REVIEW ARTICLE

Clinical Management of Infants and Children with Gastroesophageal Reflux Disease

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Gastroesophageal reflux refers to the passage of gastric contents including food, acid, and digestive enzymes up into the esophagus. Reflux is most commonly recognized in infants when it is associated with regurgitation, known as "spitting up," and it is usually a self-limited, benign process that has little or no effect on normal weight gain or development. Adults and adolescents may also have reflux, which is usually either asymptomatic or recognized as dyspepsia or "heartburn." Gastroesophageal reflux disease (GERD) is defined as symptoms or complications that result from reflux. Most evidence suggests the mechanism of reflux is due to transient relaxations of the lower esophageal sphincter at inappropriate times. The diagnosis of suspected GERD in infants and children depends on the age and the presenting symptoms. A thorough history, physical examination, and growth charts are sufficient for the evaluation and diagnosis of GERD in most infants with recurrent vomiting or children with regurgitation and heartburn. Additional evaluation may include an upper gastrointestinal series, esophageal pH monitoring, or endoscopy. The goals of GERD management are eliminating symptoms, healing esophagitis, preventing complications, promoting normal weight gain and growth, and maintaining remission. Therapeutic options include lifestyle changes, pharmacologic therapy, and antireflux surgery. Currently available pharmacologic agents for the treatment of GERD include antacids, mucosal protectants, prokinetic agents, and acid suppressants.

KEYWORDS: acid suppressants, antacids, gastroesophageal reflux disease, mucosal protectants, prokinetic agents

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INTRODUCTION

Gastroesophageal reflux refers to the passage of gastric contents including food, acid, and digestive enzymes up into the esophagus. Benign gastroesophageal reflux is so common in infants that a certain amount of spitting up in early infancy is considered normal by most parents and pediatricians. One study found recurrent vomiting to occur in 50% of infants less than three months old, in 67% of four-month-old infants and in 5% of 10- to 12-month-old infants.[1] Another study using pH probes demonstrated reflux in up to 100% of premature neonates.[2] Other studies found similar results by observing reflux symptoms in up to 100% of infants less than three months old and 20%–40% of children less than six months of age. Gastroesophageal reflux appears to be highly age specific as most infants "outgrow" the problem between three and six months of age.[2] In fact, most all gastroesophageal reflux in infants resolves by 12 months of age.[3] The spontaneous resolution of gastroesophageal reflux most likely results from the ability to remain upright after meals, improving muscle tone of the

ABBREVIATIONS: ALTE, apparent life-threatening event; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; H_2RAs, H_2-receptor antagonists; LES, lower esophageal sphincter; PPIs, proton pump inhibitors

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lower esophageal sphincter (LES), and advancing to semi-solid and solid foods. Gastroesophageal reflux disease (GERD) is defined as symptoms or complications that result from reflux.

Some infants appear to experience reflux equal to heartburn that may be expressed as grimacing, crying, tearing, arching of the back, irritability, dysphagia (difficulty swallowing), or odynophagia (painful swallowing). Other signs may include hematemesis, anemia, or failure to thrive.[4] Respiratory symptoms associated with GERD in infants can include cough, wheezing, stridor, aspiration or recurrent pneumonia, and it is one of the causes of an apparent life-threatening event (ALTE) in which the child experiences apparent apnea.[4] Children and adolescents may experience similar symptoms as infants, but more often present with intermittent vomiting, heartburn, chronic cough, or reactive airway disease. Although consistent data is lacking, GERD is considered to be a common aggravating factor in children with asthma.[4,5] Several studies have shown improvements in asthma symptoms in some children treated for reflux.[4,5] Aspirating refluxed contents is especially a problem with neurologically impaired children, often leading to recurrent aspiration pneumonia.[4] Histological changes of the esophageal epithelial lining associated with acid reflux in children include inflammatory cell infiltration, hyperplasia, and metaplasia (from squamous to columnar epithelial cell type, i.e. Barrett's esophagus).[6,7] These changes can lead to endoscopically evident complications including esophagitis, peptic strictures, pseudodiverticuli, Barrett's metaplasia, inflammatory polyps, and rarely perforations or fistulas.[4] The marketing of medications for GERD is now a major business as it is estimated that > 50% of adults will experience weekly symptoms of reflux during their lifetime.[8]

PATHOGENESIS

Reflux symptoms result from exposure of the esophageal mucosa to gastric secretions.[2,4] The severity of the symptoms is thus related to the frequency of reflux, the length of time it takes to clear such material from the esophagus, and the effectiveness of the natural mucosal resistance. Normally, gastric contents are prevented from refluxing by a combination of a healthy LES and extra-esophageal pressure of the diaphragm muscle hiatus through which the esophagus passes. Therefore, reflux may result from abnormal LES function, an abnormal opening in the diaphragm, or both.[9,10] Most evidence suggests the mechanism of reflux is due to transient relaxations of the LES at inappropriate times (i.e., not associated with swallowing).[11] The evolution of gastroesophageal reflux to GERD in children depends on the quantity of the refluxed material and its acidity. An important factor contributing to gastroesophageal reflux in infants is the high volume of fluid intake, up to 180 ml/kg/day (equivalent to ~14 L/day in adults).[12] Children with GERD have more frequent transient LES relaxations not associated with swallowing and greater inhibition of esophageal peristalsis than unaffected controls. The importance of the diaphragm's hiatus in applying external pressure on the LES is recognized as a contributing factor to normal LES function, and misplacement of LES in relation to the hiatus (hiatal hernia) is a known risk factor for developing GERD. Other possible factors in the mechanism of reflux include impairments in gastric emptying, esophageal motility, and saliva production.

DIAGNOSIS

The diagnosis of suspected GERD in infants and children depends on the age and the presenting symptoms. Difficulty can arise in diagnosing GERD particularly in infants because gastroesophageal reflux is a normal functional process, whereas GERD represents a progression to a pathological process. A thorough history, physical exam, and growth charts are sufficient for the evaluation and diagnosis of gastroesophageal reflux in most infants with recurrent vomiting or children with regurgitation and heartburn.[4] Further evaluation is indicated with the presence of warning signs such as bilious emesis, forceful vomiting, hematemesis, diarrhea, constipation, fever, lethargy, seizures, abdominal tenderness, abdominal distention, or failure to thrive.[4]

An upper gastrointestinal (GI) series (swallowed barium as a contrast medium for radiographic examination) is useful for detecting anatomic abnormalities like pyloric stenosis, intestinal malrotation, hiatal hernia, and esophageal strictures, but is not sufficiently sensitive or specific for the diagnosis of reflux.[4] A nuclear scintiscan involves swallowing technetium-labeled food or formula under fluoroscopic exam. A positive scintiscan is

useful as it allows visualization of refluxed food or aspiration of refluxed contents. It also has the advantage of detecting reflux of non-acidic gastric contents. The scintiscan is limited, however, to the time monitored under fluoroscopy, which is usually less than one hour. Thus, the scintiscan has a specificity of 83% to 100%, but the sensitivity is only 15% to 59% when compared to esophageal pH monitoring.[13-16] In contrast, esophageal pH monitoring can detect reflux of acidic gastric contents for 24 hours or more. It is performed by the intranasal placement of a pH electrode into the esophagus. The electrode can measure the pH and the duration of acid exposure to the esophagus. A diary of symptoms can help correlate suspected signs and symptoms with acid reflux. In addition, this technique allows the detection of asymptomatic reflux. There is a strong association of abnormal pH tests and esophagitis; however, the severity of esophagitis does not necessarily correlate with the degree of abnormal pH readings.[17-20] The disadvantages of the pH probe include the discomfort to the patient and the inability to measure reflux of non-acidic gastric contents.[4] Endoscopy and biopsy of the esophageal endothelium can be used to detect esophagitis evidenced by visual changes of the esophageal mucosa or histological changes on biopsy. It is also useful in detecting or excluding other disorders like Barrett's esophagitis, esophageal strictures, eosinophilic esophagitis, or esophagitis from other causes (e.g., infections, allergies, Crohn's disease). Visual changes of the esophagus are often subtle, thus the esophageal biopsy is usually performed during endoscopy.[4]

MANAGEMENT

The goals of GERD management are eliminating symptoms, healing esophagitis, preventing complications, promoting normal weight gain and growth, and maintaining remission. Therapeutic options include lifestyle changes, pharmacologic therapy, and anti-reflux surgery. Most infants with reflux do not require any treatment, thus, monitoring the child's growth, educating parents on the warning signs of GERD, and providing reassurance in uncomplicated cases of gastroesophageal reflux in infants is sufficient.

Lifestyle interventions

Using formulas thickened with rice or pre-thickened formulas may decrease the number of episodes of vomiting.[21] Also, the additional calories from thickening agents can be beneficial in underweight children. Occasionally an infant may have an allergy to the protein in cow's milk. Evidence supports a one or two week trial of hypoallergenic or elemental formula when this is suspected. However, frequent changes in the type or brand of formula is unlikely to have any effect on gastroesophageal reflux and should be avoided.[22-24] Studies have shown that positional changes during and after feedings can improve symptoms of vomiting. Placing infants in the prone (stomach down) position may decrease vomiting, but this position has been associated with an increased risk of sudden infant death syndrome (SIDS) and, thus, is not recommended.[25-27] The position of left side down also appears to reduce symptoms of reflux compared to right side down or supine position, but this is an unstable position, which limits its effectiveness.[28] Raising the head of the bed is a common recommendation in adults with GERD and it has been implied that infants would also benefit from this practice. Intuition would suggest that sitting up in a car seat would improve symptoms; however, this practice appears to flex the hips and increase abdominal pressure, which may worsen reflux and vomiting.[29] Other dietary and lifestyle modifications are usually recommended for older children and adolescents. Obviously, any known food or beverage that exacerbates symptoms should be avoided. Certain foods (e.g., chocolate, peppermint, spicy foods, caffeine, and possibly fatty foods) may relax the LES allowing an increase in reflux symptoms and should be avoided. Alcohol, smoking, and obesity have also been associated with reflux and should be addressed when appropriate.[4]

Pharmacologic therapy

Currently available pharmacologic agents for the treatment of GERD include antacids, mucosal protectants, prokinetic agents, and acid suppressants. Some, but not all of these agents are approved for use in infants and children. The Food and Drug Administration (FDA) allows for the extrapolation of drug safety and efficacy data from adults when the pathophysiological process is similar in children and adults.[30] This is the case with GERD in children above one year of age.[31] Therefore, labeling drugs for GERD in children greater than one year of age involves only dose-

finding studies and the collection of additional safety data before a drug may be approved for pediatric use. However, the FDA does not allow the extrapolation of data from adults to infants less than one year of age.[31] Extensive efficacy and safety data in infants is required before the FDA will approve a drug for the treatment of GERD in this age group. Most drugs have not been used on a long term basis in pediatric patients, although long term safety data in adults are available.

Antacids

Antacids neutralize gastric acid, thus decreasing esophageal exposure to refluxed acidic material. High dose antacid therapy (e.g., magnesium hydroxide, aluminum hydroxide) has been shown to be equal in efficacy to cimetidine for the treatment of esophagitis in children age 2 to 42 months; however, frequent administration is required, and interactions with other drugs are common.[32,33] Aluminum-containing antacids can increase the serum aluminum level in infants to levels that may cause osteopenia, microcytic anemia, and neurotoxicity.[34-36] No published data are available to support the efficacy or safety of currently available antacids (magnesium hydroxide or calcium carbonate) for long term treatment of GERD, although intermittent or short term use for reflux symptoms appears to be safe.[4]

Mucosal protectants

Sodium alginate (Gaviscon; GlaxoSmithKline, Research Triangle Park, NC) forms a protective layer that floats over gastric contents, acting as a barrier to acid reflux. Sucralfate (Carafate; Axcan Scandipharm, Birmingham, AL) forms a protective coat over inflamed mucosal lesions and promotes their healing. There is not sufficient or consistent data to support the efficacy of sodium alginate or sucralfate in the treatment of chronic GERD in children. The only randomized study of sucralfate in children suggests that it may be as effective as cimetidine in the treatment of esophagitis.[37] Sucralfate also contains aluminum. The absorption of aluminum and potential risks of aluminum toxicity in infants and children from sucralfate has not sufficiently been studied.

Prokinetic therapy

Prokinetic agents increase the speed of gastric emptying, improve esophageal peristalsis, and increase basal lower esophageal sphincter pressure, theoretically making these an ideal treatment for reflux. Cisapride is a serotonergic agonist that stimulates GI motility by enhancing the release of acetylcholine at the myenteric plexus. Several studies have shown that cisapride treatment over a four-week period can decrease the symptoms of regurgitation and vomiting in infants and children with reflux.[38-41] Other studies have shown that cisapride can improve esophageal histopathology and pulmonary function in patients with reflux esophagitis and respiratory complications.[38,39] Overall, studies have shown only marginal effectiveness of cisapride in the treatment of GERD in children. Cisapride was associated with serious cardiac arrhythmias in patients with certain risk factors and was removed from the market in 2000. It is now available only on a restricted basis in pediatric patients with refractory GERD.[4]

Metoclopramide (Reglan, Elkins-Sinn) is a dopamine receptor antagonist that stimulates upper GI tract motility. The clinical efficacy of metoclopramide in adults and children has been equivocal.[4] In four randomized controlled studies of metoclopramide in children, two reported a decrease in the frequency and volume of vomiting, but two reported symptoms to be no better or worse than the placebo treated group.[42-45] The central nervous system adverse effects of metoclopramide limit its use, most notably extrapyramidal side effects.

Other motility agents that have been evaluated in children and infants include bethanechol, domperidone, and erythromycin. Bethanechol (Urecholine, Merck, West Point, PA) is a cholinergic agonist that directly stimulates muscarinic receptors lowering GI tract motility.[46-48] Domperidone (Motilium, Janssen, Titusville, NJ) is a dopamine antagonist but, unlike metoclopramide, does not readily enter the central nervous system. There are several small studies demonstrating mixed results in the treatment of gastroesophageal reflux.[49,50] Erythromycin is a motilin receptor agonist that increases motor activity in the stomach and small intestine. Erythromycin has been used in infants with intestinal dysmotility and feeding intolerance.[51,52] Despite the apparent direct effects on gastric motility of these prokinetic agents, numerous studies have failed to consistently demonstrate that prokinetic agents reduce the frequency of transient relaxations of the LES or reduce the frequency of epi-

Table 1. Histamine Receptor Antagonist FDA-Approved Dosing

Drug	Approved Age	Pediatric		Adult	
		Doses (Max Dose)	Interval	Doses*	Interval
Cimetidine(Tagamet)	≥ 16 yr	40 mg/kg/d(400 mg QID)	TID or QID	800–1200 mg	QD-TID
Ranitidine(Zantac)	≥ 1 mo	5-10 mg/kg/d(150 mg QID)	TID	300 mg	BID
Nizatidine(Axid)	> 12 yr	10 mg/kg/d(150 mg BID)	BID	150 mg 300 mg	BID HS
Famotidine(Pepcid)	≥ 1 yr	1 mg/kg/d(40 mg BID)	BID	20 mg	BID

**mg/dose.*

sodes of acid reflux, and none are approved by the FDA for use as motility agents in infants or children.[4]

Histamine H_2-receptor antagonists

Histamine, acetylcholine, and gastrin are chemical signals that stimulate gastric parietal cells to produce acid in response to meals. Histamine acts via the histamine H_2-receptor on the parietal cell. Histamine H_2-receptor antagonists (H_2RAs) are used to decrease acid secretion of gastric parietal cells by competitively inhibiting the action of histamine. The efficacy of H_2RAs (cimetidine, ranitidine, famotidine, nizatidine) in reducing symptoms and promoting healing of esophageal mucosa has been demonstrated in numerous adult placebo-controlled trials. There are fewer trials in children, but data support their use and safety in this population as well.[4] In randomized placebo controlled studies, cimetidine 30–40 mg/kg/day orally and nizatidine 10 mg/kg/day orally were significantly more effective than placebo in healing esophagitis and reducing symptoms in infants and children.[53,54] In other studies, the duration of gastric pH < 4 was reduced 44% with ranitidine 2 mg/kg/dose orally BID and was reduced by 90% with TID dosing.[55] Although there are no randomized controlled studies using ranitidine and famotidine for the treatment of esophagitis in children, experts believe the efficacy and safety are similar to cimetidine and nizatidine.[4] Dosing information for H_2RAs is listed in Table 1. The dose of H_2RAs should be decreased for renal insufficiency.[4] A limitation to the continuous use of H_2RAs is the development of tolerance to the pH raising effects.[55,56]

The effects of H_2RAs can decrease the absorption of certain drugs. Drugs like ketoconazole, itraconazole, ampicillin, and digoxin require an acidic environment for absorption, thus, drugs that raise the gastric pH would decrease their absorption. In addition, cimetidine inhibits cytochrome P450 enzymes and may interfere with the metabolism of other drugs like phenytoin, propranolol, theophylline, and warfarin. Ranitidine's interaction with the cytochrome enzymes is different than cimetidine's, and it interacts minimally with other drugs. The other H_2RAs do not inhibit cytochrome enzymes. Other side effects include headache, rash, nausea, vomiting, diarrhea, constipation, fatigue, and irritability.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) inhibit gastric acid secretion from gastric parietal cells by irreversibly binding to the hydrogen/potassium ATPase proton pump, thus blocking the ion exchange necessary for hydrochloric acid production. These agents inhibit acid secretion by the parietal cells despite stimulation by histamine, acetylcholine, or gastrin, making these agents more effective than H_2RAs in reducing acid secretion, relieving GERD symptoms, healing esophagitis, and maintaining remission.[57-59]

PPIs are activated by acid in the canaliculi of parietal cells and are most effective when taken about 30 minutes before breakfast so that peak plasma concentrations coincide with meal-stimulated acid secretion. These drugs are less effective during fasting conditions when acid secretion is lower and when administered concomitantly with H_2RAs. In contrast, gastric acid will inactivate PPIs prior to absorption requiring them to have an enteric coating to allow the drug to pass through the stomach to be absorbed in the small intestine where there is less acid. Like H_2RAs, PPIs can interact with other drugs that require a low pH for absorption (i.e., ketoconazole, itraconazole, ampicillin, and digoxin). PPIs are metabolized by cytochrome P450 enzymes and could interact with other drugs that are metabolized by these enzymes. Omeprazole inhibits the

Table 2. Proton Pump Inhibitor FDA-Approved Dosing

PPI	Approved Age	Pediatric Dose	Adult Dose*
Omeprazole (Prilosec)	2–16 yr	≤ 20 kg, 2–5 years: 10 mg QD > 20 kg, 6–16 years: 20 mg QD	20–40 mg
Lansoprazole (Prevacid)	1–17 yr	≤ 30 kg: 15 mg QD > 30 kg: 30 mg QD	15–30 mg
Pantoprazole (Protonix)	>18 yr†	40 mg QD or BID	40 mg
Rabeprazole (Aciphex)	> 18 yr	None	20 mg
Esomeprazole (Nexium)	> 18 yr	None	20–40 mg

**all doses given QD.*
†patients 11–17 yr have been studied.

metabolism of phenytoin, diazepam and warfarin. No dose adjustment is necessary for renal impairment, but these agents should be used with caution in patients with hepatic impairment. PPIs are well tolerated but may rarely be associated with diarrhea, abdominal pain, nausea, or headache.[60]

The use of PPIs in children has become more popular in recent years. Omeprazole and lansoprazole were the first PPIs approved for use in children, and long term use in children appears safe and effective. They are available as capsules containing enteric coated granules that may be sprinkled in applesauce or fruit juice and as oral packets that can be used to prepare a suspension. These enteric coated granules should not be crushed or chewed, as it will disrupt the delayed release characteristics of the enteric coating. Lansoprazole is also available as an orally disintegrating tablet containing enteric coated microgranules. A simple suspension for oral or feeding tube administration can be prepared using the granules from omeprazole or lansoprazole capsules and 10 mL of sodium bicarbonate.[61] Esomeprazole, rabeprazole, and pantoprazole are available as enteric coated tablets that also should not be crushed or chewed. Pantoprazole and lansoprazole are available in an intravenous form for use in hospitalized patients who cannot take anything by mouth. Dosing guidelines for the PPIs are summarized in Table 2.

Adult studies have shown that PPIs are superior to H_2RAs in relieving symptoms, healing esophagitis, and maintaining remission of esophagitis. There are no randomized controlled trials comparing PPIs and standard dose H_2RAs. One study demonstrated comparable effectiveness of 8 weeks of omeprazole (40 mg/kg/day) and very high dose ranitidine (20 mg/kg/day).[62] Other case series of pediatric patients with esophagitis resistant to H_2RAs found omeprazole was superior in improving symptoms and healing esophagitis.[63-66] Healing of esophagitis was demonstrated by endoscopy in infants taking omeprazole who had previously failed treatment with H_2RAs, cisapride, and antacids.[66] Esophageal pH monitoring revealed that the number of postprandial reflux episodes decreased from 36 to 8.5 in a study of 10 children with severe esophagitis who received omeprazole 20 mg or 40 mg once daily. Six of these 10 patients experienced relapse after discontinuing omeprazole.[57] Pediatric patients required larger mg/kg doses of omeprazole for healing chronic severe esophagitis compared to adult patients. Other studies suggested that children metabolize PPIs more rapidly than adults, supporting the use of higher mg/kg doses in children.[67] The recommended dose for omeprazole is up to 1 mg/kg/day in infants.[4] In a study of 115 infants receiving omeprazole 0.5, 1.0, or 1.5 mg/kg/day for 8 weeks, the time to onset of symptom relief was shorter with higher doses than with the lower dosages.[68]

Lansoprazole has also been shown to improve symptoms and promote healing of esophagitis in children 4 months to 15 years of age with GERD refractory to H_2RAs.[69-71] One study demonstrated that higher doses (1.3–1.5 mg/kg/day) had higher healing rates compared to lower doses (0.8–1 mg/kg/day).[69] Another study that measured the 24-hour intragastric pH in children ages 18 days to 14 years with GERD found that multiple daily doses provided greater acid suppression than did single daily doses.[71] All agents in this class are believed to have similar effectiveness, but comparative studies and studies of newer agents like pantoprazole and rabeprazole in infants and children are not yet available.

Surgical Management

Anti-reflux surgery is often considered for children with GERD refractory to medical management and is one of the most common pediatric

surgeries performed in the United States. The most common anti-reflux surgical procedure in pediatric patients is the Nissen fundoplication, which involves wrapping and suturing folds of the fundus around the lower esophagus to increase the LES pressure. It can be performed by a traditional open laparotomy, but is more often performed laparoscopically. Indications for anti-reflux surgery include the presence of life-threatening aspiration, apnea, anatomic abnormalities, or inadequate response to medical therapy that has been optimized. Common case scenarios that may benefit from fundoplication include patients with chronic aspiration, failure to thrive, chronic esophagitis, strictures, or Barrett's esophagus who have failed medical therapy. Many children with neurologic impairments have increased risks of reflux and require surgical management.[4] Complete symptom relief following fundoplication has varied from 57% to 92% of cases.[4] However, symptomatic relief is not always permanent, and reoperation rates of 3% to 18.9% have been reported. The reported overall surgical complication rate has varied between 2.2% and 45%.[4,72,73] The most commonly reported complications include release of the wrap, small bowel obstruction, infection, atelectasis or pneumonia, perforation, persistent esophageal stricture, and esophageal obstruction. Neurologically impaired recipients of a fundoplication tend to have much higher failure and complication rates from the procedure.[74,75] Laparoscopically performed fundoplication usually has the benefit of shortened hospitalization, but studies comparing laparoscopic with open procedures are lacking. Reoperation rates appear to be similar between open and laparoscopic Nissen fundoplication; although, there is some evidence that repeat laparoscopic surgeries were required earlier than repeat open procedures (7 months versus 18 months).[74,75] Newer definitions of optimal medical management and the lack of trials comparing anti-reflux surgery to pharmacologic therapy make it difficult to compare the two treatment approaches at this time.

TREATMENT APPROACH

The first step in the management of GER in infants and children is to use appropriate diagnostic tests, when necessary, to rule out the possibility of other disorders. In general, when reflux is suggested by symptoms and no warning signs are present, lifestyle and dietary changes are initially employed with or without pharmacologic therapy. Numerous studies in adults have shown PPIs to be superior to H_2RAs in providing symptomatic relief, promoting healing of esophagitis and maintaining remission of GERD.[4] When starting drug therapy, two approaches have been described. A "step-up" approach starts with an H_2RA for one or two months, and then increasing the dose or changing to a PPI if there is poor response. In a "step-down" approach the patient is started on a PPI and after a month or two of controlled symptoms, the dose or frequency of the PPI is reduced or the drug is changed to an H_2RA for maintenance therapy. The step approach was questioned by a recent adult study comparing four treatment strategies: a) H_2RA alone (ranitidine 150 mg BID × 20 weeks), b) PPI alone (lansoprazole 30 mg QD × 20 weeks), c) the step-up approach (ranitidine 150 mg BID × 12 wks, then lansoprazole 30 mg QD × 8 weeks), d) and the step-down approach (lansoprazole 30 mg × 12 weeks, then ranitidine 150 mg BID × 8 weeks). The results showed that the median heartburn severity score was lower for the continuous PPI therapy group than for the other groups.[76] A cost-utility analysis found empiric treatment with either PPIs or H_2RAs is more cost effective than diagnostic testing with endoscopy or upper GI series. The estimated cost per year from each strategy was: $1,230 for H_2RA, $1,411 for PPI, $1,598 for UGI series, and $2,159 for endoscopy.[77] From these adult studies, it is reasonable to extrapolate evidence supporting empiric treatment of pediatric patients with GERD without alarm signs, and a rational choice would be to use PPIs for more severe symptoms and use H_2RAs for mild to moderate symptoms. With moderate to severe GERD not responsive to empiric PPI therapy, the dose of PPIs may be increased, but referral to the gastroenterologist is warranted to eliminate causes other than GERD and evaluate the need for possible surgical treatment.

It is difficult to apply adult guidelines to pediatric patients, as most reflux in infants is self-limited and most reflux in adults is a chronic problem. Cost benefit analyses and empiric treatment trials in the pediatric population are lacking. Also, the most recognized forms of GER in infants are uncomplicated regurgitation (the happy spitter) in which there is no evidence that pharmacologic

therapy changes the natural history, and reflux with alarm signals (poor weight gain, hematemesis, irritability, etc.) in which most experts would recommend a pH probe, upper gastrointestinal series, or endoscopy with biopsy to confirm the diagnosis. In general, most infants with GER need only reassurance and lifestyle changes with close following of weight gain. Persistent vomiting or evidence of pain from reflux warrants a trial of thickened formula, a trial of hypoallergenic formula, or possibly a trial of acid suppression starting with an H_2RA, with or without an endoscopy, pH probe monitoring, or upper GI series. Evaluating infants with vomiting and poor weight gain starts with assessing calories consumed and often requires an upper GI series followed by an endoscopy with biopsy. A trial of thickened or hypoallergenic formula and acid suppression with an H_2RA or PPI would then be started if gastritis or reflux esophagitis were confirmed. Older children and adolescents with a history of chronic heartburn can begin empiric acid suppression therapy. Confirmed reflux esophagitis can be treated with higher doses of PPIs or, rarely, fundoplication. As mentioned previously, there is an apparent association between GER and some persistent asthma. A two- or three-month trial of high dose H_2RA or PPI therapy is appropriate in asthmatics with persistent symptoms despite optimal pulmonary evaluation and treatment.[4]

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REFERENCES

1. Nelson SP, Chen EH, Syniar GM, Christoffel KK. 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.
2. Gold BD, Freston JW. Gastroesophageal reflux in children: pathogenesis, prevalence, diagnosis, and role of proton pump inhibitors in treatment. Paediatr Drugs 2002;4:673-85.
3. Nelson SP, Chen EH, Syniar GM, Christoffel KK. One year follow-up of symptoms of gastroesophageal reflux during infancy. Pediatric Practice Research Group. Pediatrics 1998;102:E67.
4. Rudolph CD, Mazur LI, Liptalk GS, Baker RD, Boyle JT, Colletti RB, et al. North American Society for Pediatric Gastroenterology and Nutrition. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 2001;32 Suppl 2:S1-31.
5. Harding SM. Gastroesophageal reflux: a potential asthma trigger. Immunol Allergy Clin N Am 2005;25:141-8.
6. Hassall E. Co-morbidities in childhood Barrett's esophagus. J Pediatr Gastroenterol Nutr 1997;25:255-60.
7. Hassall E. Columnar-lined esophagus in children. Gastroenterol Clin North Am. 1997;26:533-48.
8. Sonnenberg,A, Indomi JM, Becker LA. Economic analysis of stepwise treatment of gastrooesophageal reflux disease. Aliment Pharmacol Ther 1999;13:1003-13.
9. Fankalrud EW, Ament ME. Gastroesophageal reflux in childhood. Curr Probl Surg 1996;33:1-70.
10. Mittal RK, Balaban RH. The esophagogastric junction. N Engl J Med 1997;336:924-32.
11. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children. Gastroenterology 1997;113:399-408.
12. Poets CF. Gastroesophageal reflux: A critical review of its role in preterm infants. Pediatrics 2004;113:e128-32.
13. Seibert JJ, Byrne WJ, Euler AR, Latture T, Leach M, Campbell M. Gastroesophageal reflux-the acid test: scintigraphy or the pH probe? Am J Roentgenol 1983;140:1087-90.
14. Arasu TS, Wyllie R, Fitzgerald JF, Franken EA, Siddiqui AR, Lehman GA**,** et al. Gastroesophageal reflux in infants and children comparative accuracy of diagnostic methods. J Pediatr 1980;96:798-803.
15. 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.
16. 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.

17. Euler AR, Byrne WJ. Twenty-four-hour esophageal intraluminal pH probe testing: a comparative analysis. Gastroenterology 1998;80:957-61.
18. Vandenplas Y, Franckx-Goossens A, Pipeleers-Marichal M, Derde MP, Sacre-Smits L. Area under pH 4: advantages of a new parameter in the interpretation of esophageal pH monitoring data in infants. J Pediatr Gastroenterol Nutr 1989;9:34-9.
19. Cucchiara S, Staiano A, Gobio Casali L, Boccieri A, Paone FM. Value of the 24 hour intraesophageal pH monitoring in children. Gut 1990;31:129-33.
20. Biller JA, Winter HS, Grand RJ, Allred EN. Are endoscopic changes predictive of histologic esophagitis in children? J Pediatr 1983;103:215-8.
21. Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. J Pediatr 1987;110:181-6.
22. Iacono G, Carroccio A, Cavataio F, Soresi M, Tumminello M, Carroccio A. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol 1996;97:822-7.
23. Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Campagna P, et al. Gastroesophageal reflux associated with cow's milk allergy in infants: which diagnostic examinations are useful? Am J Gastroenterol 1996;91:1215-20.
24. Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Carroccio A. Clinical and pH-metric characteristics of gastro-esophageal reflux secondary to cow's milk protein allergy. Arch Dis Child 1996;75:51-6.
25. Meyers WF, Herbst JJ. Effectiveness of positioning therapy for gastroesophageal reflux. Pediatrics 1982;69:768-72.
26. 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;1:356-61.
27. Oyen N, Markestad T, Skaervan R, Irgens LM, Helweg-Larsen K, Alm B, 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.
28. Tobin JM, McCloud P, Cameron DJ. Posture and gastroesophageal reflux: a case for left lateral positioning. Arch Dis Child 1997;76:254-8.
29. Orenstein SR, Whitington PF, Orenstein DM. The infant seat as treatment for gastroesophageal reflux. N Engl J Med 1983;309:760-3.
30. Rodriguez WJ, Roberts R, Murphy D. Current regulatory policies regarding pediatric indications and exclusivity. J Pediatr Gastroenerol Nutr 2003;37:S40-45.
31. www.fda.gov/ohrms/dockets/ac/02/briefing/3870B1_03_Sample%20Request.pdf. Accessed 6/29/05.
32. Cucchiara S, Staiano A, Romaniello G, Capobianco S, Auricchio S. Antacids and cimetidine treatment for gastro-esophageal reflux and peptic esophagitis. Arch Dis Child 1984;59:842-7.
33. Iacono G, Carroccio A, Montalto G, Cavataio F, Ippolito S, Kazmierska I, Balsamo V. Magnesium hydroxide and aluminum hydroxide in the treatment of gastroesophageal reflux. Minerva Pediatr 1991;43:797-800.
34. Tsou VM, Young RM, Hart MH, Vanderhoof JA. Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. Pediatrics 1991;87:148-51.
35. Woodard-Knight L, Fudge A, Teubner J, Simmer K. Aluminum absorption and antacid therapy in infancy. J Paediatr Child Health 1992;28:257-9.
36. Aluminum toxicity in infants and children. American Academy of Pediatrics, Committee on Nutrition. Pediatrics 1996:97:413-6.
37. 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.
38. Cucchiara S, Staiano A, Boccieri A, De Stefano M, Capozzi C, Manzi G, 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.
39. Cucchiara S, Staiano A, Capozzi C, Di Lorenzo C, Boccieri A, Auricchio S. Cisapride for gastroesophageal reflux and peptic oesophagitis. Arch Dis Child 1987;62:454-7.
40. Scott RB, Ferreira C, Smith L, et al. Cisapride in pediatric gastroesophageal reflux. J Pediatr Gastroenterol Nutr 1997;25:499-506.

41. Cohen RC, O'Loughlin EV, Davidson GP, Moore DJ, Lawrence DM. Cisapride in the control of symptoms in infants with gastroesophageal reflux: a randomized, double-blind, placebo-controlled trial. J Pediatr 1999;134:287-92.
42. Leung C, Lai W. Use of metoclopramide for the treatment of gastroesophageal reflux in infants and children. Curr Ther Res 1984;36:911-15.
43. 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.
44. Machida HM, Forbes DA, Gall DG, Scott RB**.** Metoclopramide in gastroesophageal reflux of infancy. J Pediatr 1988;112:483-7.
45. Bellissant E, Duhamel JF, Guillot M, Pariente-Khayat A, Olive G, Pons G**.** The triangular test to assess the efficacy of metoclopramide in gastroesophageal reflux. Clin Pharmacol Ther 1997;61:377-84.
46. Euler AR. Use of bethanechol for the treatment of gastroesophageal reflux. J Pediatr 1980;96:321-4.
47. Orenstein SR, Lofton SW, Orenstein DM. Bethanechol for pediatric Gastroesophageal reflux: A prospective, blind, controlled study. J Pediatr Gastroenterol Nutr 1986;5:549-555.
48. Sondheimer JM, Arnold GL. Early effects of bethanechol on the esophageal motor function in infants with gastroesophageal reflux. J Pediatr Gastroenterol Nutr 1986;5:47-51.
49. Bines JE, Quinlan JE, Treves S, Kleinman RE, Winter HS. Efficacy of domperidone in infants and children with gastroesophageal reflux. J Pediatr Gastroenterol Nutr 1992;14:400-5.
50. Grill BB, Hillemeier AC, Semeraro LA, McCallum RW, Gryboski JD. Effects of domperidone therapy on symptoms and upper gastrointestinal motility in infants with gastroesophageal reflux. J Pediatr 1985;106:311-16.
51. Stenson BJ, Middlemist L, Lyon AJ. Influence of erythromycin on establishment of feeding in preterm infants: Observation from a randomized controlled trial. Arch Dis Child Fetal Neonatal Ed 1998;79:F12-14.
52. Costalos C, Gounaris A, Varhalama E, et al. Erythromycin as a prokinetic agent in preterm infants. J Pediatr Gastroenterol Nutr 2002;34:23-5.
53. Cucchiara S, Gobio-Casali L, Balli F, Magazzu G, Staiano A, Astolfi R**,** et al. Cimetidine treatment of reflux esophagitis in children: an Italian multicentric study. J Pediatr Gastroenterol Nutr 1989;8:150-6.
54. Simeone D, Caria MC, Miele E, Staiano A. Treatment of childhood peptic esophagitis: a double-blind placebo-controlled trial of nizatidine. J Pediatr Gastroenterol Nutr 1997;25:51-5.
55. Sutphen JL, Dillard VL. Effect of ranitidine on twenty-four-hour gastric acidity in infants. J Pediatr 1989;114:472-4.
56. Lachman L, Howden CW. Twenty-four-hour intragastric pH: tolerance within 5 days of continuous ranitidine administration. Am J Gastroenterol 2000;95:57-61.
57. Cucchiara S, Minella R, Campanozzi A, Salvia G, Borrelli O, Ciccimarra E, Emiliano M. Effects of omeprazole on mechanisms of gastroesophageal reflux in childhood. Dig Dis Sci 1997;42:293-9.
58. Martin PB, Imong SM, Krischer J, Noblett HR, Sandhu BK. The use of omeprazole for resistant oesophagitis in children. Eur J Pediatr Surg 1996:6:195-7.
59. Kato S, Ebina K, Fujii K, Chiba H, Nakagawa H. 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.
60. McEvoy GK, ed. Omeprazole. In: AHFS Drug Information 2002. Bethesda, MD: American Society of Health-System Pharmacists 2002:2859-63.
61. Prevacid package insert. Lake Forest, IL. TAP Pharmaceuticals. September 2002.
62. Cucchiara S, Minella R, Iervolino MR, Franco MT, Campanozzi A, Franceschi M, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Arch Dis Child 1993;69:655-9.
63. Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. J Pediatr 1993;123:148-54.

64. De Giacomo C, Bawa P, Franceschi M, Luinetti O, Fiocca R. Omeprazole for severe reflux esophagitis in children. J Pediatr Gastroenterol Nutr 1997;24:528-32.
65. Alliet P, Raes M, Bruneel E, Gillis P. Omeprazole in infants with cimetidine-resistant peptic esophagitis. J Pediatr 1998;132:352-4.
66. Strauss RS, Calenda KA, Dayal Y, Mobassaleh M. Histological esophagitis: clinical and histological response to omeprazole in children. Dig Dis Sci 1999;44:134-9.
67. Israel DM, Hassall E. Omeprazole and other proton pump inhibitors: pharmacology, efficacy, and safety, with special reference to use in children. J Pediatr Gastroenterol Nutr 1998;27:568-79.
68. Kraynak RA, Kuczmanski M, Levine D. Omeprazole treatment of GERD symptoms in infants [abstract]. J Pediatr Gastroenterol Nutr 2001;33:424.
69. Welage LS, Beradi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. J Am Pharm Assoc 2000;40:52-62.
70. Franco MT, Salvia G, Terrin G, Spadaro R, De Rosa I, Iula VD, Cucchiara S. Lansoprazole in the treatment of gastro-esophageal reflux disease in childhood. Dig Liver Dis 2002;32:660-6.
71. Faure C, Michaud L, Shaghaghi EK, Popon M, Laurence M, Mougenot JF, et al. Lansoprazole in children: Pharmacokinetics and efficacy in reflux oesophagitis. Aliment Pharmacol Ther 2001;5:1397-402.
72. Tran A, Rey E, Pons G, Pariente-Khayat A, D'Athis P, Sallerin V, Dupont C. Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. Clin Pharmacol Ther 2002;71:359-67.
73. Tovar JA, Olivares P, Diaz M, Pace RA, Prieto G, Molina M. Functional results of laparoscopic fundoplication in children. J Pediatr Gastroenterol Nutr 1998;26:429-31.
74. Rothenberg SS. Experience with 220 consecutive laparoscopic Nissen fundoplications in infants and children. J Pediatr Surg 1998;33:274-8.
75. Fonkalsrud EW, Ashcraft KW, Coran AG, Ellis DG, Grosfeld JL, Tunell WP, Weber TR. Surgical treatment of gastroesophageal reflux in children: a combined hospital study of 7467 patients. Pediatrics 1998;101:419-22.
76. Howden CW, Henning JM, Huang B, Lukasik N, Freston JW. Management of heartburn in a large, randomized, community-based study: Comparison of four therapeutic strategies. Am J Gastroenterol 2001;96:1704-10.
77. Heudebert GR, Marks R, Wilcox CM, Centor RM. Choice of long-term strategy for the management of patients with severe esophagitis: a cost-utility analysis. Gastroenterology 1997;112:1078-86.