see comments]. *Gut* 1996;38:649–54.
242. Catto-Smith AG, Machida H, Butzner JD, et al. The role of gastroesophageal reflux in pediatric dysphagia. *J Pediatr Gastroenterol Nutr* 1991;12:159–65.
243. Lundquist A, Olsson R, Ekberg O. Clinical and radiologic evaluation reveals high prevalence of abnormalities in young adults with dysphagia. *Dysphagia* 1998;13:202–7.
244. Dellert SF, Hyams JS, Treem WR, et al. Feeding resistance and gastroesophageal reflux in infancy. *J Pediatr Gastroenterol Nutr* 1993;17:66–71.
245. Shepherd RW, Wren J, Evans S, et al. Gastroesophageal reflux in children. Clinical profile, course and outcome with active therapy in 126 cases. *Clin Pediatr (Phila)* 1987;26:55–60.
246. Mathisen B, Worrall L, Masel J, et al. Feeding problems in infants with gastro-oesophageal reflux disease: a controlled study. *J Paediatr Child Health* 1999;35:163–9.
247. Rudolph CD. Feeding disorders in infants and children. *J Pediatr* 1994;125:S116-24.
248. National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring, Sept 29 to Oct 1, 1986. *Pediatrics* 1987;79:292–9.
249. Tirosh E, Kessel A, Jaffe M, et al. Outcome of idiopathic apparent life-threatening events: infant and mother perspectives. *Pediatr Pulmonol* 1999;28:47–52.
250. Steinschneider A, Richmond C, Ramaswamy V, et al. Clinical characteristics of an apparent life-threatening event (ALTE) and the subsequent occurrence of prolonged apnea or prolonged bradycardia. *Clin Pediatr (Phila)* 1998;37:223–9.
251. Cote A, Hum C, Brouillette RT, et al. Frequency and timing of recurrent events in infants using home cardiorespiratory monitors [see comments]. *J Pediatr* 1998;132:783–9.
252. Rosen CL, Frost JD, Jr, Harrison GM. Infant apnea: polygraphic studies and follow-up monitoring. *Pediatrics* 1983;71:731–6.
253. Burchfield DJ, Rawlings DJ. Sudden deaths and apparent life-threatening events in hospitalized neonates presumed to be healthy [see comments]. *Am J Dis Child* 1991;145:1319–22.
254. Kahn A, Blum D, Rebuffat E, et al. Polysomnographic studies of infants who subsequently died of sudden infant death syndrome. *Pediatrics* 1988;82:721–7.
255. Kelly DH, Golub H, Carley D, et al. Pneumograms in infants who subsequently died of sudden infant death syndrome. *J Pediatr* 1986;109:249–54.
256. Kelly DH, Shannon DC, O'Connell K. Care of infants with near-miss sudden infant death syndrome. *Pediatrics* 1978;61:511–4.

257. Oren J, Kelly D, Shannon DC. Identification of a high-risk group for sudden infant death syndrome among infants who were resuscitated for sleep apnea. Pediatrics 1986;77:495–9.
258. Steinschneider A, Weinstein SL, Diamond E. The sudden infant death syndrome and apnea/obstruction during neonatal sleep and feeding. *Pediatrics* 1982;70:858–63.
259. Friesen CA, Streed CJ, Carney LA, et al. Esophagitis and modified Bernstein tests in infants with apparent life- threatening events. *Pediatrics* 1994;94:541–4.
260. Newman LJ, Russe J, Glassman MS, et al. Patterns of gastroesophageal reflux (GER) in patients with apparent life-threatening events. *J Pediatr Gastroenterol Nutr* 1989;8:157–60.
261. Veereman-Wauters G, Bochner A, Van Caillie-Bertrand M. Gastroesophageal reflux in infants with a history of near-miss sudden infant death. *J Pediatr Gastroenterol Nutr* 1991;12:319–23.
262. Herbst JJ, Minton SD, Book LS. Gastroesophageal reflux causing respiratory distress and apnea in newborn infants. *J Pediatr* 1979; 95:763–8.
263. Leape LL, Holder TM, Franklin JD, et al. Respiratory arrest in infants secondary to gastroesophageal reflux. *Pediatrics* 1977;60: 924–8.
264. Herbst JJ, Book LS, Bray PF. Gastroesophageal reflux in the "near miss" sudden infant death syndrome. *J Pediatr* 1978;92: 73–5.
265. Menon AP, Schefft GL, Thach BT. Apnea associated with regurgitation in infants. *J Pediatr* 1985;106:625–9.
266. Sacre L, Vandenplas Y. Gastroesophageal reflux associated with respiratory abnormalities during sleep. *J Pediatr Gastroenterol Nutr* 1989;9:28–33.
267. Ariagno RL. Evaluation and management of infantile apnea. *Pediatr Ann* 1984;13:210-3, 216-7.
268. Kahn A, Rebuffat E, Sottiaux M, et al. Lack of temporal relation between acid reflux in the proximal oesophagus and cardiorespiratory events in sleeping infants. *Eur J Pediatr* 1992;151:208–12.
269. Paton JY, Nanayakkara CS, Simpson H. Observations on gastro-oesophageal reflux, central apnoea and heart rate in infants. *Eur J Pediatr* 1990;149:608–12.
270. Paton JY, Macfadyen U, Williams A, et al. Gastro-oesophageal reflux and apnoeic pauses during sleep in infancy– no direct relation. *Eur J Pediatr* 1990;149:680–6.
271. Walsh JK, Farrell MK, Keenan WJ, et al. Gastroesophageal reflux in infants: relation to apnea. *J Pediatr* 1981;99:197–201.
272. Suys B, De Wolf D, Hauser B, et al. Bradycardia and gastroesophageal reflux in term and preterm infants: is there any relation? *J Pediatr Gastroenterol Nutr* 1994;19:187–90.
273. Spitzer AR, Boyle JT, Tuchman DN, et al. Awake apnea associated with gastroesophageal reflux: a specific clinical syndrome. *J Pediatr* 1984;104:200–5.
274. Jolley SG, Halpern LM, Tunell WP, et al. The risk of sudden infant death from gastroesophageal reflux [see comments]. *J Pediatr Surg* 1991;26:691–6.
275. Meadow R. Suffocation, recurrent apnea, and sudden infant death. *J Pediatr* 1990;117:351–7.
276. Expert Panel Report II. Guidelines for the Diagnosis and Management of Asthma. 1997: National Institute of Health, Bethesda, MD.
277. Field SK. A critical review of the studies of the effects of simulated or real gastroesophageal reflux on pulmonary function in asthmatic adults. *Chest* 1999;115:848–56.
278. Boyle JT, Tuchman DN, Altschuler SM, et al. Mechanisms for the association of gastroesophageal reflux and bronchospasm. *Am Rev Respir Dis* 1985;131:S16-20.
279. Malfroot A, Dab I. Pathophysiology and mechanisms of gastroesophageal reflux in childhood asthma. *Pediatr Pulmonol Suppl* 1995;11:55–6.
280. Herve P, Denjean A, Jian R, et al. Intraesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects. *Am Rev Respir Dis* 1986;134:986–9.
281. Nelson HS. Gastroesophageal reflux and pulmonary disease. *J Allergy Clin Immunol* 1984;73:547–56.
282. Sheikh S, Goldsmith LJ, Howell L, et al. Lung function in infants with wheezing and gastroesophageal reflux [see comments]. *Pediatr Pulmonol* 1999;27:236–41.
283. Vijayaratnam V, Lin CH, Simpson P, et al. Lack of significant proximal esophageal acid reflux in infants presenting with respiratory symptoms [see comments]. *Pediatr Pulmonol* 1999;27: 231–5.
284. Andze GO, Brandt ML, St. Vil D, et al. Diagnosis and treatment of gastroesophageal reflux in 500 children with respiratory symptoms: the value of pH monitoring. *J Pediatr Surg* 1991;26:295-9;discussion 299-300.
285. Gustafsson PM, Kjellman NI, Tibbling L. Bronchial asthma and acid reflux into the distal and proximal oesophagus. Arch Dis Child 1990;65:1255–8.
286. Wilson NM, Charette L, Thomson AH, et al. Gastro-oesophageal reflux and childhood asthma: the acid test. *Thorax* 1985;40: 592–7.
287. Martin ME, Grunstein MM, Larsen GL. The relationship of gastroesophageal reflux to nocturnal wheezing in children with asthma. *Ann Allergy* 1982;49:318–22.
288. Berquist WE, Rachelefsky GS, Kadden M, et al. Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children. *Pediatrics* 1981;68:29–35.
289. Shapiro GG, Christie DL. Gastroesophageal reflux in steroid-dependent asthmatic youths. *Pediatrics* 1979;63:207–12.
290. Euler AR, Byrne WJ, Ament ME, et al. Recurrent pulmonary disease in children: a complication of gastroesophageal reflux. *Pediatrics* 1979;63:47–51.
291. Eid NS, Shepherd RW, Thomson MA. Persistent wheezing and gastroesophageal reflux in infants. *Pediatr Pulmonol* 1994;18: 39–44.
292. Gustafsson PM, Kjellman NI, Tibbling L. A trial of ranitidine in asthmatic children and adolescents with or without pathological gastro-oesophageal reflux. *Eur Respir J* 1992;5:201–6.
293. Harding SM, Richter JE, Guzzo MR, et al. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996;100:395–405.
294. Harding SM. Nocturnal asthma: role of nocturnal gastroesophageal reflux. *Chronobiol Int* 1999;16:641–62.
295. Rothenberg SS, Bratton D, Larsen G, et al. Laparoscopic fundoplication to enhance pulmonary function in children with severe reactive airway disease and gastroesophageal reflux disease. *Surg Endosc* 1997;11:1088–90.
296. Foglia RP, Fonkalsrud EW, Ament ME, et al. Gastroesophageal fundoplication for the management of chronic pulmonary disease in children. *Am J Surg* 1980;140:72–9.
297. Field SK, Gelfand GA, McFadden SD. The effects of antireflux surgery on asthmatics with gastroesophageal reflux. *Chest* 1999; 116:766–74.
298. Carre IJ. Pulmonary infections in children with a partial thoracic stomach ('hiatus hernia'). *Arch Dis Child* 1960;35:481–4.
299. Chen PH, Chang MH, Hsu SC. Gastroesophageal reflux in children with chronic recurrent bronchopulmonary infection. *J Pediatr Gastroenterol Nutr* 1991;13:16–22.
300. Mays EE, Dubois JJ, Hamilton GB. Pulmonary fibrosis associated with tracheobronchial aspiration. A study of the frequency of hiatal hernia and gastroesophageal reflux in interstitial pulmonary fibrosis of obscure etiology. *Chest* 1976;69:512–5.
301. Regelmann WE. Diagnosing the cause of recurrent and persistent pneumonia in children. *Pediatr Ann* 1993;22:561–8.
302. Wilkinson JD, Dudgeon DL, Sondheimer JM. A comparison of medical and surgical treatment of gastroesophageal reflux in severely retarded children. *J Pediatr* 1981;99:202–5.
303. Nussbaum E, Maggi JC, Mathis R, et al. Association of lipid-laden alveolar macrophages and gastroesophageal reflux in children. *J Pediatr* 1987;110:190–4.
304. Staugas R, Martin AJ, Binns G, et al. The significance of fat-filled

macrophages in the diagnosis of aspiration associated with gastro-oesophageal reflux. Aust Paediatr J 1985;21:275–7.
305. Colombo JL, Hallberg TK. Recurrent aspiration in children: lipid-laden alveolar macrophage quantitation. Pediatr Pulmonol 1987; 3:86–9.
306. Ahrens P, Noll C, Kitz R, et al. Lipid-laden alveolar macrophages (LLAM): a useful marker of silent aspiration in children [see comments]. *Pediatr Pulmonol* 1999;28:83–8.
307. Bauer ML, Lyrene RK. Chronic aspiration in children: evaluation of the lipid-laden macrophage index [see comments]. *Pediatr Pulmonol* 1999;28:94–100.
308. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. *Pediatr Pulmonol* 1999;27:419–22.
309. Morton RE, Wheatley R, Minford J. Respiratory tract infections due to direct and reflux aspiration in children with severe neurodisability. *Dev Med Child Neurol* 1999;41:329–34.
310. Taniguchi MH, Moyer RS. Assessment of risk factors for pneumonia in dysphagic children: significance of videofluoroscopic swallowing evaluation. *Dev Med Child Neurol* 1994;36:495–502.
311. Arvedson J, Rogers B, Buck G, et al. Silent aspiration prominent in children with dysphagia. *Int J Pediatr Otorhinolaryngol* 1994; 28:173–81.
312. Aviv JE, Kim T, Sacco RL, et al. FEESST: a new bedside endoscopic test of the motor and sensory components of swallowing. *Ann Otol Rhinol Laryngol* 1998;107:378–87.
313. Link DT, Willging JP, Miller CK, et al. Pediatric laryngopharyngeal sensory testing during FEES: Feasible and Correlative. *Ann Otol Rhinol Laryngol* 2000;XX: XX-XX.
314. Koufman JA. The otolaryngologic manifestations of gastro-esophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24- hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991;101:1–78.
315. Fitzgerald JM, Allen CJ, Craven MA, et al. Chronic cough and gastroesophageal reflux. *Cmaj* 1989;140:520–4.
316. Ing AJ, Ngu MC, Breslin AB. Chronic persistent cough and gastro-oesophageal reflux. *Thorax* 1991;46:479–83.
317. Woo P, Noordzij P, Ross JA. Association of esophageal reflux and globus symptom: comparison of laryngoscopy and 24-hour pH manometry. *Otolaryngol Head Neck Surg* 1996;115:502–7.
318. Curran AJ, Barry MK, Callanan V, et al. A prospective study of acid reflux and globus pharyngeus using a modified symptom index. *Clin Otolaryngol* 1995;20:552–4.
319. Wilson JA, White A, von Haacke NP, et al. Gastroesophageal reflux and posterior laryngitis. *Ann Otol Rhinol Laryngol* 1989; 98:405–10.
320. Shaw GY, Searl JP. Laryngeal manifestations of gastroesophageal reflux before and after treatment with omeprazole. *South Med J* 1997;90:1115–22.
321. Jacob P, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with 'reflux laryngitis'. *Gastroenterology* 1991;100: 305–10.
322. Shaker R, Milbrath M, Ren J, et al. Esophagopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. *Gastroenterology* 1995;109:1575–82.
323. Contencin P, Narcy P. Gastropharyngeal reflux in infants and children. A pharyngeal pH monitoring study. *Arch Otolaryngol Head Neck Surg* 1992;118:1028–30.
324. Gumpert L, Kalach N, Dupont C, et al. Hoarseness and gastro-esophageal reflux in children. *J Laryngol Otol* 1998;112:49–54.
325. Corrado G, D'Eufemia P, Pacchiarotti C, et al. Irritable oesophagus syndrome as cause of chronic cough. *Ital J Gastroenterol* 1996;28:526–30.
326. Halstead LA. Gastroesophageal reflux: a critical factor in pediatric subglottic stenosis. *Otolaryngol Head Neck Surg* 1999;120: 683–8.
327. Kamel PL, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis [see comments]. *Am J Med* 1994;96:321–6.
328. Hanson DG, Kamel PL, Kahrilas PJ. Outcomes of antireflux therapy for the treatment of chronic laryngitis. *Ann Otol Rhinol Laryngol* 1995;104:550–5.
329. Putnam PE, Orenstein SR. Hoarseness in a child with gastro-esophageal reflux. *Acta Paediatr* 1992;81:635–6.
330. Conley SF, Werlin SL, Beste DJ. Proximal pH-metry for diagnosis of upper airway complications of gastroesophageal reflux. *J Otolaryngol* 1995;24:295–8.
331. Allen CJ, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. *Thorax* 1998;53: 963–8.
332. Bartlett DW, Coward PY, Nikkah C, et al. The prevalence of tooth wear in a cluster sample of adolescent schoolchildren and its relationship with potential explanatory factors [see comments]. *Br Dent J* 1998;184:125–9.
333. O'Sullivan EA, Curzon ME, Roberts GJ, et al. Gastroesophageal reflux in children and its relationship to erosion of primary and permanent teeth. *Eur J Oral Sci* 1998;106:765–9.
334. Bothwell MR, Parsons DS, Talbot A, et al. Outcome of reflux therapy on pediatric chronic sinusitis. *Otolaryngol Head Neck Surg* 1999;121:255–62.
335. Contencin P, Narcy P. Nasopharyngeal pH monitoring in infants and children with chronic rhinopharyngitis. *Int J Pediatr Otorhinolaryngol* 1991;22:249–56.
336. Gibson WS, Jr, Cochran W. Otalgia in infants and children–a manifestation of gastroesophageal reflux. Int *J Pediatr Otorhinolaryngol* 1994;28:213–8.

Appendix A. *Summary of recommendations for diagnostic approaches and the quality of the evidence*

Section	Recommendations	Quality of evidence*
	Diagnostic approaches	
3.1	In most cases a history and physical examination are sufficient to reliably diagnose GER and initiate management.	III
3.2	The upper GI series is neither sensitive nor specific for the diagnosis of GER, but is useful for the evaluation of the presence of anatomic abnormalities, such as pyloric stenosis, malrotation and annular pancreas in the vomiting infant, as well as hiatal hernia and esophageal stricture in the older child.	III
3.3	Esophageal pH monitoring is a valid and reliable measure of acid reflux.	II-2
3.4	Endoscopy and biopsy can determine the presence and severity of esophagitis, strictures and Barrett's esophagus, as well as exclude other disorders. Esophageal biopsy is recommended when endoscopy is performed to detect inapparent esophagitis and to exclude causes of esophagitis other than GER.	II-2
3.5	The role of nuclear scintigraphy (milk scan) in the diagnosis and management of GERD in infants and children is unclear.	III
3.6	A trial of time–limited medical therapy for GER is useful for determining if GER is causing a specific symptom.	III

* Categories of the Quality of Evidence [16]
I Evidence obtained from at least one properly designed randomized controlled study.
II-1 Evidence obtained from well–designed cohort or case–controlled trials without randomization.
II-2 Evidence obtained from well–designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940's) could also be regarded as this type of evidence.
III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Appendix B. *Summary of recommendations for treatment options and the quality of the evidence*

Section	Recommendation	Quality of evidence*
	Treatment options	
4.1.1	There is evidence to support a one to two week trial of a hypoallergenic formula in formula fed infants with vomiting.	I
4.1.1	Milk–thickening agents do not improve reflux index scores but do decrease the number of episodes of vomiting.	I
4.1.2	Esophageal pH monitoring has demonstrated that infants have significantly less GER when placed in the prone position than in the supine position.	I
4.1.2	Prone positioning is associated with a higher rate of the sudden infant death syndrome (SIDS). In infants from birth to 12 months of age with GERD, the risk of SIDS generally outweighs the potential benefits of prone sleeping. Therefore, non–prone positioning during sleep is generally recommended.	I
4.1.2	In children older than one year it is likely that there is a benefit to left side positioning and elevation of the head of the bed.	I
4.1.3	It is recommended that children and adolescents with GERD avoid caffeine, chocolate and spicy foods that provoke symptoms. Obesity, exposure to tobacco smoke and alcohol are also associated with GER.	III
4.2.1.1	Histamine–$_2$ receptor antagonists (H_2RAs) produce relief of symptoms and mucosal healing. Proton pump inhibitors (PPIs), the most effective acid suppressant medications, are superior to H_2RAs in relieving symptoms and healing esophagitis.	I
4.2.1.3	Since more convenient and safe alternatives are available (H_2RAs and PPIs), chronic antacid therapy is generally not recommended.	III
4.2	Cisapride reduces the frequency of regurgitation and vomiting. However, because of concerns about the potential for serious cardiac arrhythmias in patients receiving cisapride, appropriate patient selection and monitoring as well as proper use, including correct dosage (0.2 mg/kg/dose QID) and avoidance of co–administration of contraindicated medications, are important. Cisapride is available in the USA only through a limited–access program. Other prokinetic agents have not been shown to be effective in the treatment of GERD in children.	I
4.3	Case series indicate that surgical therapy generally results in favorable outcomes. The potential risks, benefits and costs of successful prolonged medical therapy versus fundoplication have not been well studied in infants or children with varying symptom presentations.	II-3 III

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	Quality of evidence*
	Evaluation and management of infants and children with possible GERD	
5.1.1	In the infant with recurrent vomiting, a thorough history and physical examination with attention to warning signals is generally sufficient to allow the clinician to establish a diagnosis of uncomplicated GER.	III
5.1.2	In the infant who has uncomplicated GER, parental education, reassurance and anticipatory guidance are recommended. Generally, no other intervention is necessary. Thickening of formula and a short trial of a hypoallergenic formula are other treatment options. If symptoms worsen or do not improve by 18 to 24 months of age, re–evaluation for complications of GER is recommended.	III
5.1.3	In the vomiting infant with poor weight gain in whom adequate calories are being offered, it is recommended that tests be performed to uncover other causes of vomiting, including an upper GI series to evaluate anatomy and swallowing. Management options include thickening the formula, increasing the caloric density of the formula, acid suppression therapy, prokinetic therapy and, in selected cases, prone positioning. Further management options include endoscopy with biopsy, hospitalization, tube feedings and rarely surgical therapy.	III
5.1.4	In infants with vomiting and irritability, potentially harmful interventions are undertaken with caution because pathological findings are so infrequent. One approach to management is initial empiric therapy; an alternate approach is initial diagnostic evaluation.	III
5.1.5	In otherwise normal children who have recurrent vomiting after the age of 2 years, management options include an upper GI series and upper endoscopy with biopsy.	II-2
	Prokinetic therapy is also an option.	III
5.2	For the treatment of heartburn in children or adolescents, lifestyle changes accompanied by a two– to four–week therapeutic trial of an H_2RA or PPI are recommended. If symptoms persist or recur, the child can be referred to a pediatric gastroenterologist for upper endoscopy with biopsy and in some cases long–term therapy.	III
5.3	In the infant or child with esophagitis, initial treatment consists of lifestyle changes and H_2RA or PPI therapy. In patients with only histologic esophagitis, the efficacy of therapy can be monitored by the degree of symptom relief. In patients with erosive esophagitis, repeat endoscopy is recommended to assure healing.	I
5.4	In the child with dysphagia or odynophagia, a barium esophagram is recommended. If the initial history is suggestive of esophagitis, upper endoscopy may be performed as the initial diagnostic test. Treatment without prior diagnostic evaluation is not recommended. In the infant with feeding refusal, because a large variety of disorders may contribute to infant feeding difficulties, empiric therapy for GER is generally not recommended. However, if there are other signs or symptoms suggestive of GERD then a time–limited course of medical therapy can be considered.	III
5.5	In the infant with apnea or an apparent life–threatening event, if symptoms occur frequently and the role of GER is uncertain, esophageal pH monitoring may be useful to determine if there is a temporal association of acid reflux with ALTE.	II-2
	Therapeutic options include thickened feedings and prokinetic and acid suppressant therapy. Since most infants improve with medical management, surgery is considered only in severe cases.	III
5.6	In patients where symptoms of asthma and esophagitis co–exist, and in infants and toddlers with chronic vomiting or regurgitation and recurrent episodes of cough and wheezing, a three–month trial of vigorous acid suppressant therapy of GER is recommended. If patients with persistent asthma do not have symptoms of GER, esophageal pH monitoring is recommended in selected patients who are more likely to benefit from GER therapy.	III