Review Article

Gastroesophageal reflux in children

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Summary

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus and is a normal physiologic process occurring several times per day in healthy individuals. In older children and adolescents, history and physical examination may be sufficient to diagnose gastroesophageal reflux disease (GERD).

Endoscopically-visible breaks in the distal esophageal mucosa are the most reliable evidence of reflux esophagitis. Esophageal pH monitoring quantitatively measures esophageal acid exposure. Combined multiple intraluminal impedance and pH monitoring (MII-pH) measures acidic, weakly acidic, non-acidic and gas reflux episodes. MII-pH is superior to pH monitoring alone for evaluation of the temporal relationship between symptoms and GER. Barium contrast radiography is not useful for the GERD diagnosis, but may be used to detect anatomic abnormalities. Parental education, guidance, and support are always required and usually sufficient to manage healthy, thriving infants with symptoms likely due to physiologic GER. Use of a thickened, commercially available anti-regurgitation formula by preference, may decrease visible regurgitation. Buffering agents, alginate and sucralfate, can be beneficial if used as needed for occasional heartburn. Proton-pump inhibitors (PPIs) are superior to histamine-2 receptor antagonists (H[2]RAs). **[Paediatr Indones. 2011;51:361-71]**.

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Gastroesophageal reflux (GER) episodes occur most often during transient relaxations of the lower esophageal sphincter (LES) unaccompanied by swallowing, permitting gastric contents to flow into the esophagus. Most episodes of physiologic GER last <3 minutes, occur in the postprandial period, and cause few or no symptoms.[1-3] In contrast, Gastroesophageal reflux disease (GERD) is present when GER causes troublesome symptoms and/or complications.[1]

Regurgitation is the passage of refluxed gastric contents into the pharynx or mouth, and sometimes followed by expectoration. Other terms, such as 'spitting-up' and 'spilling,' are considered equivalent to regurgitation. Regurgitation resolves spontaneously in most healthy infants by 12-14 months of age. Alterations in protective mechanisms allow physiologic reflux to become disease, such as insufficient clearance and buffering of refluxate, delayed gastric emptying, abnormalities in epithelial restitution and repair, and decreased neural protective reflexes of the

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aero-digestive tract. Erosive esophagitis, by itself, may promote esophageal shortening, a phenomenon having greater impact in infants due to their shorter esophageal length.[4] The pathophysiology of GERD is considered to be similar in people of all ages.

Diagnosis

The diagnosis of GERD is often made clinically, based upon signs or symptoms normally associated with GER (**Table 1**). Symptom descriptions are unreliable in infants and children less than 8 to 12 years of age. Tests are able to document the presence of (pathologic) reflux or its complications, establish an association or sometimes even a causal relationship between reflux and symptoms, evaluate therapy and exclude other conditions. However, no single test addresses all these questions. Therefore, tests must be carefully selected.

Table 1. Signs and symptoms associated with gastro-esophageal reflux[2]

Signs	Esophagitis, esophageal stricture
	Barrett's esophagus, laryngeal inflammation
	Recurrent pneumonia
	Anemia, dental erosion
	Feeding refusal
	Dystonic neck posturing (Sandifer syndrome)
	Apnea spells , apparent life-threatening events
Symptoms	Recurrent regurgitation with/without vomiting
	Weight loss or poor weight gain
	Irritability in infants
	Ruminative behavior
	Heartburn or chest pain
	Hematemesis
	Dysphagia, odynophagia
	Wheezing, stridor, cough, hoarseness

History and physical examination

Signs and symptoms associated with reflux are non-specific. The overlap between reflux-like symptoms of cow milk allergy and that of GERD has recently become an area of interest. Heartburn and irritability may be caused by GER, as well as by other conditions. There is no relation between the severity of symptoms and the degree of abnormality in investigations.[5,6]

Experts feel that the diagnosis of GERD can be made in adolescents and adults presenting with typical heartburn symptoms. However, a clinical diagnosis based on a history of heartburn cannot be used in children under the age of 10 years or in non-verbal adolescents, as such individuals cannot communicate reliably. The verbal child can express pain, but descriptions of quality, intensity, location and severity are generally unreliable until at least 8 to 12 years of age.[7] Patient-reported questionnaires based on clusters of symptoms have been developed. It is debatable whether these are truly helpful for the individual patient. An important advantage of questionnaires, though, is the standardization and monitoring of patients.

Motility studies

Esophageal manometry measures esophageal peristalsis, upper and lower esophageal sphincter pressures and the coordinated function of these structures during swallowing. Manometric studies are critical to identifying transient lower esophageal sphincter relaxations (TLESR) as a causative mechanism for GERD.[8] However, GERD cannot be diagnosed by esophageal manometry.

Investigations that visualise (postprandial) reflux

Barium contrast radiography

The upper gastrointestinal (GI) series is neither sensitive nor specific for diagnosing GERD. The sensitivity, specificity and positive predictive value of a barium contrast study, range from 29-86%, 21-83% and 80-82%, respectively, when compared to esophageal pH monitoring.[1] The brief duration of the upper GI series produces false negative results, while the frequent occurrence of non-pathological reflux during the examination itself may induce false positive results. However, the upper GI series is useful for detecting anatomic abnormalities.

Nuclear scintigraphy

Nuclear scan is useful for evaluating only postprandial reflux, and demonstrating reflux independent of

gastric pH. Scintigraphy can provide information about gastric emptying, which may be delayed in children with GERD.[9] A lack of standardized techniques and the absence of age-specific normal ranges limit the utility of this test. Limited data has suggested that pulmonary aspiration may be detected during a one-hour scintigraphic study, or on images obtained up to 24 hours after administration of the radionuclide.[10] However, this data has not been reproduced, and aspiration of both gastric contents and saliva also occurs in healthy adults during deep sleep.[11]

Esophageal and gastric ultrasonography

Ultrasonography is not recommended as a test for GERD, but it can provide information not available through other technologies. Ultrasonography of the GE junction can detect fluid movements over short periods of time, and thereby detect non-acid reflux events.

Investigations that measure intra-esophageal reflux

Esophageal pH monitoring

By convention, a drop in intra-esophageal pH to less than 4.0 is considered to correspond to an acid reflux episode. This pH cut-off was initially chosen because heartburn induced by acid perfusion of the esophagus in adults generally occurs at pH < 4.0.[12] Slow electrode response times (antimony electrodes being the slowest) do not substantially alter the assessment of total reflux time, but may affect the accuracy of correlation between symptoms and reflux episodes.[13] It has been shown in adults and children that the percentage of time with acid reflux differs about 50% between glass and antimony electrodes. Recently, wireless sensors that can be clipped to the esophageal mucosa during endoscopy have allowed pH monitoring without a nasal cannula, for up to 48 hours. These sensors are not commercially available worldwide. An abnormal reflux index (RI) is more frequently observed in adults with erosive esophagitis than in normal adults, or in those with non-erosive reflux disease, but there is substantial overlap among groups.[14] In pediatric patients, the calculated area

under the pH 4.0 curve has been associated with erosive esophagitis.[15]

The reflux index (percentage of the entire record when esophageal pH is <4.0) is the most commonly used summary score. Several scoring systems for pH monitoring studies have been developed,[16-18] but no system is clearly superior for measuring the RI.[1] The normal pediatric ranges previously in general use were obtained using glass electrodes, but this data correlated poorly with that obtained with antimony electrodes now in common use. The reproducibility of pH studies has been contradictory.

Oropharyngeal pH monitoring has been developed as a new way to diagnose supra-esophageal gastric reflux (SEGR), but has not been well validated. Potential oropharyngeal (OP) events have been identified by the conventional pH threshold of <4 and by the following alternative criteria: (i) relative pH drop >10% from 15-min baseline and (ii) absolute pH drop below thresholds of <5.5, 5.0, and 4.5. Application of alternative pH criteria increases the identification of potential OP pH events, however, a higher proportion of OP events showed no temporal correlation to GER (45-81%), compared to the conventional definition of pH <4 (40%).[19] Oropharyngeal pH monitoring without concurrent esophageal measurements may lead to overestimating the presence of SEGR in children.[19]

Monitoring for bilirubin

Continuous monitoring of biluribin in the esophagus has been suggested as a means of detecting esophageal reflux of duodenal juice or duodeno-gastroesophageal reflux (DGER). Duodenal juice components appear to damage the esophagus in a pH-dependent manner.[20] However, technical difficulties related to investigation conditions resulted in abandonment of this technique.

Combined multiple intraluminal impedance and pH monitoring (MII-pH)

MII is a procedure for measuring the movement of fluids, solids and air in the esophagus.[21] MII and pH electrodes are combined on a single catheter. The relationship between weakly acidic reflux and GERD symptoms requires clarification. Measurement of

other parameters, such as symptom index (SI) or symptom association probability (SAP), may be of additional value to prove symptoms association with reflux. Whether combined esophageal pH and impedance monitoring will provide useful measurements that vary directly with disease severity, prognosis and response to therapy in pediatric patients has yet to be determined. MII-pH measurements provide more information than pH monitoring alone.[22]

Endoscopy and biopsy

Upper gastrointestinal tract endoscopy with biopsies is the only method to reliably diagnose GERD with esophageal manifestations, such as erosive esophagitis or Barrett's esophagus. Macroscopic lesions associated with GERD include esophagitis, erosions, exudate, ulcers, strictures, hiatal hernia, areas of esophageal metaplasia, and polyps. Recent guidelines define reflux esophagitis as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the GE junction.[23] The Hetzel-Dent classification has been used in several pediatric studies,[24] while the Los Angeles classification is generally used for adults, although it is also suitable for children. The presence of endoscopically normal esophageal mucosa does not exclude non-erosive reflux disease. Esophagitis may also be secondary to other diseases.

Although it is likely that esophagitis is mainly caused by GERD, other disorders such as eosinophilic esophagitis (EE), Crohn's disease, infections (*Candida albicans, Herpes simplex, cytomegalovirus)*, bulimia, pill-induced, graft-versus-host disease, caustic ingestion, post-sclerotherapy/banding, radiation/chemotherapy, connective tissue disease, bullous skin diseases, or lymphoma may also be culprits.[25] EE and GERD have very similar signs and symptoms, and endoscopy with biopsy is able to best distinguish these conditions. A major difference is that EE is not generally an erosive disease, but has its own typical endoscopic features, such as speckled exudates, trachealization of the esophagus, or linear furrowing. When eosinopilic esophagitis is considered as part of the differential diagnosis, it is advisable to take esophageal biopsies from the proximal and distal esophagus.[26] Mucosal eosinophilia may be present in the esophageal mucosa

in asymptomatic infants <1 year of age.[27] In infants, the eosinophilic infiltrate may be due to cow's milk protein allergy.

When esophageal biopsies show columnar epithelium, the term Barrett's esophagus (BE) should be applied, and the presence or absence of intestinal metaplasia specified. Thus, BE may be diagnosed in the presence of only cardia-type mucosa.[28] BE occurs with greatest frequency in children with severe GERD.

Tests on ear, lung and esophageal fluids

Several studies have reported finding pepsin, a gastric enzyme, in middle ear effusions of children with chronic otitis media, suggesting that GER may have an etiologic role.[29] However, there are also studies reporting otherwise, and the finding of pepsin has not been validated in controlled treatment trials. Similarly, the presence of lactose, glucose, pepsin, or lipid-filled macrophages in bronchoalveolar lavage fluids has been proposed to implicate aspiration secondary to reflux, as a cause of chronic upper and lower airway manifestations.[30] It is not clear if the children also present with esophageal manifestations of reflux in these situations.

Empiric trial of acid suppression as a diagnostic test

Empiric acid-suppressing treatment, without diagnostic testing, has been used in adults. However, empiric therapy has only modest sensitivity and specificity as a diagnostic test for GERD, and the appropriate duration of a "diagnostic trial" has not been clarified. An uncontrolled trial of esomeprazole therapy in adolescents with heartburn, epigastric pain and acid regurgitation showed complete resolution of symptoms in 30 to 43% of subjects by 1 week, but the responders increased to 65% following 8 weeks of treatment.[31] Another uncontrolled treatment trial with pantoprazole in children aged 5 to 11 years, reported greater symptom improvement at 1 week with a 40 mg dose compared to a 10 mg or 20 mg dose.[32] After 8 weeks, all treatment groups improved. Studies in infants (< 1 year of age) with symptoms suggestive of GERD treated empirically with different PPIs showed no efficacy over placebo.

The treatment period required to achieve uniform therapeutic responses with PPI therapy probably varies with disease severity, treatment dose and specific symptoms or complications.[33] The 2-week "PPI test" lacks adequate specificity and sensitivity for use in clinical practice. In an older child or adolescent with symptoms suggesting GERD, an empiric PPI-trial is justified for up to 4 weeks. Improvement following treatment does not confirm a diagnosis of GERD since symptoms may improve spontaneously or respond by a placebo effect.

Treatment

Management options for physiologic GER and for GERD include lifestyle changes, pharmacologic therapy and surgery. Parental education, guidance and support are always required and usually sufficient to manage healthy, thriving infants with symptoms likely due to physiologic GER.

Feeding changes in infants

About 50% of 3-4 month old infants regurgitate at least once a day.[34,35] Up to 20% of caregivers in the United States seek medical help for this normal behavior.[35] According to data from Indonesia, regurgitation may be more frequent in formula-fed than in breastfed infants.[36] In infants with allergy to cow's milk protein, vomiting frequency decreases significantly (usually within 2 weeks) after the elimination of cow's milk protein from the diet, while reintroduction causes recurrence of symptoms.[37,38]

One study in infants suggested that large-volume feedings promote regurgitation, probably by increasing the frequency of transient LES relaxation, while reduced feeding volume decreased reflux frequency.[39] However, attention should be given to caloric intake, which should always be sufficient to allow normal growth and development. Adding thickening agents also decreases the frequency of overt regurgitation.[40]

In the United States, rice cereal is the most commonly used thickening agent for formula.[41] Excessive caloric intake is a potential problem with long-term use of non-commercialised thickened feeds. In Europe, bean gum, which has no nutritional value, is often used as a thickener. Commercially available anti-regurgitant (AR) formulas contain processed rice, corn or potato starch, guar gum or locust bean gum. These formulas decrease overt regurgitation, as well as vomiting frequency and volume compared with unthickened formulas or formulas thickened with rice cereal. A potential advantage of AR formulas is that they contain a caloric density, osmolarity, protein, calcium, and fatty acid content appropriate to an infant's nutritional needs when taken in normal volume, whereas a formula with added thickener has a higher caloric density. A decrease of acid reflux has only been shown in the literature for corn starch-thickened formula, and in one study with bean gum as the thickening agent. In the bean gum study, the number of acid reflux episodes decreased, but the contact time of the esophageal electrode with acid was prolonged (suggesting a decreased esophageal clearance), resulting in a similar reflux index.

Nasojejunal feeding is occasionally useful in infants with recurrent, reflux-related pneumonia to prevent recurrent aspiration. Although this approach to therapy is widely used, there have been no controlled studies comparing it to pharmacological or surgical treatments.[42]

Positioning therapy for infants

In the 1980s, prone positioning was recommended for the treatment of GERD in infants, because studies showed less reflux to occur in this position. The semi-supine positioning as attained in an infant car-seat exacerbates GER.[43] Although the full, upright position appears to decrease measured reflux, one study suggested that using formula thickened with rice cereal was more effective in decreasing the frequency of regurgitation than upright positioning after feeds.[44]

Prone sleep positioning is associated with longer uninterrupted sleep periods, while supine sleep positioning causes more frequent arousals and crying.[45] The evidence that prone positioning is a risk factor for sudden infant death syndrome (SIDS) required a reassessment of the benefits and risks of prone positioning for reflux management. A Nordic epidemiological SIDS study demonstrated that the odds ratio of mortality from SIDS to be over 10 times higher in prone-sleeping infants and 3 times higher in side-sleeping infants than in supine-sleeping infants.[46]

Therefore, prone positioning is only acceptable if the infant is observed and awake. Prone and side-sleeping positions cannot be recommended in infants under 1 year of age. Prone positioning may be beneficial in children over 1 year of age with GER or GERD whose risk of SIDS is negligible.

Lifestyle changes in children and adolescents

Recommended lifestyle changes include dietary modification, avoidance of alcohol, weight loss, positioning changes and cessation of smoking. Alcohol, chocolate, and high-fat meals reduce LES pressure. Most studies investigating these recommendations have been performed in adults. A review of lifestyle changes in adults with GERD concluded weight loss to be the only change that improved pH profiles and symptoms.[47] Current evidence generally does not support or refute the use of specific dietary changes to treat reflux beyond infancy. Expert opinions suggest that children and adolescents with GERD should avoid caffeine, chocolate, alcohol and spicy foods if they provoke symptoms. Smoking should be avoided because it has been linked to adenocarcinoma of the esophagus. Several studies have shown that chewing sugarless gum after a meal decreases reflux.[1]

The effectiveness of positioning for treatment of GER and GERD in children over 1 year of age has not been studied. Studies have shown that adults who sleep with the head of the bed elevated have fewer and shorter episodes of reflux, and fewer reflux symptoms. Other studies in adults have shown that reflux increases in the right lateral decubitus position.[48] It is likely, therefore, that adolescents, like adults, may benefit from the left lateral decubitus sleeping position with the head of the bed elevated.

Pharmacologic therapies

The major pharmacologic agents currently used for treating GERD in children are gastric acid-buffering agents, mucosal surface barriers and gastric anti-secretory agents. Since the withdrawal of cisapride from commercial availability, prokinetic agents have been less frequently used. Domperidone is commercially available in most parts of the world, but it has been poorly studied to date.

Histamine-2 receptor antagonists

Histamine-2 receptor antagonists (H$_2$RA) decrease acid secretion by inhibiting histamine-2 receptors on gastric parietal cells. Pharmacokinetic studies in 4-11 year old children suggested that peak plasma ranitidine concentration occurs 2.5 hours after dosing, with a half-life of 2 hours. The efficacy of H$_2$RA in achieving mucosal healing is much greater in mild esophagitis than in severe esophagitis. H$_2$RAs are less effective than proton pump inhibitors (PPIs) for both symptom relief and healing of esophagitis.[49]

Development of tolerance to oral H$_2$RA in adults is well-recognized.[50] The fairly rapid tachyphylaxis that develops with H$_2$RA is a drawback to chronic use. In some infants, H$_2$RA therapy causes irritability, head-banging, headache, somnolence and other side effects which, if interpreted as persistent symptoms of GERD, can result in an inappropriate increase in dosage.[51]

Proton pump inhibitors

PPIs inhibit acid secretion by blocking Na$+$/K$+$-ATPase, the final common pathway of parietal cell acid secretion, often called the proton pump. Studies in adults have shown that PPIs produce higher and faster healing rates for erosive esophagitis than those of H$_2$RAs.[52] The potent suppression of acid secretion by PPIs also results in decreased 24-hour intragastric volumes, thereby facilitating gastric emptying and decreasing volume reflux. PPIs must be taken once a day, before breakfast, and must be protected from gastric acid by enteric coatings. Achievement of the maximal acid suppressant effect can take up to 4 days, although adult data has suggested that PPIs can also be used for 'on-demand' treatment of symptoms.

Until now, no PPI has been approved for use in infants < 1 year of age. No placebo-controlled treatment trial in which enrollment was based upon "typical" GERD symptoms has demonstrated symptom improvement in infants. This result may be due to the lack of specificity of symptom-based diagnosis of GERD, especially with esophagitis, in this age group.

There are four main categories of adverse events associated with PPI therapy: idiosyncratic reactions, drug-drug interactions, drug-induced

hypergastrinemia, and drug-induced hypochlorhydria. The most common idiosyncratic effects are headache, diarrhea, constipation and nausea, each occurring in 2-7% of patients. These effects may resolve with decreased dose or changing to a different PPI. Parietal cell hyperplasia and occasional fundic gland polyps are benign changes. Enterochromaffin-like cell (ECL) hyperplasia is also a result of acid suppression. A recent retrospective study showed ECL hyperplasia in the gastric body to be in almost half of children receiving long-term PPI continuously for a median of about 3 years. The hyperplasia was clinically insignificant, and no patient developed atrophic gastritis, or carcinoid tumors.[53,54] PPIs have also been shown to alter the gastric and intestinal bacterial flora.

Prokinetic therapy

After cisapride was found to produce prolongation of the corrected QT interval (QTc) by electrocardiogram, its use was restricted to limited-access programs. Domperidone and metoclopramide are anti-dopaminergic agents that facilitate gastric emptying.

Metoclopramide has cholinomimetic and mixed serotonergic effects. Metoclopramide commonly produces adverse side effects in infants and children, particularly lethargy, irritability, gynecomastia, galacctorhea and extrapyramidal reactions, as well as causes permanent tardive dyskinesia. A recent systematic review of studies on domperidone identified only four randomized trials in children, none providing "robust evidence" for the efficacy of domperidone in pediatric GERD.[55] Domperidone occasionally causes extrapyramidal central nervous system side effects.

Erythromycin, a dopamine-receptor antagonist, is sometimes used in patients with gastroparesis to hasten gastric emptying. Baclofen is a gamma-amino-butyric-acid receptor agonist that reduces both acid and non-acid reflux in healthy adults and in those with GERD. In children, it was shown to accelerate gastric emptying for 2 hours after dosing, without any deleterious effect on LES resting pressure or esophageal peristalsis.[56] Baclofen is known to cause dyspeptic symptoms, drowsiness, dizziness, fatigue, and lowered the threshold for seizures. Such side effects preclude its routine use.

Recent experience with arbaclofen showed no benefit over placebo.

Currently, there is insufficient evidence to justify the routine use of any prokinetic (cisapride, metoclopramide, domperidone, bethanechol, erythromycin, or (ar)baclofen).

Other agents

Antacids directly buffer gastric contents, thereby reducing heartburn. On-demand use of antacids may provide rapid symptom relief in non-erosive reflux disease. Prolonged treatment with aluminum-containing antacids significantly increases plasma aluminum in infants. Some studies have reported plasma aluminum concentrations close to those associated with osteopenia, rickets, microcytic anemia and neurotoxicity.[1,57] Milk-alkali syndrome, a triad of hypercalcemia, alkalosis and renal failure, can occur due to chronic or high-dose ingestion of calcium carbonate. Because alternatives are available, chronic antacid therapy is not recommended.

Most surface protective agents contain either alginate or sucralfate. Alginates are insoluble salts of alginic acid, a component of algal cell walls. Alginate is also available in tablet form, and is useful for on-demand treatment of symptoms. Sucralfate is a compound of sucrose, sulfate and aluminum which, in an acid environment, forms a gel that binds to the exposed mucosa of peptic erosions. The available data is inadequate to determine the safety or efficacy of sucralfate, particularly with regards to the risk of aluminum toxicity with long-term use.

Surgical therapy

Fundoplication decreases reflux by increasing the LES baseline pressure, decreasing the number of TLESRs and the nadir pressure during swallow-induced relaxation, increasing the length of the esophagus that is intra-abdominal, accentuating the angle of His and reducing a hiatal hernia if present.[64] Fundoplication usually eliminates reflux, including physiologic reflux. Fundoplication does not correct underlying esophageal clearance, gastric emptying or other gastrointestinal dysmotility disorders.[58,59]

Laparoscopic Nissen fundoplication has largely replaced open Nissen fundoplication, as the

preferred anti-reflux surgery for adults and children, due to its decreased morbidity, shorter hospital stay, and fewer perioperative problems. In operated children, those with neurologic impairment (NI) have more than twice the complications, 3 times the morbidity and 4 times the re-operation rate of children without NI.[60] Fundoplication in early infancy has a higher failure rate than fundoplication performed later in childhood.[61]

A significant reduction in the number of adverse respiratory events was observed in the year following surgery in those operated on at < 4 years of age (1.95 vs 0.67 events per year). But, children with developmental delays are hospitalized more frequently in the year following anti-reflux surgery than before surgery.[62] In a recent pediatric study, Nissen fundoplication does not decrease hospital admissions for pneumonia, respiratory distress, apnea, or failure to thrive, even in those with underlying neurological impairment.[63]

Complications following anti-reflux surgery may be due to alterations in fundic capacity, gastric compliance and/or sensory responses, which may persist from months to years. Early and late operative failure may result from disruption of the wrap or slippage of the wrap into the chest.

Endoluminal endoscopic gastroplication has been described to be of benefit in children as an alternative to surgical fundoplication. When a group of 16 children with GERD refractory to or dependent on medical therapy was evaluated after endoluminal gastroplication, four had recurrent symptoms requiring a repeat procedure 2-24 months post-operatively. Three years after surgery, 9 patients (56%) were taking no anti-reflux medication.[64]

Anti-reflux surgery may be of benefit in children with confirmed GERD in whom optimal medical therapy has failed, who are dependent on medical therapy over a long period of time, who are significantly non-adherent to medical therapy, or who have life-threatening complications of GERD.

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